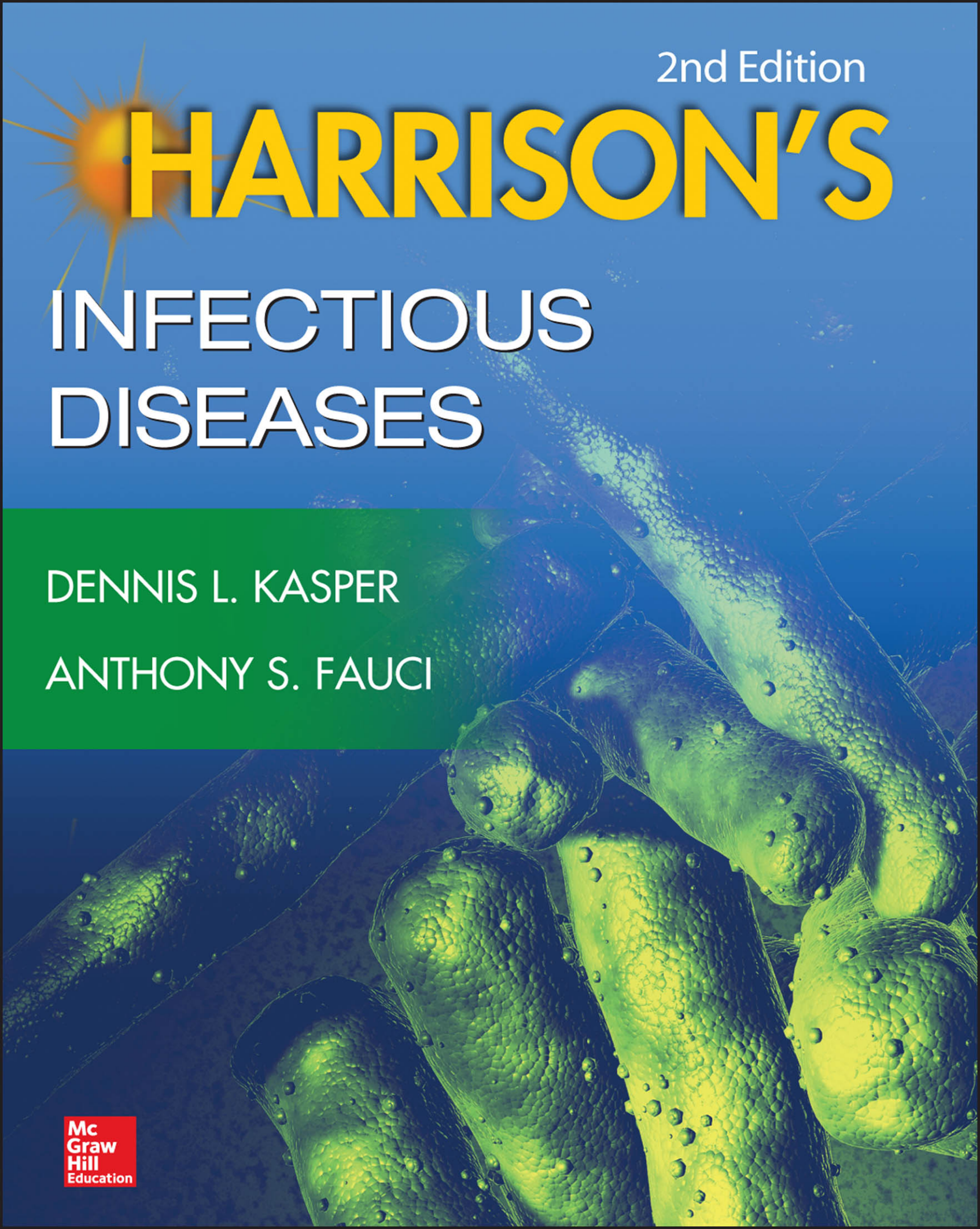
2nd Edition

HARRISON'S

INFECTIOUS DISEASES

DENNIS L. KASPER

ANTHONY S. FAUCI



Mc Graw Hill Education

2nd Edition

HARRISON'S™

INFECTIOUS DISEASES

Derived from Harrison's Principles of Internal Medicine, 18th Edition

Editors

DAN L. LONGO, MD
Professor of Medicine, Harvard Medical School;
Senior Physician, Brigham and Women's Hospital;
Deputy Editor, New England Journal of Medicine,
Boston, Massachusetts

ANTHONY S. FAUCI, MD
Chief, Laboratory of Immunoregulation; Director,
National Institute of Allergy and Infectious Diseases,
National Institutes of Health, Bethesda, Maryland

DENNIS L. KASPER, MD
William Ellery Channing Professor of Medicine and
Professor of Microbiology and Immunobiology,
Division of Immunology, Department of Microbiology
and Immunobiology, Harvard Medical School,
Boston, Massachusetts

STEPHEN L. HAUSER, MD
Robert A. Fishman Distinguished Professor and Chairman,
Department of Neurology,
University of California, San Francisco,
San Francisco, California

J. LARRY JAMESON, MD, PhD
Robert G. Dunlop Professor of Medicine;
Dean, University of Pennsylvania School of Medicine;
Executive Vice-President of the University of Pennsylvania for the
Health System, Philadelphia, Pennsylvania

JOSEPH LOSCALZO, MD, PhD
Hersey Professor of the Theory and Practice of Medicine,
Harvard Medical School;
Chairman, Department of Medicine;
Physician-in-Chief, Brigham and Women's Hospital,
Boston, Massachusetts

2nd Edition

HARRISON'S™

INFECTIOUS DISEASES

EDITORS

Dennis L. Kasper, MD
William Ellery Channing Professor of Medicine and
Professor of Microbiology and Immunobiology,
Division of Immunology, Department of Microbiology
and Immunobiology, Harvard Medical School,
Boston, Massachusetts

Anthony S. Fauci, MD
Chief, Laboratory of Immunoregulation;
Director, National Institute of Allergy and Infectious Diseases,
National Institutes of Health,
Bethesda, Maryland

Mc Graw Hill Education | Medical

New York Chicago San Francisco Lisbon London Madrid Mexico City
Milan New Delhi San Juan Seoul Singapore Sydney Toronto

ISBN: 978-0-07-181483-6

MHID: 0-07-181483-3

The material in this eBook also appears in the print version of this title: ISBN: 978-0-07-181482-9,
MHID: 0-07-181482-5.

Dr. Fauci's work as an editor and author was performed outside the scope of his employment as a U.S. government employee. This work represents his personal and professional views and not necessarily those of the U.S. government.

CONTENTS

SECTION V

VIRAL INFECTIONS

SECTION IX

ENVENOMATIONS, INFESTATIONS, BITES, AND STINGS

This page intentionally left blank

CONTRIBUTORS

Numbers in brackets refer to the chapter(s) written or co-written by the contributor.

Neil M. Ampel, MD
Professor of Medicine, University of Arizona, Tucson, Arizona [107]

Gordon L. Archer, MD
Professor of Medicine and Microbiology/Immunology; Senior Associate Dean for Research and Research Training, Virginia Commonwealth University School of Medicine, Richmond, Virginia [36]

Cesar A. Arias, MD, PhD
Assistant Professor, University of Texas Medical School, Houston, Texas; Director, Molecular Genetics and Antimicrobial Resistance Unit, Universidad El Bosque, Bogotá, Colombia [40]

John C. Atherton, MD, FRCP
Nottingham Digestive Diseases Centre Biomedical Research Unit (NDDC BRU), University of Nottingham and Nottingham University Hospitals NHS Trust, Nottingham, United Kingdom [56]

Paul S. Auerbach, MD, MS
Redlich Family Professor, Department of Surgery, Division of Emergency Medicine, Stanford University School of Medicine, Palo Alto, California [131]

Lindsey R. Baden, MD
Associate Professor of Medicine, Harvard Medical School; Dana-Farber Cancer Institute, Brigham and Women's Hospital, Boston, Massachusetts [83]

Tamar F. Barlam, MD
Associate Professor of Medicine, Boston University School of Medicine, Boston, Massachusetts [15, 51]

Miriam J. Baron, MD
Assistant Professor of Medicine, Harvard Medical School; Associate Physician, Brigham and Women's Hospital, Boston, Massachusetts [25]

Rebecca M. Baron, MD
Assistant Professor, Harvard Medical School; Associate Physician, Department of Pulmonary and Critical Care Medicine, Brigham and Women's Hospital, Boston, Massachusetts [19]

John G. Bartlett, MD
Professor of Medicine and Chief, Division of Infectious Diseases, Department of Medicine, Johns Hopkins School of Medicine, Baltimore, Maryland [19]

Robert C. Basner, MD
Professor of Clinical Medicine, Division of Pulmonary, Allergy, and Critical Care Medicine, Columbia University College of Physicians and Surgeons, New York, New York [Appendix]

Nicholas J. Beeching, MA, BM BCh, FRCP, FRACP, FFTM RCPS (Glasg), DCH, DTM&H
Senior Lecturer (Clinical) in Infectious Diseases, Liverpool School of Tropical Medicine; Clinical Lead, Tropical and Infectious Disease Unit, Royal Liverpool University Hospital; Honorary Consultant, Health Protection Agency; Honorary Civilian Consultant in Infectious Diseases, Army Medical Directorate, Liverpool, United Kingdom [62]

Jean Bergounioux, MD, PhD
Pediatric Intensive Care Unit, Hôpital Necker-Enfants Malades, Paris, France [59]

William R. Bishai, MD, PhD
Professor and Co-Director, Center for Tuberculosis Research, Department of Medicine, Division of Infectious Diseases, Johns Hopkins University School of Medicine, Baltimore, Maryland [42]

Martin J. Blaser, MD
Frederick H. King Professor of Internal Medicine; Chair, Department of Medicine; Professor of Microbiology, New York University School of Medicine, New York, New York [56, 60]

Gijs Bleijenberg, PhD
Professor; Head, Expert Centre for Chronic Fatigue, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands [33]

Eugene Braunwald, MD, MA (Hon), ScD (Hon) FRCP
Distinguished Hersey Professor of Medicine, Harvard Medical School; Founding Chairman, TIMI Study Group, Brigham and Women's Hospital, Boston, Massachusetts [21]

Joel G. Breman, MD, DTPH
Scientist Emeritus, Fogarty International Center, National Institutes of Health, Bethesda, Maryland [119, 121]

Cynthia D. Brown, MD
Assistant Professor of Medicine, Division of Pulmonary and Critical Care Medicine, University of Virginia, Charlottesville, Virginia [Review and Self-Assessment]

Kevin E. Brown, MD, MRCP, FRCPath
Consultant Medical Virologist, Virus Reference Department, Health Protection Agency, London, United Kingdom [89]

Amy E. Bryant, PhD
Research Scientist, Veterans Affairs Medical Center, Boise, Idaho; Affiliate Assistant Professor, University of Washington School of Medicine, Seattle, Washington [46]

Stephen B. Calderwood, MD
Morton Swartz MD Academy Professor of Medicine (Microbiology and Molecular Genetics), Harvard Medical School; Chief, Division of Infectious Diseases, Massachusetts General Hospital, Boston, Massachusetts [26]

Michael V. Callahan, MD, DTM&H (UK), MSPH
Clinical Associate Physician, Division of Infectious Diseases, Massachusetts General Hospital, Boston, Massachusetts; Program Manager, Biodefense, Defense Advanced Research Project Agency (DARPA), United States Department of Defense, Washington, DC [10]

Jonathan R. Carapetis, PhD, MBBS, FRACP, FAFPHM
Director, Menzies School of Health Research, Charles Darwin University, Darwin, Australia [41]

Kathryn M. Carbone, MD
Deputy Scientific Director, Division of Intramural Research, National Institute of Dental and Craniofacial Research, Bethesda, Maryland [100]

Arturo Casadevall, MD, PhD
Chair, Department of Microbiology and Immunology, Albert Einstein College of Medicine, Bronx, New York [109]

Stanley W. Chapman, MD
Professor of Medicine, University of Mississippi Medical Center, Jackson, Mississippi [108]

Jeffrey I. Cohen, MD
Chief, Medical Virology Section, Laboratory of Clinical Infectious Diseases, National Institutes of Health, Bethesda, Maryland [86, 97]

Ronit Cohen-Poradosu, MD
Senior Physician, Department of Clinical Microbiology and Infectious Diseases, Hadassah Hebrew Medical Center, Jerusalem, Israel [69]

Michael J. Corbel, PhD, DSc, FRCPath
Head, Division of Bacteriology, National Institute for Biological Standards and Control, Hertfordshire, United Kingdom [62]

Lawrence Corey, MD
Professor of Medicine and Laboratory Medicine and Head, Virology Division, Department of Laboratory Medicine, University of Washington; Head, Program in Infectious Diseases, Fred Hutchinson Cancer Research Center, Seattle, Washington [84]

Charles E. Davis, MD
Professor of Pathology and Medicine, Emeritus, University of California, San Diego School of Medicine; Director Emeritus, Microbiology, University of California, San Diego Medical Center, San Diego, California [115]

David W. Denning, MB BS, FRCP, FRCPath
Professor of Medicine and Medical Mycology; Director, National Aspergillosis Centre, The University of Manchester and Wythenshawe Hospital, Manchester, United Kingdom [111]

Jules L. Dienstag, MD
Carl W. Walter Professor of Medicine and Dean for Medical Education, Harvard Medical School; Physician, Gastrointestinal Unit, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts [95, 96]

Charles A. Dinarello, MD
Professor of Medicine, Division of Infectious Diseases, University of Colorado School of Medicine, Aurora, Colorado [8]

Raphael Dolin, MD
Maxwell Finland Professor of Medicine (Microbiology and Molecular Genetics), Harvard Medical School; Beth Israel Deaconess Medical Center; Brigham and Women's Hospital, Boston, Massachusetts [83, 91, 92]

J. Stephen Dumler, MD
Professor, Division of Medical Microbiology, Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, Maryland [79]

Mark S. Dworkin, MD, MPH&TM
Associate Professor, Division of Epidemiology and Biostatistics, University of Illinois at Chicago School of Public Health, Chicago, Illinois [77]

John E. Edwards, Jr., MD
Chief, Division of Infectious Diseases, Harbor-University of California, Los Angeles (UCLA) Medical Center, Torrance, California; Professor of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, California [105, 110]

Andrew J. Einstein, MD, PhD
Assistant Professor of Clinical Medicine, Columbia University College of Physicians and Surgeons; Department of Medicine, Division of Cardiology, Department of Radiology, Columbia University Medical Center and New York-Presbyterian Hospital, New York, New York [Appendix]

Moshe Ephros, MD
Senior Lecturer, Faculty of Medicine, Technion—Israel Institute of Technology; Pediatric Infectious Disease Unit, Carmel Medical Center; Haifa, Israel [65]

Anthony S. Fauci, MD, DSc (Hon), DM&S (Hon), DHL (Hon), DPS (Hon), DLM (Hon), DMS (Hon)
Chief, Laboratory of Immunoregulation; Director, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland [7, 93]

Gregory A. Filice, MD
Professor of Medicine, University of Minnesota; Chief, Infectious Disease Section, Veterans Affairs Medical Center, Minneapolis, Minnesota [67]

Robert Finberg, MD
Chair, Department of Medicine, University of Massachusetts Medical School, Worcester, Massachusetts [12, 13]

Joyce Fingeroth, MD
Associate Professor of Medicine, Harvard Medical School, Boston, Massachusetts [13]

Larry C. Ford, MD
Associate Researcher, Divisions of Clinical Epidemiology and Infectious Diseases, University of Utah, Salt Lake City, Utah [17]

Charlotte A. Gaydos, DrPh, MPH, MS
Professor of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland [81]

Robert H. Gelber, MD
Clinical Professor of Medicine and Dermatology, University of California, San Francisco, San Francisco, California [71]

Jeffrey A. Gelfand, MD
Clinical Professor of Medicine, Harvard Medical School; Physician, Massachusetts General Hospital, Boston, Massachusetts [10, 120]

Dale N. Gerding, MD
Professor of Medicine, Loyola University Chicago Stritch School of Medicine; Associate Chief of Staff for Research and Development, Edward Hines, Jr. VA Hospital, Hines, Illinois [47]

Michael Giladi, MD, MSc
Associate Professor of Medicine, Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel [65]

Roger I. Glass, MD, PhD
Director, Fogarty International Center, Bethesda, Maryland [94]

David Goldblatt, PhD, MBChB, FRCP, FRCPCH
Professor of Vaccinology and Immunology; Consultant in Paediatric Immunology; Director of Clinical Research and Development; Director, NIHR Biomedical Research Centre, Institute of Child Health; University College London; Great Ormond Street Hospital for Children NHS Trust, London, United Kingdom [37]

Ralph Gonzales, MD, MSPH
Professor of Medicine, University of California, San Francisco, San Francisco, California [17]

Jeffrey I. Gordon, MD
Dr. Robert J. Glaser Distinguished University Professor; Director, Center for Genome Sciences, Washington University School of Medicine, St. Louis, Missouri [3]

Kalpana Gupta, MD, MPH
Associate Professor, Department of Medicine, Boston University School of Medicine; Chief, Section of Infectious Diseases, VA Boston Healthcare System, Boston, Massachusetts [28]

Chadi A. Hage, MD
Assistant Professor of Medicine, Pulmonary–Critical Care and Infectious Diseases, Roudebush VA Medical Center; Indiana University, Indianapolis, Indiana [106]

Scott A. Halperin, MD
Professor of Pediatrics and Microbiology and Immunology; CIHR/Wyeth Chair in Clinical Vaccine Research; Head, Pediatric Infectious Diseases; Director, Canadian Center for Vaccinology, Dalhousie University, Halifax, Nova Scotia, Canada [53]

R. Doug Hardy, MD
Associate Professor of Internal Medicine and Pediatrics, University of Texas Southwestern Medical Center, Dallas, Texas [80]

Anna R. Hemnes, MD
Assistant Professor, Division of Allergy, Pulmonary, and Critical Care Medicine, Vanderbilt University Medical Center, Nashville, Tennessee [Review and Self-Assessment]

Martin S. Hirsch, MD
Professor of Medicine, Harvard Medical School; Professor of Immunology and Infectious Diseases, Harvard School of Public Health; Physician, Massachusetts General Hospital, Boston, Massachusetts [87]

Elizabeth L. Hohmann, MD
Associate Professor of Medicine and Infectious Diseases, Harvard Medical School; Massachusetts General Hospital, Boston, Massachusetts [43]

Steven M. Holland, MD
Chief, Laboratory of Clinical Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland [72]

King K. Holmes, MD, PhD
Chair, Global Health; Professor of Medicine and Global Health; Adjunct Professor, Epidemiology; Director, Center for AIDS and STD; University of Washington School of Medicine; Head, Infectious Diseases Section, Harborview Medical Center, Seattle, Washington [30]

Ashraf S. Ibrahim, PhD
Associate Professor of Medicine, Geffen School of Medicine, University of California, Los Angeles (UCLA); Division of Infectious Diseases, Los Angeles Biomedical Research Institute at Harbor–UCLA Medical Center, Torrance, California [112]

Alan C. Jackson, MD, FRCPC
Professor of Medicine (Neurology) and Medical Microbiology, University of Manitoba; Section Head of Neurology, Winnipeg Regional Health Authority, Winnipeg, Manitoba, Canada [101]

Lisa A. Jackson, MD, MPH
Senior Investigator, Group Health Research Institute; Research Professor, Department of Epidemiology; Adjunct Professor, Department of Medicine, University of Washington, Seattle, Washington [4]

Richard F. Jacobs, MD
Robert H. Fiser, Jr., MD Endowed Chair in Pediatrics; Professor and Chairman, Department of Pediatrics, University of Arkansas for Medical Sciences; President, Arkansas Children's Hospital Research Institute, Little Rock, Arkansas [63]

James R. Johnson, MD
Professor of Medicine, University of Minnesota, Minneapolis, Minnesota [54]

Stuart Johnson, MD
Associate Professor of Medicine, Loyola University Chicago Stritch School of Medicine; Staff Physician, Edward Hines, Jr. VA Hospital, Hines, Illinois [47]

Adolf W. Karchmer, MD
Professor of Medicine, Harvard Medical School; Division of Infectious Diseases, Beth Israel Deaconess Medical Center, Boston, Massachusetts [20]

Dennis L. Kasper, MD, MA (Hon)
William Ellery Channing Professor of Medicine and Professor of Microbiology and Molecular Genetics, Harvard Medical School; Director, Channing Laboratory, Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts [1, 15, 25, 51, 69]

Lloyd H. Kasper, MD
Professor of Medicine (Neurology) and Microbiology and Immunology, Dartmouth Medical School, Lebanon, New Hampshire [124]

Carol A. Kauffman, MD
Professor of Internal Medicine, University of Michigan Medical School; Chief, Infectious Diseases Section, Veterans Affairs Ann Arbor Healthcare System, Ann Arbor, Michigan [113]

Elaine T. Kaye, MD
Assistant Clinical Professor of Dermatology, Harvard Medical School, Boston, Massachusetts [9, 11]

Kenneth M. Kaye, MD
Associate Professor of Medicine, Harvard Medical School, Boston, Massachusetts [9, 11]

Jay S. Keystone, MD, FRCPC, MSc (CTM)
Professor of Medicine, University of Toronto, Toronto, Ontario, Canada [5]

Elliott Kieff, MD, PhD
Harriet Ryan Albee Professor, Harvard Medical School; Chief, Infectious Diseases Division, Brigham and Women's Hospital, Boston, Massachusetts [82]

Kami Kim, MD
Professor of Medicine (Infectious Diseases) and of Microbiology and Immunology, Albert Einstein College of Medicine, Bronx, New York [124]

Louis V. Kirchhoff, MD, MPH
Professor of Internal Medicine (Infectious Diseases) and Epidemiology, Department of Internal Medicine, The University of Iowa, Iowa City, Iowa [123]

Rob Knight, PhD
Assistant Professor, Department of Chemistry and Biochemistry, University of Colorado, Boulder, Colorado [3]

Walter J. Koroshetz, MD
National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland [32]

Phyllis E. Kozarsky, MD
Professor of Medicine and Infectious Diseases, Emory University School of Medicine, Atlanta, Georgia [5]

Alexander Kratz, MD, PhD, MPH
Associate Professor of Pathology and Cell Biology, Columbia University College of Physicians and Surgeons; Director, Core Laboratory, Columbia University Medical Center, New York, New York [Appendix]

H. Clifford Lane, MD
Clinical Director; Director, Division of Clinical Research; Deputy Director, Clinical Research and Special Projects; Chief, Clinical and Molecular Retrovirology Section, Laboratory of Immunoregulation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland [7, 93]

Regina C. LaRocque, MD
Assistant Professor of Medicine, Harvard Medical School; Assistant Physician, Massachusetts General Hospital, Boston, Massachusetts [26]

Franklin D. Lowy, MD
Professor of Medicine and Pathology, Columbia University College of Physicians and Surgeons, New York, New York [38]

Sheila A. Lukehart, PhD
Professor, Departments of Medicine and Global Health, University of Washington, Seattle, Washington [74, 75]

Lawrence C. Madoff, MD
Professor of Medicine, University of Massachusetts Medical School, Worcester, Massachusetts; Director, Division of Epidemiology and Immunization, Massachusetts Department of Public Health, Jamaica Plain, Massachusetts [1, 24, 34, 35]

Adel A. F. Mahmoud, MD, PhD
Professor, Department of Molecular Biology and the Woodrow Wilson School of Public and International Affairs, Princeton University, Princeton, New Jersey [129]

Lionel A. Mandell, MD, FRCP(C), FRCP(LOND)
Professor of Medicine, McMaster University, Hamilton, Ontario, Canada [18]

Jeanne M. Marrazzo, MD, MPH
Associate Professor of Medicine, Division of Infectious Diseases, Harborview Medical Center, Seattle, Washington [30]

Thomas Marrie, MD
Dean, Faculty of Medicine, Dalhousie University, Halifax, Nova Scotia, Canada [79]

Susan Maslanka, PhD
Enteric Diseases Laboratory Branch, Centers for Disease Control and Prevention, Atlanta, Georgia [45]

Alexander J. McAdam, MD, PhD
Assistant Professor of Pathology, Harvard Medical School, Children's Hospital, Boston, Massachusetts [6]

Bruce L. Miller, MD
AW and Mary Margaret Clausen Distinguished Professor of Neurology, University of California, San Francisco School of Medicine, San Francisco, California [104]

Samuel I. Miller, MD
Professor of Genome Sciences, Medicine, and Microbiology, University of Washington, Seattle, Washington [58]

Thomas A. Moore, MD, FACP, FIDSA
Chairman, Department of Infectious Diseases, Ochsner Health System, New Orleans, Louisiana [116, 117]

William J. Moss, MD, MPH
Associate Professor, Departments of Epidemiology, International Health, and Molecular Microbiology and Immunology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland [98]

Robert S. Munford, MD
Bethesda, Maryland [16]

John R. Murphy, PhD
Professor of Medicine and Microbiology, Boston University School of Medicine, Boston, Massachusetts [42]

Timothy F. Murphy, MD
UB Distinguished Professor of Medicine and Microbiology, University of Buffalo, State University of New York, Buffalo, New York [50]

Barbara E. Murray, MD
J. Ralph Meadows Professor and Director, Division of Infectious Diseases, University of Texas Medical School, Houston, Texas [40]

Robert L. Norris, MD
Professor, Department of Surgery, Division of Emergency Medicine, Stanford University School of Medicine, Palo Alto, California [131]

Thomas B. Nutman, MD
Head, Helminth Immunology Section; Head, Clinical Parasitology Unit, Laboratory of Parasitic Diseases, National Institutes of Health, Bethesda, Maryland [127, 128]

Katherine L. O'Brien, MDCM, MPH, FRCPC
Associate Professor, Center for American Indian Health; Departments of International Health and Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland [37]

Richard J. O'Brien, MD
Head, Product Evaluation and Demonstration, Foundation for Innovative and New Diagnostics (FIND), Geneva, Switzerland [70]

Max R. O'Donnell, MD
Assistant Professor of Medicine, Albert Einstein College of Medicine, Bronx, New York [73]

Nigel O'Farrell, MSc, MD, FRCP
Ealing Hospital, London, United Kingdom [66]

Andrew B. Onderdonk, PhD
Professor of Pathology, Harvard Medical School; Brigham and Women's Hospital, Boston, Massachusetts [6]

Umesh D. Parashar, MBBS, MPH
Lead, Viral Gastroenteritis Epidemiology Team, Division of Viral Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia [94]

David L. Paterson, MD, PhD
Professor of Medicine, University of Queensland Centre for Clinical Research; Royal Brisbane and Women's Hospital, Brisbane, Australia [55]

David A. Pegues, MD
Hospital Epidemiologist, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, California [58]

Anton Y. Peleg, MBBS, PhD, MPH, FRACP
Infectious Diseases Physician, Senior Lecturer, and NHMRC Biomedical Fellow, Department of Infectious Diseases and Microbiology, The Alfred Hospital and Monash University, Melbourne, Victoria, Australia [55]

Florencia Pereyra, MD
Assistant Professor of Medicine, Harvard Medical School; Associate Physician, Infectious Disease Division, Brigham and Women's Hospital, Boston, Massachusetts [34, 35]

Michael A. Pesce, PhD
Professor Emeritus of Pathology and Cell Biology, Columbia University College of Physicians and Surgeons; Columbia University Medical Center, New York, New York [Appendix]

Clarence J. Peters, MD
John Sealy Distinguished University Chair in Tropical and Emerging Virology; Professor, Department of Mirobiology and Immunology; Department of Pathology; Director for Biodefense, Center for Biodefense and Emerging Infectious Diseases, University of Texas Medical Branch, Galveston, Texas [102, 103]

Gerald B. Pier, PhD
Professor of Medicine (Microbiology and Molecular Genetics), Harvard Medical School; Microbiologist, Brigham and Women's Hospital, Boston, Massachusetts [2]

Ronald E. Polk, PharmD
Professor of Pharmacy and Medicine; Chairman, Department of Pharmacy, School of Pharmacy, Virginia Commonwealth University/Medical College of Virginia Campus, Richmond, Virginia [36]

Richard J. Pollack, PhD
Research Associate Professor, Department of Biology, Boston University; Research Associate, Department of Immunology and Infectious Diseases, Harvard School of Public Health, Boston, Massachusetts [132]

Andrew J. Pollard, PhD, FRCPCH
Professor of Pediatric Infection and Immunity; Director of the Oxford Vaccine Group, Department of Pediatrics, University of Oxford, Oxford, United Kingdom [48]

Reuven Porat, MD
Internal Medicine Department, Tel-Aviv Sourasky Medical Centre; Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel [8]

Daniel A. Portnoy, PhD
Professor of Biochemistry and Molecular Biology, Department of Molecular and Cell Biology, The School of Public Health, University of California, Berkeley, California [43]

Michael B. Prentice, MB ChB, PhD, MRCP(UK), FRCPath, FFPRCPI
Professor of Medical Microbiology, Department of Microbiology, University College Cork, Cork, Ireland [64]

Stanley B. Prusiner, MD
Director, Institute for Neurodegenerative Diseases; Professor, Department of Neurology, University of California, San Francisco, California [104]

Thomas C. Quinn, MD
Professor of Medicine, Johns Hopkins University, Baltimore, Maryland; Senior Investigator, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland [81]

Sanjay Ram, MD
Associate Professor of Medicine, Division of Infectious Diseases and Immunology, University of Massachusetts Medical School, Worcester, Massachusetts [49]

Reuben Ramphal, MD
Professor of Medicine, Molecular Genetics and Microbiology, University of Florida College of Medicine, Gainesville, Florida [57]

Anis Rassi, Jr., MD, PhD, FACC, FACP, FAHA
Scientific Director, Anis Rassi Hospital, Goiânia, Brazil [123]

Mario C. Raviglione, MD
Director, Stop TB Department, World Health Organization, Geneva, Switzerland [70]

Sharon L. Reed, MD
Professor of Pathology and Medicine; Director, Microbiology and Virology Laboratories, University of California, San Diego Medical Center, San Diego, California [115]

Susan E. Reef, MD
Medical Epidemiologist, Centers for Disease Control and Prevention, Atlanta, Georgia [99]

Richard C. Reichman, MD
Professor of Medicine and of Microbiology and Immunology, University of Rochester School of Medicine and Dentistry, Rochester, New York [90]

Peter A. Rice, MD
Professor of Medicine, Division of Infectious Diseases and Immunology, University of Massachusetts Medical School, Worcester, Massachusetts [49]

Michael A. Rubin, MD, PhD
Assistant Professor of Medicine, University of Utah School of Medicine, Salt Lake City, Utah [17]

Karen L. Roos, MD
John and Nancy Nelson Professor of Neurology and Professor of Neurological Surgery, Indiana University School of Medicine, Indianapolis, Indiana [31]

Steven Rubin, MS
Acting Principal Investigator, Center for Biologics Evaluation and Research, Food and Drug Administration, Bethesda, Maryland [100]

Thomas A. Russo, MD, CM, FIDSA
Professor of Medicine and Microbiology and Immunology; Chief, Division of Infectious Diseases, University at Buffalo, State University of New York, Buffalo, New York [54, 68]

Edward T. Ryan, MD, DTM&H
Associate Professor of Medicine, Harvard Medical School; Associate Professor of Immunology and Infectious Diseases, Harvard School of Public Health; Director, Tropical and Geographic Medicine, Massachusetts General Hospital, Boston, Massachusetts [26, 61]

Miguel Sabria, MD
Professor of Medicine, Autonomous University of Barcelona; Chief, Infectious Diseases Section, Germans Trias I Pujl Hospital, Barcelona, Spain [52]

Philippe Sansonetti, MD, MS
Professor, Collège de France; Institut Pasteur, Paris, France [59]

Jussi J. Saukkonen, MD
Associate Professor of Medicine, Section of Pulmonary, Allergy, and Critical Care Medicine, Boston University School of Medicine, Boston, Massachusetts [73]

Anne Schuchat, MD
Director, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia [4]

Gordon E. Schutze, MD
Professor of Pediatrics, Section of Retrovirology; Vice President, Baylor International Pediatric AIDS Initiative at Texas Children's Hospital, Baylor College of Medicine, Houston, Texas [63]

William Silen, MD
Johnson and Johnson Professor Emeritus of Surgery, Harvard Medical School, Auburndale, Massachusetts [27]

A. George Smulian, MBBCh
Associate Professor of Medicine, University of Cincinnati College of Medicine; Chief, Infectious Disease Section, Cincinnati VA Medical Center, Cincinnati, Ohio [114]

Jeremy Sobel, MD, MPH
Medical Officer, Office of Global Health, Centers for Disease Control and Prevention, Atlanta, Georgia [45]

Brad Spellberg, MD
Associate Professor of Medicine, Geffen School of Medicine, University of California, Los Angeles (UCLA); Divisions of General Internal Medicine and Infectious Diseases, Los Angeles Biomedical Research Institute at Harbor–UCLA Medical Center, Torrance, California [112]

Samuel L. Stanley, Jr., MD
President, Stony Brook University, Stony Brook, New York [118]

Allen C. Steere, MD
Professor of Medicine, Harvard Medical School; Massachusetts General Hospital, Boston, Massachusetts [78]

Dennis L. Stevens, MD, PhD
Professor of Medicine, University of Washington School of Medicine, Seattle, Washington; Chief, Infectious Disease Section, Veterans Affairs Medical Center, Boise, Idaho [22, 46]

Donna C. Sullivan, PhD
Professor, Department of Medicine, Division of Infectious Diseases, University of Mississippi Medical School, Jackson, Mississippi [108]

Shyam Sundar, MD
Professor of Medicine, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India [122]

Morton N. Swartz, MD
Professor of Medicine, Harvard Medical School; Chief, Jackson Firm Medical Service and Infectious Disease Unit, Massachusetts General Hospital, Boston, Massachusetts [32]

C. Louise Thwaites, MD, MBBS
Musculoskeletal Physician, Horsham, West Sussex; Oxford University Clinical Research Unit, Hospital for Tropical Diseases, Ho Chi Minh City, Vietnam [44]

Alan D. Tice, MD, FACP
Infections Limited Hawaii; John A. Burns School of Medicine, University of Hawaii, Honolulu, Hawaii [23]

Barbara W. Trautner, MD, PhD
Assistant Professor, Section of Infectious Diseases, Baylor College of Medicine; The Michael E. DeBakey Veterans Affairs Medical Center, Houston VA Health Services Research and Development Center of Excellence, Houston, Texas [28]

Kenneth L. Tyler, MD
Reuler-Lewin Family Professor and Chair, Department of Neurology; Professor of Medicine and Microbiology, University of Colorado School of Medicine, Denver, Colorado; Chief of Neurology, University of Colorado Hospital, Aurora, Colorado [31]

Jos W. M. van der Meer, MD, PhD
Professor of Medicine; Head, Department of General Internal Medicine, Radboud University, Nijmegen Medical Centre, Nijmegen, Netherlands [33]

Edouard Vannier, PhD, PharmD
Assistant Professor, Division of Geographic Medicine and Infectious Diseases, Tufts University School of Medicine; Tufts Medical Center, Boston, Massachusetts [120]

Joseph M. Vinetz, MD
Professor of Medicine, Division of Infectious Diseases, Department of Medicine, University of California, San Diego, California [76]

Matthew K. Waldor, MD, PhD
Edward H. Kass Professor of Medicine, Channing Laboratory, Brigham and Women's Hospital; Harvard Medical School and Howard Hughes Medical Institute, Boston, Massachusetts [61]

David H. Walker, MD
The Carmage and Martha Walls Distinguished University Chair in Tropical Diseases; Professor and Chairman, Department of Pathology; Executive Director, Center for Biodefense and Emerging Infectious Diseases, University of Texas Medical Branch, Galveston, Texas [79]

Peter D. Walzer, MD, MSc
Professor of Medicine, University of Cincinnati College of Medicine; Associate Chief of Staff for Research, Cincinnati VA Medical Center, Cincinnati, Ohio [114]

Fred Wang, MD
Professor of Medicine, Harvard Medical School; Brigham and Women's Hospital, Boston, Massachusetts [82, 88]

John W. Warren, MD
Professor of Medicine, University of Maryland School of Medicine, Baltimore, Maryland [29]

Robert A. Weinstein, MD
The C Anderson Hedberg MD Professor of Internal Medicine, Rush Medical College; Interim Chairman, Department of Medicine, John Stroger Hospital, Chicago, Illinois [14]

Peter F. Weller, MD
Chief, Infectious Disease Division; Chief, Allergy and Inflammation Division, Beth Israel Deaconess Medical Center, Boston, Massachusetts [125-128, 130]

Michael R. Wessels, MD
John F. Enders Professor of Pediatrics; Professor of Medicine, Harvard Medical School; Chief, Division of Infectious Diseases, Children's Hospital, Boston, Massachusetts [39]

L. Joseph Wheat, MD
MiraVista Diagnostics and MiraBella Technologies, Indianapolis, Indiana [106]

A. Clinton White, Jr., MD
Director, Infectious Disease Division, Department of Internal Medicine, University of Texas Medical Branch, Galveston, Texas [130]

Nicholas J. White, MD, DSc, FRCP, F Med Sci, FRS
Professor of Tropical Medicine, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand [119, 121]

Richard J. Whitley, MD
Distinguished Professor of Pediatrics, Loeb Eminent Scholar Chair in Pediatrics; Professor of Pediatrics, Microbiology, Medicine, and Neurosurgery, University of Alabama at Birmingham, Birmingham, Alabama [85]

Charles M. Wiener, MD
Dean/CEO Perdana University Graduate School of Medicine, Selangor, Malaysia; Professor of Medicine and Physiology, Johns Hopkins University School of Medicine, Baltimore, Maryland [Review and Self-Assessment]

Richard Wunderink, MD
Professor of Medicine, Division of Pulmonary and Critical Care, Northwestern University Feinberg School of Medicine, Chicago, Illinois [18]

Lam Minh Yen, MD
Director, Tetanus Intensive Care Unit, Hospital for Tropical Diseases, Ho Chi Minh City, Vietnam [44]

Victor L. Yu, MD
Professor of Medicine, Department of Medicine, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania [52]

Laura A. Zimmerman, MPH
Epidemiologist, Centers for Disease Control and Prevention, Atlanta, Georgia [99]

This page intentionally left blank

PREFACE

Despite enormous advances in diagnosis, treatment, and prevention during the twentieth century, physicians caring for patients with infectious diseases today must cope with extraordinary new challenges, including a never-ending deluge of new information, the rapid evolution of the microorganisms responsible for these diseases, and formidable time and cost constraints. In no other area of medicine is the differential diagnosis so wide, and often the narrowing of the differential to a precise infection caused by a specific organism with established antimicrobial susceptibilities is a matter of great urgency.

To inform crucial decisions about management, today's care providers are typically turning to a variety of sources, including both print publications and online services. Our goal in publishing *Harrison's Infectious Diseases* as a stand-alone volume is to provide students and practitioners with a single convenient resource that quickly yields accurate, accessible, up-to-date information to meet immediate clinical needs and that presents this information in the broader context of underlying epidemiologic, pathophysiologic, and genetic factors. The authors of the chapters herein are experts in their fields whose points of view represent decades of medical practice and a comprehensive knowledge of the literature. The specific recommendations of these authorities regarding diagnostic options and therapeutic regimens—including drugs of choice, doses, durations, and alternatives—take into account not just the trends and concerns of the moment but also the longer-term factors and forces that have shaped present circumstances and will continue to influence future developments. Among these forces are the changing prevalences, distributions, features, and management alternatives in different regions of the world; accordingly, these topics are addressed from an international perspective.

Prominent among the 132 chapters in this volume, that on HIV infections and AIDS by Anthony S. Fauci and H. Clifford Lane (Chap. 93) is widely considered to be a classic in the field. Its clinically pragmatic focus, along with its comprehensive and analytical approach to the pathogenesis of HIV disease, has led to its use as the sole complete reference on HIV/AIDS in medical schools. Also particularly comprehensive in scope are the classic chapters on tuberculosis (Chap. 70, authored by Mario C. Raviglione and Richard J. O'Brien) and malaria (Chap. 119, by Nicholas J. White and Joel G. Breman). A new chapter by Jeffrey I. Gordon and Rob Knight, "The Human Microbiome" (Chap. 3), summarizes and offers expert perspective on recent revolutionary information elucidating the intricate, critical relationship of the human body with its trillions of resident microbes and the associated microbial genes. A highly practical chapter by Robert A Weinstein (Chap. 14) addresses health care–associated infections, a topic of enormous significance in terms of patient care in general and antimicrobial resistance in particular. A superb chapter by David Goldblatt and Katherine L. O'Brien (Chap. 37) emphasizes the changing epidemiology of pneumococcal infections resulting from the introduction and use of pneumococcal conjugate vaccine, with rates of invasive disease among U.S. children and infants reduced by >75% overall and rates of vaccine-serotype infections reduced by >90% in the whole population. Previously covered in a combined chapter with streptococci, enterococcal infections have become sufficiently common to merit separate and more detailed coverage, which is provided in a fine chapter by Cesar A. Arias and Barbara E. Murray (Chap. 40).

Harrison's Infectious Diseases is available both in print and as an eBook obtainable via McGraw-Hill or via the Apple iBookstore. With a full-color format, this volume offers abundant illustrations that provide key information in a readily understandable format. Two chapters comprise atlases of images that can be invaluable in clinical assessments: Chap. 11 presents images of rashes associated with fever, while Chap. 121 shows blood smears of the various stages of the parasites causing malaria and babesiosis. Self-assessment questions and answers appear in an appendix at the end of the book.

The Editors thank our authors for their hard work in distilling their experience and the relevant literature into this volume, which we hope you will enjoy using as an authoritative source of current information on infectious diseases.

Dennis L. Kasper, MD
Anthony S. Fauci, MD

NOTICE

Medicine is an ever-changing science. As new research and clinical experience broaden our knowledge, changes in treatment and drug therapy are required. The authors and the publisher of this work have checked with sources believed to be reliable in their efforts to provide information that is complete and generally in accord with the standards accepted at the time of publication. However, in view of the possibility of human error or changes in medical sciences, neither the authors nor the publisher nor any other party who has been involved in the preparation or publication of this work warrants that the information contained herein is in every respect accurate or complete, and they disclaim all responsibility for any errors or omissions or for the results obtained from use of the information contained in this work. Readers are encouraged to confirm the information contained herein with other sources. For example and in particular, readers are advised to check the product information sheet included in the package of each drug they plan to administer to be certain that the information contained in this work is accurate and that changes have not been made in the recommended dose or in the contraindications for administration. This recommendation is of particular importance in connection with new or infrequently used drugss.

Review and self-assessment questions and answers were taken from Wiener CM, Brown CD, Hemnes AR (eds). *Harrison's Self-Assessment and Board Review*, 18th ed. New York, McGraw-Hill, 2012, ISBN 978-0-07-177195-5.

The global icons call greater attention to key epidemiologic and clinical differences in the practice of medicine throughout the world.

The genetic icons identify a clinical issue with an explicit genetic relationship.

SECTION I

INTRODUCTION TO INFECTIOUS DISEASES

CHAPTER 1

INTRODUCTION TO INFECTIOUS DISEASES: HOST–PATHOGEN INTERACTIONS

Lawrence C. Madoff ■ Dennis L. Kasper

Despite decades of dramatic progress in their treatment and prevention, infectious diseases remain a major cause of death and debility and are responsible for worsening the living conditions of many millions of people around the world. Infections frequently challenge the physician's diagnostic skill and must be considered in the differential diagnoses of syndromes affecting every organ system.

CHANGING EPIDEMIOLOGY OF INFECTIOUS DISEASES

With the advent of antimicrobial agents, some medical leaders believed that infectious diseases would soon be eliminated and become of historic interest only. Indeed, the hundreds of chemotherapeutic agents developed since World War II, most of which are potent and safe, include drugs effective not only against bacteria but also against viruses, fungi, and parasites. Nevertheless, we now realize that as we developed antimicrobial agents, microbes developed the ability to elude our best weapons and to counterattack with new survival strategies. Antibiotic resistance occurs at an alarming rate among all classes of mammalian pathogens. Pneumococci resistant to penicillin and enterococci resistant to vancomycin have become commonplace. Even *Staphylococcus aureus* strains resistant to vancomycin have appeared. Such pathogens present real clinical problems in managing infections that were easily treatable just a few years ago. Diseases once thought to have been nearly eradicated from the developed world—tuberculosis, cholera, and rheumatic fever, for example—have rebounded with renewed ferocity. Newly discovered and emerging infectious agents appear to have been brought into contact with humans by changes in the environment and by movements of human and animal populations. An example of the propensity for pathogens to escape from their usual niche is the alarming 1999 outbreak in New York of encephalitis due to West Nile virus, which had never previously been isolated in the Americas. In 2003, severe acute respiratory syndrome (SARS) was first recognized. This clinical entity was caused by a novel coronavirus that may have jumped from an animal host to become a significant human pathogen. For more than 10 years, the world's attention has been focused on H5N1 avian influenza, which spread rapidly through poultry farms in Asia, caused deaths in exposed humans, and reached Europe and Africa, heightening fears of a new influenza pandemic. When the pandemic came in 2009, however, it emerged unexpectedly in North America from an H1N1 strain whose origins were apparently in swine.

Many infectious agents have been discovered only in recent decades **(Fig. 1-1)**. Ebola virus, human metapneumovirus, *Anaplasma phagocytophila* (the agent of human granulocytotropic anaplasmosis), and retroviruses such as HIV humble us despite our deepening understanding of pathogenesis at the most basic molecular level. Even in developed countries, infectious diseases have made a resurgence. Between 1980 and 1996, mortality rates from infectious diseases in the United States increased by 64% to levels not seen since the 1940s.

The role of infectious agents in the etiology of diseases once believed to be noninfectious is increasingly recognized. For example, it is accepted that *Helicobacter pylori* is the causative agent of peptic ulcer disease and perhaps of gastric malignancy. Human papillomavirus is likely to be the most important cause of invasive cervical cancer. Human herpesvirus type 8 is believed to be the cause of most cases of Kaposi's sarcoma. Epstein-Barr virus is a cause of certain lymphomas and may play a role in the genesis of Hodgkin's disease. The possibility certainly exists that other diseases of unknown cause, such as rheumatoid arthritis, sarcoidosis, or inflammatory bowel disease, have infectious etiologies. There is even evidence that atherosclerosis may have an infectious component. In contrast, there are data to suggest that decreased exposures to pathogens in childhood may be contributing to an increase in the observed rates of allergic diseases.

Medical advances against infectious diseases have been hindered by changes in patient populations.

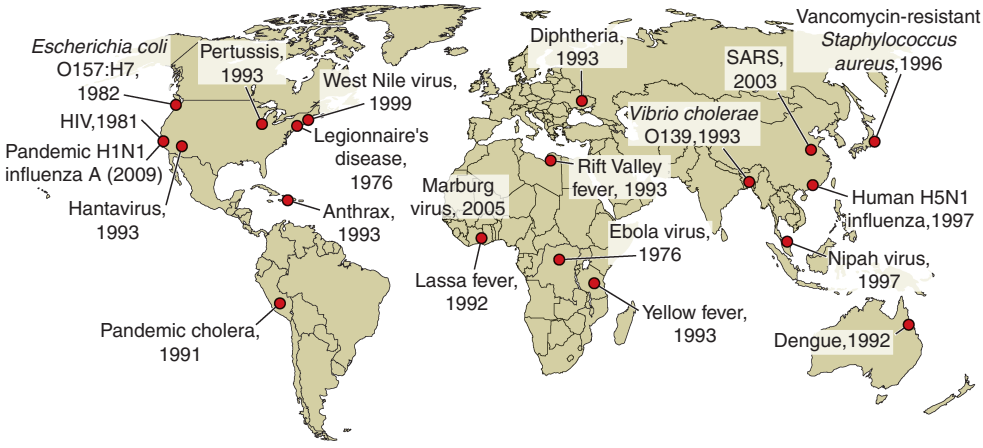


FIGURE 1-1
Map of the world showing examples of geographic locales where infectious diseases were noted to have emerged or resurged. (*Adapted from Addressing Emerging Infectious Disease Threats: A Prevention Strategy for the United States, Department of Health and Human Services, Centers for Disease Control and Prevention, 1994.*)

Immunocompromised hosts now constitute a significant proportion of the seriously infected population. Physicians immunosuppress their patients to prevent the rejection of transplants and to treat neoplastic and inflammatory diseases. Some infections, most notably that caused by HIV, immunocompromise the host in and of themselves. Lesser degrees of immunosuppression are associated with other infections, such as influenza and syphilis. Infectious agents that coexist peacefully with immunocompetent hosts wreak havoc in those who lack a complete immune system. AIDS has brought to prominence once-obscure organisms such as *Pneumocystis*, *Cryptosporidium parvum*, and *Mycobacterium avium*.

FACTORS INFLUENCING INFECTION

For any infectious process to occur, the pathogen and the host must first encounter each other. Factors such as geography, environment, climate, and behavior thus influence the likelihood of infection. Although the initial encounter between a susceptible host and a virulent organism frequently results in disease, some organisms can be harbored in the host for years before disease becomes clinically evident. For a complete view, individual patients must be considered in the context of the population to which they belong. Infectious diseases do not often occur in isolation; rather, they spread through a group exposed from a point source (e.g., a contaminated water supply) or from one individual to another (e.g., via respiratory droplets). Thus, the clinician must be alert to infections prevalent in the community as a whole. A detailed history, including information on travel, behavioral factors, exposures to animals or potentially contaminated environments, and living and occupational conditions, must be elicited. For example, the likelihood of infection by *Plasmodium falciparum* can be significantly affected by altitude, climate, terrain, season, and even time of day. Antibiotic-resistant strains of *P. falciparum* are localized to specific geographic regions, and a seemingly minor alteration in a travel itinerary can dramatically influence the likelihood of acquiring chloroquine-resistant malaria. If such important details in the history are overlooked, inappropriate treatment may result in the death of the patient. Likewise, the chance of acquiring a sexually transmitted disease can be greatly affected by a relatively minor variation in sexual practices, such as the method used for contraception. Knowledge of the relationship between specific risk factors and disease allows the physician to influence a patient's health even before the development of infection by modification of these risk factors and—when a vaccine is available—by immunization. Climate can affect the ecological niche of a pathogen or its vector, and climate change can lead to alterations in the endemicity of infectious diseases in different regions. For example, an outbreak of chikungunya caused by a mosquito-borne alphavirus recently occurred in central Italy; previous outbreaks had been confined to the tropics, and some have attributed this expansion to global warming.

Many specific host factors influence the likelihood of acquiring an infectious disease. Age, immunization history, prior illnesses, level of nutrition, pregnancy, coexisting illness, and perhaps emotional state all have some impact on the risk of infection after exposure to a potential pathogen. The importance of individual host defense mechanisms, either specific or nonspecific, becomes apparent in their absence, and our understanding of these immune mechanisms is enhanced by studies of clinical syndromes developing in immunodeficient patients **(Table 1-1)**. For example, the higher attack rate of meningococcal disease among people with deficiencies in specific complement proteins of the so-called membrane attack complex (see "Adaptive Immunity," discussed later) than in the general population underscores the importance of an intact complement system in the prevention of meningococcal infection. However, the genetic basis of susceptibility to infectious diseases is more complex than these examples of defects in

TABLE 1-1

INFECTIONS ASSOCIATED WITH SELECTED DEFECTS IN IMMUNITY

HOST DEFECT	DISEASE OR THERAPY ASSOCIATED WITH DEFECT	COMMON ETIOLOGIC AGENT OF INFECTION
Nonspecific Immunity		
Impaired cough	Rib fracture, neuromuscular dysfunction	Bacteria causing pneumonia, aerobic and anaerobic oral flora
Loss of gastric acidity	Achlorhydria, histamine blockade	*Salmonella* spp., enteric pathogens
Loss of cutaneous integrity	Penetrating trauma, athlete's foot	*Staphylococcus* spp., *Streptococcus* spp.
	Burn	*Pseudomonas aeruginosa*
	IV catheter	*Staphylococcus* spp., *Streptococcus* spp., gram-negative rods, coagulase-negative staphylococci
Implantable device	Heart valve	*Streptococcus* spp., coagulase-negative staphylococci, *Staphylococcus aureus*
	Artificial joint	*Staphylococcus* spp., *Streptococcus* spp., gram-negative rods
Loss of normal bacterial flora	Antibiotic use	*Clostridium difficile, Candida* spp.
Impaired clearance		
Poor drainage	Urinary tract infection	*Escherichia coli*
Abnormal secretions	Cystic fibrosis	Chronic pulmonary infection with *P. aeruginosa*
Inflammatory Response		
Neutropenia	Hematologic malignancy, cytotoxic chemotherapy, aplastic anemia, HIV infection	Gram-negative enteric bacilli, *Pseudomonas* spp., *Staphylococcus* spp., *Candida* spp.
Chemotaxis	Chédiak-Higashi syndrome, Job's syndrome, protein-calorie malnutrition	*S. aureus, Streptococcus pyogenes, Haemophilus influenzae*, gram-negative bacilli
	Leukocyte adhesion defects 1 and 2	Bacteria causing skin and systemic infections, gingivitis
Phagocytosis (cellular)	Systemic lupus erythematosus (SLE), chronic myelogenous leukemia, megaloblastic anemia	*Streptococcus pneumoniae, H. influenzae*
Splenectomy	—	*H. influenzae, S. pneumoniae*, other streptococci, *Capnocytophaga* spp., *Babesia microti*, *Salmonella* spp.
Microbicidal defect	Chronic granulomatous disease	Catalase-positive bacteria and fungi: staphylococci, *E. coli, Klebsiella* spp., *P. aeruginosa, Aspergillus* spp., *Nocardia* spp.
	Chédiak-Higashi syndrome	*S. aureus, S. pyogenes*
	Interferon γ receptor defect, interleukin 12 deficiency, interleukin 12 receptor defect	*Mycobacterium* spp., *Salmonella* spp.
Innate Immunity		
Complement system		
C3	Congenital liver disease, SLE, nephrotic syndrome	*S. aureus, S. pneumoniae, Pseudomonas* spp., *Proteus* spp.
C5	Congenital	*Neisseria* spp., gram-negative rods
C6, C7, C8	Congenital, SLE	*Neisseria meningitidis, N. gonorrhoeae*
Alternative pathway	Sickle cell disease	*S. pneumoniae, Salmonella* spp.
Toll-like receptor 4	Congenital	Gram-negative bacilli
Interleukin 1 receptor–associated kinase (IRAK) 4	Congenital	*S. pneumoniae, S. aureus*, other bacteria
Mannan-binding lectin	Congenital	*N. meningitidis*, other bacteria

(*continued*)

TABLE 1-1

INFECTIONS ASSOCIATED WITH SELECTED DEFECTS IN IMMUNITY (*CONTINUED*)

HOST DEFECT	DISEASE OR THERAPY ASSOCIATED WITH DEFECT	COMMON ETIOLOGIC AGENT OF INFECTION
Adaptive Immunity		
T lymphocyte deficiency/ dysfunction	Thymic aplasia, thymic hypoplasia, Hodgkin's disease, sarcoidosis, lepromatous leprosy	*Listeria monocytogenes, Mycobacterium* spp., *Candida* spp., *Aspergillus* spp., *Cryptococcus neoformans*, herpes simplex virus, varicella-zoster virus
	AIDS	*Pneumocystis*, cytomegalovirus, herpes simplex virus, *Mycobacterium avium-intracellulare, C. neoformans, Candida* spp.
	Mucocutaneous candidiasis	*Candida* spp.
	Purine nucleoside phosphorylase deficiency	Fungi, viruses
B cell deficiency/ dysfunction	Bruton's X-linked agammaglobulinemia	*S. pneumoniae*, other streptococci
	Agammaglobulinemia, chronic lymphocytic leukemia, multiple myeloma, dysglobulinemia	*H. influenzae, N. meningitidis, S. aureus, Klebsiella pneumoniae, E. coli, Giardia lamblia, Pneumocystis,* enteroviruses
	Selective IgM deficiency	*S. pneumoniae, H. influenzae, E. coli*
	Selective IgA deficiency	*G. lamblia*, hepatitis virus, *S. pneumoniae, H. influenzae*
Mixed T and B cell deficiency/dysfunction	Common variable hypogammaglobulinemia	*Pneumocystis*, cytomegalovirus, *S. pneumoniae, H. influenzae*, various other bacteria
	Ataxia-telangiectasia	*S. pneumoniae, H. influenzae, S. aureus*, rubella virus, *G. lamblia*
	Severe combined immunodeficiency	*S. aureus, S. pneumoniae, H. influenzae, Candida albicans, Pneumocystis*, varicella-zoster virus, rubella virus, cytomegalovirus
	Wiskott-Aldrich syndrome	Agents of infections associated with T and B cell abnormalities
	X-linked hyper-IgM syndrome	*Pneumocystis*, cytomegalovirus, *Cryptosporidium parvum*

any single gene would suggest. Human predisposition to infectious diseases involves a spectrum ranging from monogenic to polygenic traits that are the subject of ongoing study.

Medical care itself increases the patient's risk of acquiring an infection in several ways: (1) through contact with pathogens during hospitalization, (2) through breaching of the skin (with IV devices or surgical incisions) or mucosal surfaces (with endotracheal tubes or bladder catheters), (3) through introduction of foreign bodies, (4) through alteration of the natural flora with antibiotics, and (5) through treatment with immunosuppressive drugs.

Infection involves complicated interactions of microbe and host and inevitably affects both. In most cases, a pathogenic process consisting of several steps is required for the development of infections. Since the competent host has a complex series of barricades in place to prevent infection, the successful pathogen must use specific strategies at each of these steps. The specific strategies used by bacteria, viruses, and parasites (Chap. 2) have some remarkable conceptual similarities, but the strategic details are unique not only for each class of microorganism but also for individual species within a class.

THE IMMUNE RESPONSE

INNATE IMMUNITY

As they have co-evolved with microbes, higher organisms have developed mechanisms for recognizing and responding to microorganisms. Many of these mechanisms, referred to together as *innate immunity*, are evolutionarily ancient, having been conserved from insects to humans. In general, innate immune mechanisms exploit molecular patterns found specifically in pathogenic microorganisms. These "pathogen signatures" are recognized by host molecules that either directly interfere with the pathogen or initiate a response that does so. Innate immunity serves to protect the host without prior exposure to an infectious agent—i.e., before specific or adaptive immunity has had a chance to develop. Innate immunity also functions as a warning system that activates components of adaptive immunity early in the course of infection. The innate immune system does not confer long-lasting immunity to the host but rather provides immediate defense against infection. Innate immunity is mediated by cells, various proteins found in the host (i.e., the complement system), and cytokines.

Toll-like receptors (TLRs) are instructive in illustrating how organisms are detected and send signals to the immune system. There are at least 11 TLRs, each specific for detecting different biologic classes of molecules. TLRs are found on the surface and within the endosomes of several types of host cells. For example, even minuscule amounts of lipopolysaccharide (LPS), a molecule found uniquely in gram-negative bacteria, are detected by LPS-binding protein, CD14, and TLR4 (see Fig. 2-3). The interaction of LPS with these components of the innate immune system prompts macrophages, via the transcriptional activator nuclear factor κB (NF-κB), to produce cytokines that lead to inflammation and enzymes that enhance the clearance of microbes. These initial responses serve not only to limit infection but also to initiate specific or adaptive immune responses.

Other receptor systems have been defined as important in regulating inflammation as well. The NOD-like receptors (i.e., the nucleotide-binding domain– and leucine-rich repeat–containing family of receptors, or NLRs) are cytoplasmic proteins that also recognize molecular patterns and activate inflammation through caspases, whose modification of proinflammatory cytokines such as interleukin (IL)-1 results in activation of NF-κB signaling to induce inflammatory molecules. The activated mediators of inflammation within the cytoplasm form multiprotein complexes called *inflammasomes*, which promote the inflammatory process.

ADAPTIVE IMMUNITY

Once in contact with the host immune system, the microorganism faces the host's tightly integrated cellular and humoral immune responses. Cellular immunity comprising T lymphocytes, macrophages, and natural killer cells, primarily recognizes and combats pathogens that proliferate intracellularly. Cellular immune mechanisms are important in immunity to all classes of infectious agents, including most viruses and many bacteria (e.g., *Mycoplasma*, *Chlamydophila*, *Listeria*, *Salmonella*, and *Mycobacterium*), parasites (e.g., *Trypanosoma*, *Toxoplasma*, and *Leishmania*), and fungi (e.g., *Histoplasma*, *Cryptococcus*, and *Coccidioides*). Usually, T lymphocytes are activated by dendritic cells, macrophages, and B lymphocytes, which present foreign antigens in the context of the host's own major histocompatibility complex antigen to the T cell receptor. Activated T cells may then act in several ways to fight infection. *Cytotoxic* CD8+ T cells may directly attack and lyse host cells that express foreign antigens. *Helper* CD4+ T cells stimulate the proliferation of B cells and the production of immunoglobulins. Antigen-presenting cells and T cells communicate with each other via a variety of signals, acting coordinately to instruct the immune system to respond in a specific fashion. T cells elaborate cytokines (e.g., interferon) that directly inhibit the growth of pathogens or stimulate killing by host macrophages and cytotoxic cells. Cytokines also augment the host's immunity by stimulating the inflammatory response (fever, the production of acute-phase serum components, and the proliferation of leukocytes). Cytokine stimulation does not always result in a favorable response in the host; septic shock (Chap. 16) and toxic shock syndrome (Chaps. 38 and 39) are among the conditions that are mediated by these inflammatory substances.

The immune system has also developed cells that specialize in controlling or downregulating immune responses. For example, T_{reg} cells, a subgroup of CD4+ T cells, prevent autoimmune responses by other T cells and are thought to be important in downregulating immune responses to foreign antigens. There appear to be both naturally occurring and acquired T_{reg} cells. One mechanism used by T_{reg} cells to downregulate inflammation is the production of the anti-inflammatory cytokine IL-10.

The reticuloendothelial system, which clears circulating microorganisms, comprises monocyte-derived phagocytic cells (Kupffer cells) and Ito cells in the liver, alveolar macrophages in the lungs, macrophages and dendritic cells in the spleen, mesangial cells in the kidneys, microglia in the brain, and macrophages and dendritic cells in the lymph nodes. Although these tissue macrophages and polymorphonuclear leukocytes (PMNs) are capable of killing microorganisms without help, they function much more efficiently when pathogens are first *opsonized* (Greek, "prepared for eating") by components of the complement system such as C3b and/or by antibodies.

Extracellular pathogens, including most encapsulated bacteria (those surrounded by a complex polysaccharide coat), are attacked by the humoral immune system, which includes antibodies, the complement cascade, and phagocytic cells. *Antibodies* are complex glycoproteins (also called *immunoglobulins*) that are produced by mature B lymphocytes, circulate in body fluids, and are secreted on mucosal surfaces. Antibodies specifically recognize and bind to foreign antigens. One of the most impressive features of the immune system is the ability to generate an incredible diversity of antibodies capable of recognizing virtually every foreign antigen yet not reacting with self. In addition to being exquisitely specific for antigens, antibodies come in different structural and functional classes: IgG predominates in the circulation and persists for many years after exposure; IgM is the earliest specific antibody to appear in response to infection; secretory IgA is important in immunity at mucosal surfaces, while monomeric IgA appears in the serum; and IgE is important in allergic and parasitic diseases. Antibodies may directly impede the function of an invading organism, neutralize secreted toxins and enzymes, or facilitate the removal of the antigen (invading organism) by phagocytic cells. Immunoglobulins participate in cell-mediated immunity by promoting the antibody-dependent cellular cytotoxicity functions of certain T lymphocytes. Antibodies also promote the deposition of complement components on the surface of the invader.

The *complement* system consists of a group of serum proteins functioning as a cooperative, self-regulating cascade of enzymes that adhere to—and in some cases disrupt—the surface of invading organisms. Some of these surface-adherent proteins (e.g., C3b) can then act

as opsonins for destruction of microbes by phagocytes. The later, "terminal" components (C7, C8, and C9) can directly kill some bacterial invaders (notably, many of the neisseriae) by forming a membrane attack complex and disrupting the integrity of the bacterial membrane, thus causing bacteriolysis. Other complement components, such as C5a, act as chemoattractants for PMNs (see below). Complement activation and deposition occur by either or both of two pathways: the *classic* pathway is activated primarily by immune complexes (i.e., antibody bound to antigen), and the *alternative* pathway is activated by microbial components, frequently in the absence of antibody. PMNs have receptors for both antibody and C3b, and antibody and complement function together to aid in the clearance of infectious agents.

PMNs, short-lived white blood cells that engulf and kill invading microbes, are first attracted to inflammatory sites by chemoattractants such as C5a, which is a product of complement activation at the site of infection. PMNs localize to the site of infection by adhering to cellular adhesion molecules expressed by endothelial cells. Endothelial cells express these receptors, called *selectins* (CD-62, ELAM-1), in response to inflammatory cytokines such as tumor necrosis factor α and IL-1. The binding of these selectin molecules to specific receptors on PMNs results in the adherence of the PMNs to the endothelium. Cytokine-mediated upregulation and expression of intercellular adhesion molecule 1 (ICAM-1) on endothelial cells then take place, and this latter receptor binds to β_2 integrins on PMNs, thereby facilitating diapedesis into the extravascular compartment. Once the PMNs are in the extravascular compartment, various molecules (e.g., arachidonic acids) further enhance the inflammatory process.

APPROACH TO THE PATIENT **Infectious Diseases**

The clinical manifestations of infectious diseases at presentation are myriad, varying from fulminant life-threatening processes to brief and self-limited conditions to indolent chronic maladies. A careful history is essential and must include details on underlying chronic diseases, medications, occupation, and travel. Risk factors for exposure to certain types of pathogens may give important clues to diagnosis. A sexual history may reveal risks for exposure to HIV and other sexually transmitted pathogens. A history of contact with animals may suggest numerous diagnoses, including rabies, Q fever, bartonellosis, *Escherichia coli* O157 infection, or cryptococcosis. Blood transfusions have been linked to diseases ranging from viral hepatitis to malaria to prion disease. A history of exposure to insect vectors (coupled with information about the season and geographic site of exposure) may lead to consideration of such diseases as Rocky Mountain spotted fever, other rickettsial diseases, tularemia, Lyme disease, babesiosis, malaria, trypanosomiasis, and numerous arboviral infections. Ingestion of contaminated liquids or foods may lead to enteric infection with *Salmonella*, *Listeria*, *Campylobacter*, amebas, cryptosporidia, or helminths. Since infectious diseases may involve many organ systems, a careful review of systems may elicit important clues as to the disease process.

The physical examination must be thorough, and attention must be paid to seemingly minor details, such as a soft heart murmur that might indicate bacterial endocarditis or a retinal lesion that suggests disseminated candidiasis or cytomegalovirus infection. Rashes are extremely important clues to infectious diagnoses and may be the only sign pointing to a specific etiology (Chaps. 9 and 11). Certain rashes are so specific as to be pathognomonic—e.g., the childhood exanthems (measles, rubella, varicella), the target lesion of erythema migrans (Lyme disease), ecthyma gangrenosum (*Pseudomonas aeruginosa*), and eschars (rickettsial diseases). Other rashes, although less specific, may be exceedingly important diagnostic indicators. The prompt recognition of the early scarlatiniform and later petechial rashes of meningococcal infection or of the subtle embolic lesions of disseminated fungal infections in immunosuppressed patients can hasten life-saving therapy. Fever (Chaps. 8, 9, and 10) is a common manifestation of infection and may be its sole apparent indication. Sometimes the pattern of fever or its temporally associated findings may help refine the differential diagnosis. For example, fever occurring every 48–72 h is suggestive of malaria (Chap. 119). The elevation in body temperature in fever (through resetting of the hypothalamic setpoint mediated by cytokines) must be distinguished from elevations in body temperature from other causes such as drug toxicity (Chap. 10) or heat stroke (Chap. 8).

LABORATORY INVESTIGATIONS

Laboratory studies must be carefully considered and directed toward establishing an etiologic diagnosis in the shortest possible time, at the lowest possible cost, and with the least possible discomfort to the patient. Since mucosal surfaces and the skin are colonized with many harmless or beneficial microorganisms, cultures must be performed in a manner that minimizes the likelihood of contamination with this normal flora while maximizing the yield of pathogens. A sputum sample is far more likely to be valuable when elicited with careful coaching by the clinician than when collected in a container simply left at the bedside with cursory instructions. Gram's stains of specimens should be interpreted carefully and the quality of the specimen assessed. The findings on Gram's staining should correspond to the results of culture; a discrepancy may suggest diagnostic possibilities such as infection due to fastidious or anaerobic bacteria.

The microbiology laboratory must be an ally in the diagnostic endeavor. Astute laboratory personnel

will suggest optimal culture and transport conditions or alternative tests to facilitate diagnosis. If informed about specific potential pathogens, an alert laboratory staff will allow sufficient time for these organisms to become evident in culture, even when the organisms are present in small numbers or are slow-growing. The parasitology technician who is attuned to the specific diagnostic considerations relevant to a particular case may be able to detect the rare, otherwise-elusive egg or cyst in a stool specimen. In cases where a diagnosis appears difficult, serum should be stored during the early acute phase of the illness so that a diagnostic rise in titer of antibody to a specific pathogen can be detected later. Bacterial and fungal antigens can sometimes be detected in body fluids, even when cultures are negative or are rendered sterile by antibiotic therapy. Nucleic acid amplification techniques allow the amplification of specific DNA and RNA sequences so that minute quantities of pathogens can be recognized in host specimens.

TREATMENT Infectious Diseases

Optimal therapy for infectious diseases requires a broad knowledge of medicine and careful clinical judgment. Life-threatening infections such as bacterial meningitis or sepsis, viral encephalitis, or falciparum malaria must be treated immediately, often before a specific causative organism is identified. Antimicrobial agents must be chosen empirically and must be active against the range of potential infectious agents consistent with the clinical scenario. In contrast, good clinical judgment sometimes dictates withholding of antimicrobial drugs in a self-limited process or until a specific diagnosis is made. The dictum *primum non nocere* should be adhered to, and it should be remembered that all antimicrobial agents carry a risk (and a cost). Direct toxicity may be encountered—e.g., ototoxicity due to aminoglycosides, lipodystrophy due to antiretroviral agents, and hepatotoxicity due to antituberculous agents such as isoniazid and rifampin. Allergic reactions are common and can be serious. Since superinfection sometimes follows eradication of the normal flora and colonization by a resistant organism, one invariant principle is that infectious disease therapy should be directed toward as narrow a spectrum of infectious agents as possible. Treatment specific for the pathogen should result in as little perturbation as possible of the host's microflora. Indeed, future therapeutic agents may act not by killing a microbe but by interfering with one or more of its virulence factors.

With few exceptions, abscesses require surgical or percutaneous drainage for cure. Foreign bodies, including medical devices, must generally be removed in order to eliminate an infection of the device or of the adjacent tissue. Other infections, such as necrotizing fasciitis, peritonitis due to a perforated organ, gas gangrene, and chronic osteomyelitis, require surgery as the primary means of cure; in these conditions, antibiotics play only an adjunctive role.

The role of immunomodulators in the management of infectious diseases has received increasing attention. Glucocorticoids have been shown to be of benefit in the adjunctive treatment of bacterial meningitis and in therapy for *Pneumocystis* pneumonia in patients with AIDS. The use of these agents in other infectious processes remains less clear and in some cases (in cerebral malaria, for example) is detrimental. Activated protein C (drotrecogin alfa, activated) is the first immunomodulatory agent widely available for the treatment of severe sepsis. Its usefulness demonstrates the interrelatedness of the clotting cascade and systemic immunity. Other agents that modulate the immune response include prostaglandin inhibitors, specific lymphokines, and tumor necrosis factor inhibitors. Specific antibody therapy plays a role in the treatment and prevention of many diseases. Specific immunoglobulins have long been known to prevent the development of symptomatic rabies and tetanus. Monoclonal antibodies targeting specific pathogens have been developed (e.g., for the treatment of respiratory syncytial virus infection). There is a pressing need for well-designed clinical trials to evaluate each new interventional modality.

PERSPECTIVE

The genetic simplicity of many infectious agents allows them to undergo rapid evolution and to develop selective advantages that result in constant variation in the clinical manifestations of infection. Moreover, changes in the environment and the host can predispose new populations to a particular infection. The dramatic marchof West Nile virus from a single focus in New York City in 1999 to locations throughout the North American continent by the summer of 2002 caused widespread alarm, illustrating the fear that new plagues induce in the human psyche. The intentional release of deadly spores of *Bacillus anthracis* via the U.S. Postal Service awakened many from a sense of complacency regarding biologic weapons.

"The terror of the unknown is seldom better displayed than by the response of a population to the appearance of an epidemic, particularly when the epidemic strikes without apparent cause." Edward H. Kass made this statement in 1977 in reference to the newly discovered Legionnaire's disease, but it could apply equally to SARS, pandemic H1N1 influenza, or any other new and mysterious disease. The potential for infectious agents to emerge in novel and unexpected ways requires that physicians and public health officials be knowledgeable, vigilant, and open-minded in their approach to unexplained illness. The emergence of antimicrobial-resistant pathogens (e.g., enterococci

that are resistant to all known antimicrobial agents and cause essentially untreatable infections) and the paucity of new classes of antimicrobial drugs have led some to conclude that we are entering the "postantibiotic era." Others have held to the perception that infectious diseases no longer represent as serious a concern to world health as they once did. The progress that science, medicine, and society as a whole have made in combating these maladies is impressive, and it is ironic that, as we stand on the threshold of an understanding of the most basic biology of the microbe, infectious diseases are posing renewed problems. We are threatened by the appearance of new diseases such as SARS, hepatitis C, and Ebola virus infection and by the reemergence of old foes such as tuberculosis, cholera, plague, and *Streptococcus pyogenes* infection. True students of infectious diseases were perhaps less surprised than anyone else by these developments. Those who know pathogens are aware of their incredible adaptability and diversity. As ingenious and successful as therapeutic approaches may be, our ability to develop methods to counter infectious agents so far has not matched the myriad strategies employed by the sea of microbes that surrounds us. Their sheer numbers and the rate at which they can evolve are daunting. Moreover, environmental changes, rapid global travel, population movements, and medicine itself—through its use of antibiotics and immunosuppressive agents—all increase the impact of infectious diseases. Although new vaccines, new antibiotics, improved global communication, and new modalities for treating and preventing infection will be developed, pathogenic microbes will continue to develop new strategies of their own, presenting us with an unending and dynamic challenge.

CHAPTER 2

MOLECULAR MECHANISMS OF MICROBIAL PATHOGENESIS

Gerald B. Pier

Over the past four decades, molecular studies of the pathogenesis of microorganisms have yielded an explosion of information about the various microbial and host molecules that contribute to the processes of infection and disease. These processes can be classified into several stages: microbial encounter with and entry into the host; microbial growth after entry; avoidance of innate host defenses; tissue invasion and tropism; tissue damage; and transmission to new hosts. *Virulence* is the measure of an organism's capacity to cause disease and is a function of the pathogenic factors elaborated by microbes. These factors promote *colonization* (the simple presence of potentially pathogenic microbes in or on a host), *infection* (attachment and growth of pathogens and avoidance of host defenses), and *disease* (often, but not always, the result of activities of secreted toxins or toxic metabolites). In addition, the host's inflammatory response to infection greatly contributes to disease and its attendant clinical signs and symptoms.

MICROBIAL ENTRY AND ADHERENCE

Entry sites

A microbial pathogen can potentially enter any part of a host organism. In general, the type of disease produced by a particular microbe is often a direct consequence of its route of entry into the body. The most common sites of entry are mucosal surfaces (the respiratory, alimentary, and urogenital tracts) and the skin. Ingestion, inhalation, and sexual contact are typical routes of microbial entry. Other portals of entry include sites of skin injury (cuts, bites, burns, trauma) along with injection via natural (i.e., vector-borne) or artificial (i.e., needle-stick injury) routes. A few pathogens, such as *Schistosoma* species, can penetrate unbroken skin. The conjunctiva can serve as an entry point for pathogens of the eye, which occasionally spread systemically from that site.

Microbial entry usually relies on the presence of specific factors needed for persistence and growth in a tissue.

Fecal-oral spread via the alimentary tract requires a biologic profile consistent with survival in the varied environments of the gastrointestinal tract (including the low pH of the stomach and the high bile content of the intestine) as well as in contaminated food or water outside the host. Organisms that gain entry via the respiratory tract survive well in small moist droplets produced during sneezing and coughing. Pathogens that enter by venereal routes often survive best in the warm moist environment of the urogenital mucosa and have restricted host ranges (e.g., *Neisseria gonorrhoeae*, *Treponemapallidum*, and HIV).

The biology of microbes entering through the skin is highly varied. Some of these organisms can survive in a broad range of environments, such as the salivary glands or alimentary tracts of arthropod vectors, the mouths of larger animals, soil, and water. A complex biology allows protozoan parasites such as *Plasmodium*, *Leishmania*, and *Trypanosoma* spp. to undergo morphogenic changes that permit transmission of the organism to mammalian hosts during insect feeding for blood meals. Plasmodia are injected as infective sporozoites from the salivary glands during mosquito feeding. *Leishmania* parasites are regurgitated as promastigotes from the alimentary tract of sandflies and injected by bite into a susceptible host. Trypanosomes are first ingested from infected hosts by reduviid bugs; the pathogens then multiply in the gastrointestinal tract of the insects and are released in feces onto the host's skin during subsequent feedings. Most microbes that land directly on intact skin are destined to die, as survival on the skin or in hair follicles requires resistance to fatty acids, low pH, and other antimicrobial factors on the skin. Once it is damaged (and particularly if it becomes necrotic), the skin can be a major portal of entry and growth for pathogens and elaboration of their toxic products. Burn wound infections and tetanus are clear examples. After animal bites, pathogens resident in the animal's saliva gain access to the victim's tissues through the damaged skin. Rabies is the paradigm for this pathogenic process; rabies virus grows in striated muscle cells at the site of inoculation.

Microbial adherence

Once in or on a host, most microbes must anchor themselves to a tissue or tissue factor; the possible exceptions are organisms that directly enter the bloodstream and multiply there. Specific ligands or adhesins for host receptors constitute a major area of study in the field of microbial pathogenesis. Adhesins comprise a wide range of surface structures, not only anchoring the microbe to a tissue and promoting cellular entry where appropriate but also eliciting host responses critical to the pathogenic process **(Table 2-1)**. Most microbes produce multiple adhesins specific for multiple host receptors. These adhesins are often redundant, are serologically variable, and act additively or synergistically with other microbial factors to promote microbial sticking to host tissues. In addition, some microbes adsorb host proteins onto their surface and utilize the natural host protein receptor for microbial binding and entry into target cells.

Viral adhesins

All viral pathogens must bind to host cells, enter them, and replicate within them. Viral coat proteins serve as the ligands for cellular entry, and more than one ligand-receptor interaction may be needed; for example, HIV utilizes its envelope glycoprotein (gp) 120 to enter host cells by binding to both CD4 and one of two receptors for chemokines (designated CCR5 and CXCR4). Similarly, the measles virus H glycoprotein binds to both CD46 and the membrane-organizing protein moesin on host cells. The gB and gC proteins on herpes simplex virus bind to heparan sulfate, although this adherence is not essential for entry but rather serves to concentrate virions close to the cell surface; this step is followed by attachment to mammalian cells mediated by the viral gD protein, with subsequent formation of a homotrimer of viral gB protein or a heterodimer of viral gH and gL proteins that permits fusion of the viral envelope with the host cell membrane. Herpes simplex virus can use a number of eukaryotic cell surface receptors for entry, including the herpesvirus entry mediator (related to the tumor necrosis factor receptor), members of the immunoglobulin superfamily, the proteins nectin-1 and nectin-2, and modified heparan sulfate.

Bacterial adhesins

Among the microbial adhesins studied in greatest detail are bacterial pili and flagella **(Fig. 2-1)**. *Pili* or *fimbriae* are commonly used by gram-negative bacteria for attachment to host cells and tissues; recent studies have identified similar factors produced by gram-positive organisms such as group B streptococci. In electron micrographs, these hairlike projections (up to several hundred per cell) may be confined to one end of the organism (polar pili) or distributed more evenly over the surface. An individual cell may have pili with a variety of functions. Most pili are made up of a major pilin protein subunit (molecular weight, 17,000–30,000) that polymerizes to form the pilus. Many strains of *Escherichia coli* isolated from urinary tract infections express mannose-binding type 1 pili, whose binding to integral membrane glycoproteins called *uroplakins* that coat the cells in the bladder epithelium is inhibited by D-mannose. Other strains produce the Pap (pyelonephritis-associated) or P pilus adhesin that mediates binding to digalactose (gal-gal) residues on globosides of the human P blood groups. Both of these types of pili have proteins located at the tips of the main pilus unit that are critical to the binding specificity of the whole pilus unit. Although immunization with the mannose-binding tip protein (FimH) of type 1 pili prevents experimental *E. coli* bladder infections in mice and monkeys, a human trial of this vaccine was not successful. *E. coli* cells causing diarrheal disease express pilus-like receptors for enterocytes on the small bowel, along with other receptors termed *colonization factors*.

The type IV pilus, a common type of pilus found in *Neisseria* species, *Moraxella* species, *Vibrio cholerae*, *Legionella pneumophila, Salmonella enterica* serovar Typhi, enteropathogenic *E. coli*, and *Pseudomonas aeruginosa*, mediates adherence of organisms to target surfaces. Type IV pili

TABLE 2-1

EXAMPLES OF MICROBIAL LIGAND-RECEPTOR INTERACTIONS

MICROORGANISM	TYPE OF MICROBIAL LIGAND	HOST RECEPTOR
Viral Pathogens		
Influenza virus	Hemagglutinin	Sialic acid
Measles virus		
Vaccine strain	Hemagglutinin	CD46/moesin
Wild-type strains	Hemagglutinin	Signaling lymphocytic activation molecule (SLAM)
Human herpesvirus type 6	?	CD46
Herpes simplex virus	Glycoprotein C	Heparan sulfate
HIV	Surface glycoprotein	CD4 and chemokine receptors (CCR5 and CXCR4)
Epstein-Barr virus	Envelope protein	CD21 (CR2)
Adenovirus	Fiber protein	Coxsackie-adenovirus receptor (CAR)
Coxsackievirus	Viral coat proteins	CAR and major histocompatibility class I antigens
Bacterial Pathogens		
Neisseria spp.	Pili	Membrane co-factor protein (CD46)
Pseudomonas aeruginosa	Pili and flagella	Asialo-GM1
	Lipopolysaccharide	Cystic fibrosis transmembrane conductance regulator (CFTR)
Escherichia coli	Pili	Ceramides/mannose and digalactosyl residues
Streptococcus pyogenes	Hyaluronic acid capsule	CD44
Yersinia spp.	Invasin/accessory invasin locus	β_1 Integrins
Bordetella pertussis	Filamentous hemagglutinin	CR3
Legionella pneumophila	Adsorbed C3bi	CR3
Mycobacterium tuberculosis	Adsorbed C3bi	CR3; DC-SIGN[a]
Fungal Pathogens		
Blastomyces dermatitidis	WI-1	Possibly matrix proteins and integrins
Candida albicans	Int1p	Extracellular matrix proteins
Protozoal Pathogens		
Plasmodium vivax	Merozoite form	Duffy Fy antigen
Plasmodium falciparum	Erythrocyte-binding protein 175 (EBA-175)	Glycophorin A
Entamoeba histolytica	Surface lectin	*N*-Acetylglucosamine

[a]A novel dendritic cell–specific C-type lectin.

tend to have a relatively conserved amino-terminal region and a more variable carboxyl-terminal region. For some species (e.g., *N. gonorrhoeae, Neisseria meningitidis*, and enteropathogenic *E. coli*), the pili are critical for attachment to mucosal epithelial cells. For others, such as *P. aeruginosa*, the pili only partially mediate the cells' adherence to host tissues. *V. cholerae* cells appear to use two different types of pili for intestinal colonization. Whereas interference with this stage of colonization would appear to be an effective antibacterial strategy, attempts to develop pilus-based vaccines for human diseases have not been highly successful to date.

Flagella are long appendages attached at either one or both ends of the bacterial cell (polar flagella) or distributed over the entire cell surface (peritrichous flagella). Flagella, like pili, are composed of a polymerized or aggregated basic protein. In flagella, the protein subunits form a tight helical structure and vary serologically with the species. Spirochetes such as *T. pallidum* and *Borrelia burgdorferi* have axial filaments similar to flagella running down the long axis of the center of the cell, and they "swim" by rotation around these filaments. Some bacteria can glide over a surface in the absence of obvious motility structures.

Other bacterial structures involved in adherence to host tissues include specific staphylococcal and streptococcal proteins that bind to human extracellular matrix proteins such as fibrin, fibronectin, fibrinogen, laminin, and collagen. Fibronectin appears to be a commonly used receptor for various pathogens; a particular amino acid sequence in fibronectin, Arg-Gly-Asp or RGD, is a critical target used by bacteria to bind to host tissues. Binding of a highly conserved *Staphylococcus aureus* surface protein, clumping factor A (ClfA), to fibrinogen has been implicated in many aspects of pathogenesis. However, attempts to interrupt this interaction and prevent *S. aureus* sepsis in low-birth-weight infants by administering an intravenous IgG preparation derived from the plasma of individuals with high titers of antibody to ClfA failed to show efficacy in a clinical trial

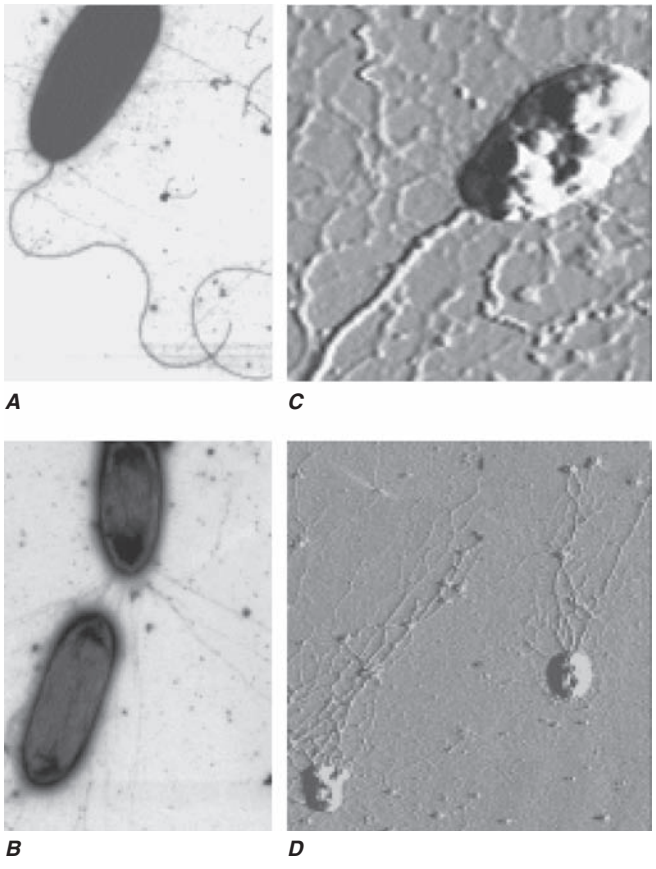


FIGURE 2-1
Bacterial surface structures. ***A*** and ***B***. Traditional electron micrographic images of fixed cells of *Pseudomonas aeruginosa*. Flagella **(*A*)** and pili **(*B*)** project out from the bacterial poles. ***C*** and ***D*.** Atomic force microscopic image of live *P. aeruginosa* freshly planted onto a smooth mica surface. This technology reveals the fine, three-dimensional detail of the bacterial surface structures. (*Images courtesy of Drs. Martin Lee and Milan Bajmoczi, Harvard Medical School.*)

completed in April 2006. The conserved outer-core portion of the lipopolysaccharide (LPS) of *P. aeruginosa* mediates binding to the cystic fibrosis transmembrane conductance regulator (CFTR) on airway epithelial cells—an event that appears to be critical for normal host resistance to infection. A number of bacterial pathogens, including coagulase-negative staphylococci, *S. aureus*, and uropathogenic *E. coli* as well as *Yersinia pestis, Y. pseudotuberculosis*, *Y. enterocolitica, Bordetella* species, and *Acinetobacter baumannii*, express a surface polysaccharide composed of β-1-6-linked-poly-*N*-acetyl-D-glucosamine. One of its functions is to promote binding to materials used in catheters and other types of implanted devices. This polysaccharide may be a critical factor in the establishment of device-related infections by pathogens such as staphylococci and *E. coli*. High-powered imaging techniques (e.g., atomic force microscopy) have revealed that bacterial cells have a nonhomogeneous surface that is probably attributable to different concentrations of cell surface molecules, including microbial adhesins, at specific places on the cell surface (Fig. 2-1*D*).

Fungal adhesins

Several fungal adhesins have been described that mediate colonization of epithelial surfaces, particularly adherence to structures like fibronectin, laminin, and collagen. The product of the *Candida albicans INT1* gene, Int1p, bears similarity to mammalian integrins that bind to extracellular matrix proteins. Transformation of normally nonadherent *Saccharomyces cerevisiae* with this gene allows these yeast cells to adhere to human epithelial cells. The agglutinin-like sequence (ALS) adhesins are large cell-surface glycoproteins mediating adherence of pathogenic *Candida* to host tissues. These adhesins possess a conserved three-domain structure composed of an N-terminal domain that mediates adherence to host tissue receptors, a central motif consisting of a number of repeats of a conserved sequence of 36 amino acids, and a C-terminal domain that varies in length and sequence and contains a glycosylphosphatidylinositol (GPI) anchor addition site that allows binding of the adhesin to the fungal cell wall. Variability in the number of central domains in different ALS proteins characterizes different adhesins with specificity for different host receptors. The ALS adhesins are expressed under certain environmental conditions—often associated with stress—and are crucial for pathogenesis of fungal infections.

For several fungal pathogens that initiate infections after inhalation of infectious material, the inoculum is ingested by alveolar macrophages, in which the fungal cells transform to pathogenic phenotypes. Like *C. albicans*, *Blastomyces dermatitidis* binds to CD11b/CD18 integrins as well as to CD14 on macrophages. *B. dermatitidis* produces a 120-kDa surface protein, designated WI-1, that mediates this adherence. The binding domain of WI-1 is homologous to the invasin protein of *Yersinia* that binds to the same type of host cell receptor. An unidentified factor on *Histoplasma capsulatum* also mediates binding of this fungal pathogen to the integrin surface proteins.

Eukaryotic pathogen adhesins

Eukaryotic parasites use complicated surface glycoproteins as adhesins, some of which are lectins (proteins that bind to specific carbohydrates on host cells). For example, *Plasmodium vivax*, one of five *Plasmodium* species causing malaria, binds (via Duffy-binding protein) to the Duffy blood group carbohydrate antigen Fy on erythrocytes. *Entamoeba histolytica*, the third leading cause of death from parasitic diseases, expresses two proteins that bind to the disaccharide galactose/N-acetyl galactosamine. Reports indicate that children with mucosal IgA antibody to one of these lectins are resistant to reinfection with virulent *E. histolytica*. A major surface glycoprotein (gp63) of *Leishmania* promastigotes is needed for these parasites to enter human macrophages—the principal target cell of infection. This glycoprotein promotes complement binding but inhibits complement lytic activity, allowing the parasite to use complement receptors for entry into macrophages; gp63 also binds to fibronectin receptors on macrophages. In addition, the pathogen can express a carbohydrate that mediates binding to host cells. Evidence suggests that, as part of hepatic

granuloma formation, *Schistosoma mansoni* expresses a carbohydrate epitope related to the Lewis X blood group antigen that promotes adherence of helminthic eggs to vascular endothelial cells under inflammatory conditions.

Host receptors

Host receptors are found both on target cells (such as epithelial cells lining mucosal surfaces) and within the mucus layer covering these cells. Microbial pathogens bind to a wide range of host receptors to establish infection (Table 2-1). Selective loss of host receptors for a pathogen may confer natural resistance to an otherwise susceptible population. For example, 70% of individuals in West Africa lack Fy antigens and are resistant to *P. vivax* infection. *S. enterica* serovar Typhi, the etiologic agent of typhoid fever, produces a pilus protein that binds to CFTR to enter the gastrointestinal submucosa after being ingested by enterocytes. As homozygous mutations in *CFTR* are the cause of the life-shortening disease cystic fibrosis, heterozygote carriers (e.g., 4–5% of individuals of European ancestry) may have had a selective advantage due to decreased susceptibility to typhoid fever. Genetic polymorphisms in CFTR besides those leading to cystic fibrosis have been associated with resistance to typhoid fever.

Numerous virus–target cell interactions have been described, and it is now clear that different viruses can use similar host cell receptors for entry. The list of certain and likely host receptors for viral pathogens is long. Among the host membrane components that can serve as receptors for viruses are sialic acids, gangliosides, glycosaminoglycans, integrins and other members of the immunoglobulin superfamily, histocompatibility antigens, and regulators and receptors for complement components. A notable example of the effect of host receptors on the pathogenesis of infection has emerged from studies comparing the binding of avian influenza A subtype H5N1 with that of influenza A strains expressing the H1 subtype of hemagglutinin. The H1 subtypes tend to be highly pathogenic and transmissible from human to human, and they bind to a receptor composed of two sugar molecules: sialic acid linked α-2-6 to galactose. This receptor is highly expressed in the airway epithelium; when virus is shed from this surface, its transmission via coughing and aerosol droplets is facilitated. In contrast, the H5N1 avian influenza virus binds to sialic acid linked α-2-3 to galactose, and this receptor is highly expressed in pneumocytes in the alveoli. Infection in the alveoli is thought to underlie the high mortality rate associated with avian influenza but also the low interhuman transmissibility of this strain, which is not readily transported to the airways from which it can be expelled by coughing.

MICROBIAL GROWTH AFTER ENTRY

Once established on a mucosal or skin site, pathogenic microbes must replicate before causing full-blown infection and disease. Within cells, viral particles release their nucleic acids, which may be directly translated into viral proteins (positive-strand RNA viruses), transcribed from a negative strand of RNA into a complementary mRNA (negative-strand RNA viruses), or transcribed into a complementary strand of DNA (retroviruses); for DNA viruses, mRNA may be transcribed directly from viral DNA, either in the cell nucleus or in the cytoplasm. To grow, bacteria must acquire specific nutrients or synthesize them from precursors in host tissues. Many infectious processes are usually confined to specific epithelial surfaces—e.g., H1 subtype influenza to the respiratory mucosa, gonorrhea to the urogenital epithelium, shigellosis to the gastrointestinal epithelium. While there are multiple reasons for this specificity, one important consideration is the ability of these pathogens to obtain from these specific environments the nutrients needed for growth and survival.

Temperature restrictions also play a role in limiting certain pathogens to specific tissues. Rhinoviruses, a cause of the common cold, grow best at 33°C and replicate in cooler nasal tissues but not in the lung. Leprosy lesions due to *Mycobacterium leprae* are found in and on relatively cool body sites. Fungal pathogens that infect the skin, hair follicles, and nails (dermatophyte infections) remain confined to the cooler, exterior, keratinous layer of the epithelium.

A topic of major interest is the ability of many bacterial, fungal, and protozoal species to grow in multicellular masses referred to as *biofilms*. These masses are biochemically and morphologically quite distinct from the free-living individual cells referred to as *planktonic cells*. Growth in biofilms leads to altered microbial metabolism, production of extracellular virulence factors, and decreased susceptibility to biocides, antimicrobial agents, and host defense molecules and cells. *P. aeruginosa* growing on the bronchial mucosa during chronic infection, staphylococci and other pathogens growing on implanted medical devices, and dental pathogens growing on tooth surfaces to form plaques represent several examples of microbial biofilm growth associated with human disease. Many other pathogens can form biofilms during in vitro growth. It is increasingly accepted that this mode of growth contributes to microbial virulence and induction of disease and that biofilm formation can also be an important factor in microbial survival outside the host, promoting transmission to additional susceptible individuals.

AVOIDANCE OF INNATE HOST DEFENSES

As microbes have probably interacted with mucosal/epithelial surfaces since the emergence of multicellular organisms, it is not surprising that multicellular hosts have a variety of innate surface defense mechanisms that can sense when pathogens are present and contribute to their elimination. The skin is acidic and is bathed with fatty acids toxic to many microbes. Skin pathogens such as staphylococci must tolerate these adverse conditions. Mucosal surfaces are covered by a barrier composed of a thick mucus layer that entraps microbes and facilitates

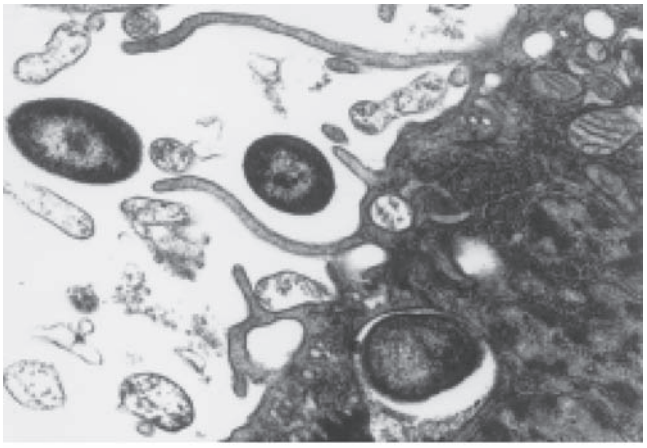
their transport out of the body by such processes as mucociliary clearance, coughing, and urination. Mucous secretions, saliva, and tears contain antibacterial factors such as lysozyme and antimicrobial peptides as well as antiviral factors such as interferons (IFNs). Gastric acidity is inimical to the survival of many ingested pathogens, and most mucosal surfaces—particularly the nasopharynx, the vaginal tract, and the gastrointestinal tract—contain a resident flora of commensal microbes that interfere with the ability of pathogens to colonize and infect a host.

Pathogens that survive these factors must still contend with host endocytic, phagocytic, and inflammatory responses as well as with host genetic factors that determine the degree to which a pathogen can survive and grow. The list of genes whose variants, usually by single-nucleotide polymorphisms, can affect host susceptibility and resistance to infection is rapidly expanding. A classic example is a 32-bp deletion in the gene for the HIV-1 co-receptor known as chemokine receptor 5 (CCR5), which, when present in the homozygous state, confers high-level resistance to HIV-1 infection. The growth of viral pathogens entering skin or mucosal epithelial cells can be limited by a variety of host genetic factors, including production of IFNs, modulation of receptors for viral entry, and age- and hormone-related susceptibility factors; by nutritional status; and even by personal habits such as smoking and exercise.

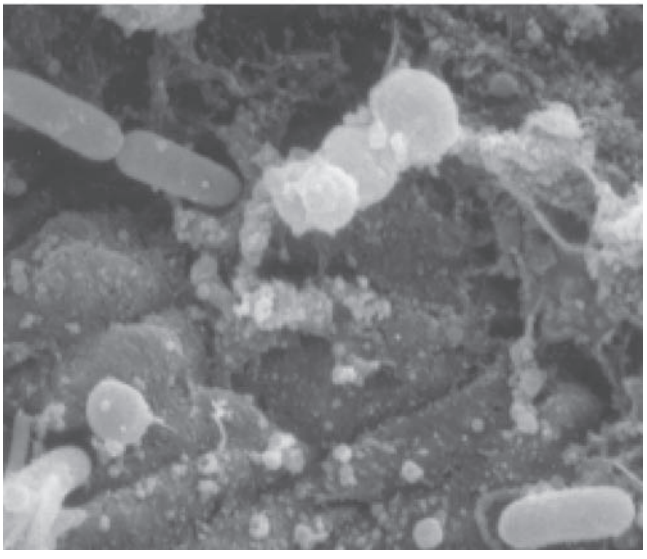
Encounters with epithelial cells

Over the past decade, many bacterial pathogens have been shown to enter epithelial cells **(Fig. 2-2)**; the bacteria often use specialized surface structures that bind to receptors, with consequent internalization. However, the exact role and the importance of this process in infection and disease are not well defined for most of these pathogens. Bacterial entry into host epithelial cells is seen as a means for dissemination to adjacent or deeper tissues or as a route to sanctuary to avoid ingestion and killing by professional phagocytes. Epithelial cell entry appears, for instance, to be a critical aspect of dysentery induction by *Shigella*.

Curiously, the less virulent strains of many bacterial pathogens are more adept at entering epithelial cells than are more virulent strains; examples include pathogens that lack the surface polysaccharide capsule needed to cause serious disease. Thus, for *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Streptococcus agalactiae* (group B *Streptococcus*), and *Streptococcus pyogenes*, isogenic mutants or variants lacking capsules enter epithelial cells better than the wild-type, encapsulated parental forms that cause disseminated disease. These observations have led to the proposal that epithelial cell entry may be primarily a manifestation of host defense, resulting in bacterial clearance by both shedding of epithelial cells containing internalized bacteria and initiation of a protective and nonpathogenic inflammatory response. However, a possible consequence of this process could be the opening of a hole in the epithelium, potentially allowing uningested organisms to enter the submucosa. This scenario has been documented in murine *S. enterica* serovar Typhimurium infections and in experimental bladder infections with uropathogenic *E. coli*. In the latter system, bacterial pilus-mediated attachment to *uroplakins* induces exfoliation of the cells with attached bacteria. Subsequently, infection is produced by residual bacterial cells that invade the superficial bladder epithelium, where they can grow intracellularly into biofilm-like masses encased in an extracellular polysaccharide-rich matrix and surrounded by uroplakin. This mode of growth produces structures that have been referred to as *bacterial pods*. It is likely that at low bacterial inocula epithelial cell ingestion and subclinical inflammation are efficient means to eliminate pathogens, while at higher inocula a proportion of surviving bacterial cells enter



A



B

FIGURE 2-2
Entry of bacteria into epithelial cells. *A*. Internalization of *P. aeruginosa* by cultured airway epithelial cells expressing wild-type cystic fibrosis transmembrane conductance regulator, the cell receptor for bacterial ingestion. ***B***. Entry of *P. aeruginosa* into murine tracheal epithelial cells after murine infection by the intranasal route.

the host tissue through the damaged mucosal surface and multiply, producing disease. Alternatively, failure of the appropriate epithelial cell response to a pathogen may allow the organism to survive on a mucosal surface where, if it avoids other host defenses, it can grow and cause a local infection. Along these lines, as noted above, *P. aeruginosa* is taken into epithelial cells by CFTR, a protein missing or nonfunctional in most severe cases of cystic fibrosis. The major clinical consequence of this disease is chronic airway-surface infection with *P. aeruginosa* in 80–90% of patients. The failure of airway epithelial cells to ingest and promote the removal of *P. aeruginosa* via a properly regulated inflammatory response has been proposed as a key component of the hypersusceptibility of these patients to chronic airway infection with this organism.

Encounters with phagocytes

Phagocytosis and inflammation

Phagocytosis of microbes is a major innate host defense that limits the growth and spread of pathogens. Phagocytes appear rapidly at sites of infection in conjunction with the initiation of inflammation. Ingestion of microbes by both tissue-fixed macrophages and migrating phagocytes probably accounts for the limited ability of most microbial agents to cause disease. A family of related molecules called *collectins*, *soluble defense collagens*, or *pattern-recognition molecules* are found in blood (mannose-binding lectins), in lung (surfactant proteins A and D), and most likely in other tissues as well and bind to carbohydrates on microbial surfaces to promote phagocyte clearance. Bacterial pathogens seem to be ingested principally by polymorphonuclear neutrophils, while eosinophils are frequently found at sites of infection by protozoan or multicellular parasites. Successful pathogens, by definition, must avoid being cleared by professional phagocytes. One of several antiphagocytic strategies employed by bacteria and by the fungal pathogen *Cryptococcus neoformans* is to elaborate large-molecular-weight surface polysaccharide antigens, often in the form of a capsule that coats the cell surface. Most pathogenic bacteria produce such antiphagocytic capsules. On occasion, proteins or polypeptides form capsule-like coatings for organisms such as group A streptococci and *Bacillus anthracis*.

As activation of local phagocytes in tissues is a key step in initiating inflammation and migration of additional phagocytes into infected sites, much attention has been paid to microbial factors that initiate inflammation. These are usually conserved factors critical to the microbes' survival and are referred to as *pathogen-associated molecular patterns* (PAMPs). Cellular responses to microbial encounters with phagocytes are governed largely by the structure of the microbial PAMPs that elicit inflammation, and detailed knowledge of these structures of bacterial pathogens has contributed greatly to our understanding of molecular mechanisms of microbial pathogenesis mediated by activation of host cell molecules such as Toll-like receptors (TLRs; **Fig. 2-3**). One of the best-studied systems involves the interaction of LPS from gram-negative bacteria and the GPI-anchored membrane protein CD14 found on the surface of professional phagocytes, including migrating and tissue-fixed macrophages and polymorphonuclear neutrophils. A soluble form of CD14 is also found in plasma and on mucosal surfaces. A plasma protein, LPS-binding protein, transfers LPS to membrane-bound CD14 on myeloid cells and promotes binding of LPS to soluble CD14. Soluble CD14/LPS/LPS-binding protein complexes bind to many cell types and may be internalized to initiate cellular responses to microbial pathogens. It has been shown that peptidoglycan and lipoteichoic acid from gram-positive bacteria and cell-surface products of mycobacteria and spirochetes can interact with CD14 (Fig. 2-3). Additional molecules, such as MD-2, also participate in the recognition of bacterial activators of inflammation.

GPI-anchored receptors do not have intracellular signaling domains; therefore, it is the TLRs that transduce signals for cellular activation due to LPS binding. Binding of microbial factors to TLRs to activate signal transduction occurs in the phagosome—and not on the surface—of dendritic cells that have internalized the microbe. This binding is probably due to the release of the microbial surface factor from the cell in the environment of the phagosome, where the liberated factor can bind to its cognate TLRs. TLRs initiate cellular activation through a series of signal-transducing molecules (Fig. 2-3) that lead to nuclear translocation of the transcription factor NF-κB, a master-switch for production of important inflammatory cytokines such as tumor necrosis factor α (TNF-α) and interleukin (IL) 1.

The initiation of inflammation can occur not only with LPS and peptidoglycan but also with viral particles and other microbial products such as polysaccharides, enzymes, and toxins. Bacterial flagella activate inflammation by binding of a conserved sequence to TLR5. Some pathogens (e.g., *Campylobacter jejuni, Helicobacter pylori,* and *Bartonella bacilliformis*) make flagella that lack this sequence and do not bind to TLR5; thus efficient host responses to infection are prevented. Bacteria also produce a high proportion of DNA molecules with unmethylated CpG residues that activate inflammation through TLR9. TLR3 recognizes double-stranded RNA, a pattern-recognition molecule produced by many viruses during their replicative cycle. TLR1 and TLR6 associate with TLR2 to promote recognition of acylated microbial proteins and peptides.

The myeloid differentiation factor 88 (MyD88) molecule and the Toll/IL-1R (TIR) domain-containing adapter protein (TIRAP) bind to the cytoplasmic domains of TLRs and also to receptors that are part of the IL-1 receptor families. Numerous studies have shown that MyD88/TIRAP-mediated transduction of signals from TLRs and other receptors is critical for innate resistance to infection, activating MAP-kinases and NF-κB and thereby leading to production of cytokines/chemokines. Mice lacking MyD88 are more susceptible than normal mice to infections with a broad range of

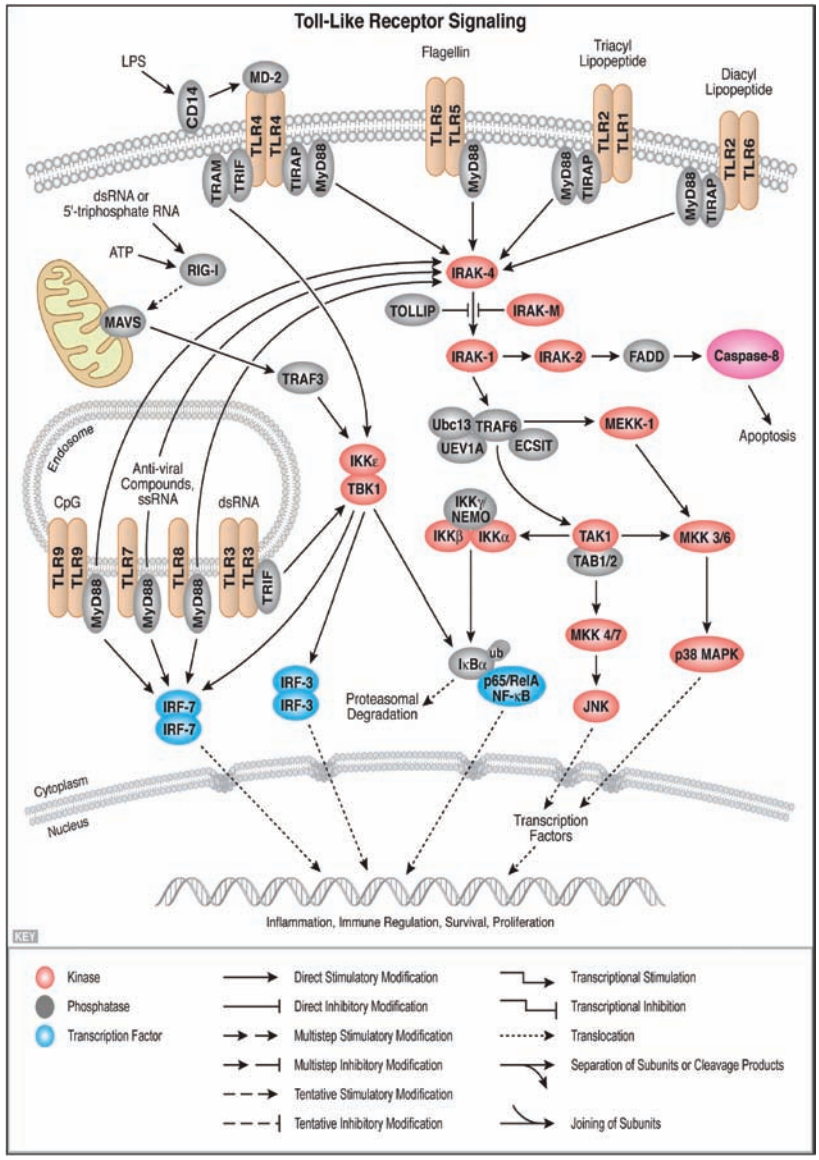


FIGURE 2-3

Cellular signaling pathways for production of inflammatory cytokines in response to microbial products. Microbial cell-surface constituents interact with Toll-like receptors (TLRs), in some cases requiring additional factors such as MD-2, which facilitates the response to lipopolysaccharide (LPS) via TLR4. Although depicted as interacting with the TLRs on the cell surface, TLRs contain extracellular leucine-rich domains that become localized to the lumen of the phagosome upon uptake of bacterial cells. The internalized TLRs can bind to microbial products. The TLRs are oligomerized, usually forming homodimers, and then bind to the general adapter protein MyD88 via the C-terminal Toll/IL-1R (TIR) domains, which also bind to TIRAP (TIR domain-containing adapter protein), a molecule that participates in the transduction of signals from TLRs 1, 2, 4, and 6. The MyD88/TIRAP complex activates signal-transducing molecules such as IRAK-4 (IL-1Rc-associated kinase 4), which in turn activates IRAK-1. This activation can be blocked by IRAK-M and TOLLIP. IRAK-1 activates TRAF 6 (tumor necrosis factor receptor–associated factor 6), TAK-1 (transforming growth factor β–activating kinase 1), and TAB1/2 (TAK1-binding protein 1/2). This signaling complex associates with the ubiquitin-conjugating enzyme Ubc13 and the Ubc-like protein UEV1A to catalyze the formation of a polyubiquitin chain on TRAF6. Polyubiquitination of TRAF6 activates TAK1, which, along with TAB1/2 (a protein that binds to lysine residue 63 in polyubiquitin chains via a conserved zinc-finger domain), phosphorylates the inducible kinase complex: IKK-α, -β, and -γ. IKK-γ is also called NEMO [nuclear factor κB (NF-κB) essential modulator]. This large complex phosphorylates the inhibitory component of NF-κB, IκBα, resulting in release of IκBα from NF-κB. Phosphorylated (PP) IκB is then ubiquinated (ub) and degraded, and the two components of NF-κB, p50 or Rel and p65, translocate to the nucleus, where they bind to regulatory transcriptional sites on target genes, many of which encode inflammatory proteins. In addition to inducing NF-κB nuclear translocation, the TAK1/TAB1/2 complex activates MAP kinase transducers such as MKK 4/7 and MKK 3/6, which can lead to nuclear translocation of transcription factors such as AP1. TLR4 can also activate NF-κB nuclear translocation via the MyD88-independent TRIF (TIR-domain-containing adapter-inducing IFN-β) and TRAM (TRIF-related adapter molecule) cofactors. Intracellular TLRs 3, 7, 8, and 9 also use MyD88 and TRIF to activate IFN response factors 3 and 7 (IRF-3 and IRF-7), which also function as transcriptional factors in the nucleus. (*Pathway diagram reproduced courtesy of Cell Signaling Technology, Inc. www.cellsignal.com.*)

pathogens. In one study, nine children homozygous for defective MyD88 genes had recurrent infections with *S. pneumoniae*, *S. aureus*, and *P. aeruginosa*—three bacterial species showing increased virulence in MyD88-deficient mice; however, unlike these mice, the MyD88-deficient children seemed to have no greater susceptibility to other bacteria, viruses, fungi, or parasites. Another component of the MyD88-dependent signaling pathway is a molecule known as IL-1 receptor–associated kinase 4 (IRAK-4). Individuals with a homozygous deficiency in genes encoding this protein are at increased risk for *S. pneumoniae* and *S. aureus* infections and, to some degree, for *P. aeruginosa* infections as well.

In addition to their role in MyD88-mediated signaling, some TLRs (e.g., TLR3 and TLR4) can activate signal transduction via a MyD88-independent pathway involving TIR domain-containing, adapter-inducing IFN-β (TRIF) and the TRIF-related adapter molecule (TRAM). Signaling through TRIF and TRAM activates the production of both NF-κB-dependent cytokines/chemokines and type 1 IFNs. The type 1 IFNs bind to the IFN-α receptor composed of two protein chains, IFNAR1 and IFNAR2. Humans produce three type 1 IFNs: IFN-α, IFN-β, and IFN-γ. These molecules activate another class of proteins known as the signal transducer and activator of transcription (STAT) complexes. The STAT factors are important in regulating immune system genes and thus play a critical role in responding to microbial infections.

Another intracellular complex of proteins found to be a major factor in the host cell response to infection is the inflammasome **(Fig. 2-4)**, where inflammatory cytokines IL-1 and Il-18 are changed from their precursor to active forms prior to secretion by the cysteine protease caspase-1. Within the inflammasome are additional proteins that are members of the nucleotide binding and oligomerization domain (NOD)-like receptor (NLR) family. Like the TLRs, NOD proteins sense the presence of the conserved microbial factors released inside a cell. Recognition of these PAMPs by NLRs leads to caspase-1 activation and to secretion of active IL-1 and IL-18 by an unknown mechanism. Studies of mice indicate that as many as four inflammasomes with different components are formed: the IPAF inflammasome, the NALP1 inflammasome, the cryopyrin/NALP3 inflammasome, and an inflammasome triggered by *Francisella tularensis* infection (Fig. 2-4). The components depend on the type of stimulus driving inflammasome formation and activation.

Additional interactions of microbial pathogens and phagocytes

Other ways that microbial pathogens avoid destruction by phagocytes include production of factors that are toxic to the phagocytes or that interfere with the chemotactic and ingestion function of phagocytes. Hemolysins, leukocidins, and the like are microbial proteins that can kill phagocytes that are attempting to ingest organisms elaborating these substances. For example, staphylococcal hemolysins inhibit macrophage chemotaxis and kill these phagocytes. Streptolysin O made by *S. pyogenes* binds to cholesterol in phagocyte membranes and initiates a process of internal degranulation, with the release of normally granule-sequestered toxic components into the phagocyte's cytoplasm. *E. histolytica*, an intestinal protozoan that causes amebic dysentery, can disrupt phagocyte membranes after direct contact via the release of protozoal phospholipase A and pore-forming peptides.

Microbial survival inside phagocytes

Many important microbial pathogens use a variety of strategies to survive inside phagocytes (particularly macrophages) after ingestion. Inhibition of fusion of the phagocytic vacuole (the phagosome) containing the ingested microbe with the lysosomal granules containing antimicrobial substances (the lysosome) allows *Mycobacterium tuberculosis*, *S. enterica* serovar Typhi, and *Toxoplasma gondii* to survive inside macrophages. Some organisms, such as *Listeria monocytogenes*, escape into the phagocyte's cytoplasm to grow and eventually spread to other cells. Resistance to killing within the macrophage and subsequent growth are critical to successful infection by herpes-type viruses, measles virus, poxviruses, *Salmonella*, *Yersinia*, *Legionella*, *Mycobacterium*, *Trypanosoma*, *Nocardia*, *Histoplasma*, *Toxoplasma*, and *Rickettsia*. *Salmonella* species use a master regulatory system—in which the *PhoP/PhoQ* genes control other genes—to enter and survive within cells, with intracellular survival entailing structural changes in the cell envelope LPS.

TISSUE INVASION AND TISSUE TROPISM

Tissue invasion

Most viral pathogens cause disease by growth at skin or mucosal entry sites, but some pathogens spread from the initial site to deeper tissues. Virus can spread via the nerves (rabies virus) or plasma (picornaviruses) or within migratory blood cells (poliovirus, Epstein-Barr virus, and many others). Specific viral genes determine where and how individual viral strains can spread.

Bacteria may invade deeper layers of mucosal tissue via intracellular uptake by epithelial cells, traversal of epithelial cell junctions, or penetration through denuded epithelial surfaces. Among virulent *Shigella* strains and invasive *E. coli*, outer-membrane proteins are critical to epithelial cell invasion and bacterial multiplication. *Neisseria* and *Haemophilus* species penetrate mucosal cells by poorly understood mechanisms before dissemination into the bloodstream. Staphylococci and streptococci elaborate a variety of extracellular enzymes, such as hyaluronidase, lipases, nucleases, and hemolysins, that are probably important in breaking down cellular and matrix structures and allowing the bacteria access to deeper tissues and blood. Organisms that colonize the gastrointestinal tract can often translocate through the mucosa into the blood and, under circumstances in which host defenses are inadequate, cause bacteremia. *Y. enterocolitica* can invade the mucosa through the activity of the invasin protein. Some bacteria (e.g., *Brucella*) can be carried from a mucosal site to a distant site by

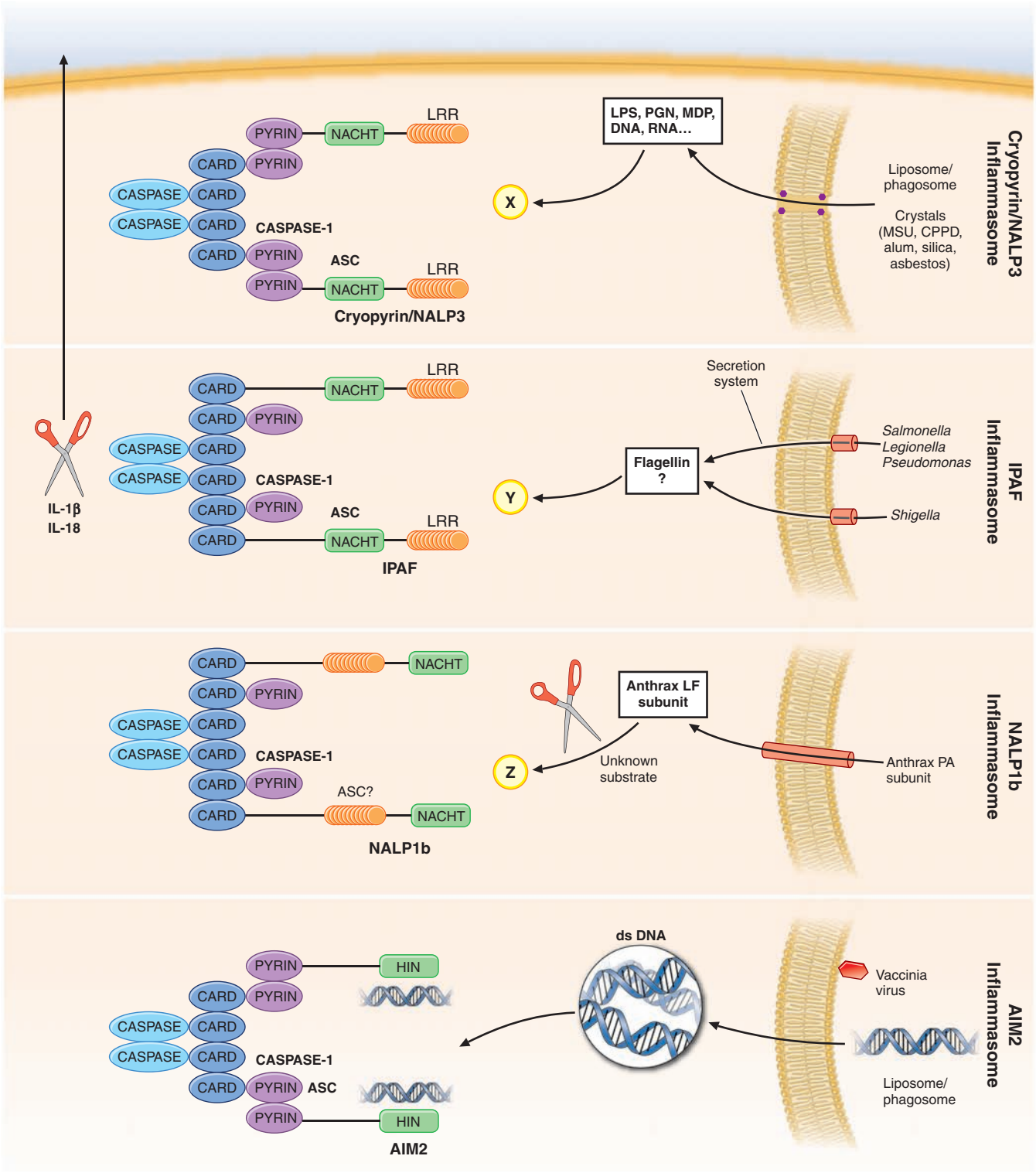


FIGURE 2-4

The NOD-like receptor (NLR) proteins NALP1b, cryopyrin/NALP3, and IPAF and the HIN-200 protein AIM2 assemble a caspase-1-activating inflammasome complex in response to specific microbial or bacterial factors. The murine NALP1b inflammasome recognizes the cytosolic presence of anthrax lethal toxin. The cryopyrin/NALP3 inflammasome recognizes multiple pathogen-associated molecular patterns (PAMPs) in combination with ATP or nigericin as well as crystalline substances including MSU, silica, and asbestos particles. The IPAF inflammasome senses *Salmonella* and *Legionella* flagellin and a yet-unidentified *Shigella flexneri* compound, all of which access the cytosol through a type III or IV secretion system. Cytosolic PAMPs may trigger assembly of a particular inflammasome complex by causing modifications in unknown host factors (X, Y, Z) that are monitored by specific NLR proteins. In contrast, AIM2 directly binds dsDNA in the cytosol to induce caspase-1 activation. The CARD/pyrin-containing adapter protein ASC is essential for all these inflammasome complexes, although its role in the NALP1b inflammasome remains to be formally established. Once activated, caspase-1 processes IL-1β and IL-18 precursors into the mature cytokines, which are secreted through an unknown mechanism. [*Figure and legend from Lamkanfi M, Dixit VM (2009) The Inflammasomes. PLoS Pathog 5(12): e1000510. doi:10.1371/journal.ppat.1000510.*]

phagocytic cells (e.g., polymorphonuclear neutrophils) that ingest but fail to kill the bacteria.

Fungal pathogens almost always take advantage of host immunocompromise to spread hematogenously to deeper tissues. The AIDS epidemic has resoundingly illustrated this principle: the immunodeficiency of many HIV-infected patients permits the development of life-threatening fungal infections of the lung, blood, and brain. Other than the capsule of *C. neoformans*, specific fungal antigens involved in tissue invasion are not well characterized. Both fungal pathogens and protozoal pathogens (e.g., *Plasmodium* species and *E. histolytica*) undergo morphologic changes to spread within a host. Malarial parasites grow in liver cells as merozoites and are released into the blood to invade erythrocytes and become trophozoites. *E. histolytica* is found as both a cyst and a trophozoite in the intestinal lumen, through which this pathogen enters the host, but only the trophozoite form can spread systemically to cause amebic liver abscesses. Other protozoal pathogens, such as *T. gondii*, *Giardia lamblia*, and *Cryptosporidium*, also undergo extensive morphologic changes after initial infection to spread to other tissues.

Tissue tropism

The propensity of certain microbes to cause disease by infecting specific tissues has been known since the early days of bacteriology, yet the molecular basis for this propensity is understood somewhat better for viral pathogens than for other agents of infectious disease. Specific receptor-ligand interactions clearly underlie the ability of certain viruses to enter cells within tissues and disrupt normal tissue function, but the mere presence of a receptor for a virus on a target tissue is not sufficient for tissue tropism. Factors in the cell, route of viral entry, viral capacity to penetrate into cells, viral genetic elements that regulate gene expression, and pathways of viral spread in a tissue all affect tissue tropism. Some viral genes are best transcribed in specific target cells, such as hepatitis B genes in liver cells and Epstein-Barr virus genes in B lymphocytes. The route of inoculation of poliovirus determines its neurotropism, although the molecular basis for this circumstance is not understood.

Compared with viral tissue tropism, the tissue tropism of bacterial and parasitic infections has not been as clearly elucidated, but studies of *Neisseria* species have provided insights. Both *N. gonorrhoeae,* which colonizes and infects the human genital tract, and *N. meningitidis*, which principally colonizes the human oropharynx but can spread to the brain, produce type IV pili (Tfp) that mediate adherence to host tissues. In the case of *N. gonorrhoeae*, the Tfp bind to a glucosamine-galactose-containing adhesin on the surface of cervical and urethral cells; in the case of *N. meningitidis*, the Tfp bind to cells in the human meninges in order to cross the blood-brain barrier. *N. meningitidis* expresses a capsular polysaccharide, while *N. gonorrhoeae* does not; however, there is no indication that this property plays a role in the different tissue tropisms displayed by these two bacterial species. *N. gonorrhoeae* can use cytidine monophosphate *N*-acetylneuraminic acid from host tissues to add *N*-acetylneuraminic acid (sialic acid) to its lipooligosaccharide O side chain, and this alteration appears to make the organism resistant to host defenses. Lactate, present at high levels on genital mucosal surfaces, stimulates sialylation of gonococcal lipooligosaccharide. Bacteria with sialic acid sugars in their capsules, such as *N. meningitidis*, *E. coli* K1, and group B streptococci, have a propensity to cause meningitis, but this generalization has many exceptions. For example, all recognized serotypes of group B streptococci contain sialic acid in their capsules, but only one serotype (III) is responsible for most cases of group B streptococcal meningitis. Moreover, both *H. influenzae* and *S. pneumoniae* can readily cause meningitis, but these organisms do not have sialic acid in their capsules.

TISSUE DAMAGE AND DISEASE

Disease is a complex phenomenon resulting from tissue invasion and destruction, toxin elaboration, and host response. Viruses cause much of their damage by exerting a cytopathic effect on host cells and inhibiting host defenses. The growth of bacterial, fungal, and protozoal parasites in tissue, which may or may not be accompanied by toxin elaboration, can also compromise tissue function and lead to disease. For some bacterial and possibly some fungal pathogens, toxin production is one of the best-characterized molecular mechanisms of pathogenesis, while host factors such as IL-1, TNF-α, kinins, inflammatory proteins, products of complement activation, and mediators derived from arachidonic acid metabolites (leukotrienes) and cellular degranulation (histamines) readily contribute to the severity of disease.

Viral disease

Viral pathogens are well known to inhibit host immune responses by a variety of mechanisms. Immune responses can be affected by decreasing production of most major histocompatibility complex molecules (adenovirus E3 protein), by diminishing cytotoxic T cell recognition of virus-infected cells (Epstein-Barr virus EBNA1 antigen and cytomegalovirus IE protein), by producing virus-encoded complement receptor proteins that protect infected cells from complement-mediated lysis (herpesvirus and vaccinia virus), by making proteins that interfere with the action of IFN (influenza virus and poxvirus), and by elaborating superantigen-like proteins (mouse mammary tumor virus and related retroviruses and the rabies nucleocapsid). Superantigens activate large populations of T cells that express particular subsets of the T cell receptor β protein, causing massive cytokine release and subsequent host reactions. Another molecular mechanism of viral virulence involves the production of peptide growth factors for host cells, which disrupt normal cellular growth, proliferation, and differentiation. In addition, viral factors can bind to and interfere with the function of host

receptors for signaling molecules. Modulation of cytokine production during viral infection can stimulate viral growth inside cells with receptors for the cytokine, and virus-encoded cytokine homologues (e.g., the Epstein-Barr virus BCRF1 protein, which is highly homologous to the immunoinhibitory IL-10 molecule) can potentially prevent immune-mediated clearance of viral particles. Viruses can cause disease in neural cells by interfering with levels of neurotransmitters without necessarily destroying the cells, or they may induce either programmed cell death (apoptosis) to destroy tissues or inhibitors of apoptosis to allow for prolonged viral infection of cells. For infection to spread, many viruses must be released from cells. In a newly identified function, viral protein U (Vpu) of HIV facilitates the release of virus, a process that is specific to certain cells. Mammalian cells produce a restriction factor involved in inhibiting the release of virus; for HIV, this factor is designated BST-2 (bone marrow stromal antigen 2)/HM1.24/CD317, or tetherin. Vpu of HIV interacts with tetherin, promoting release of infectious virus. Overall, disruption of normal cellular and tissue function due to viral infection, replication, and release promotes clinical disease.

Bacterial toxins

Among the first infectious diseases to be understood were those due to toxin-elaborating bacteria. Diphtheria, botulism, and tetanus toxins are responsible for the diseases associated with local infections due to *Corynebacterium diphtheriae*, *Clostridium botulinum*, and *Clostridium tetani*, respectively. Enterotoxins produced by *E. coli*, *Salmonella*, *Shigella*, *Staphylococcus*, and *V. cholerae* contribute to diarrheal disease caused by these organisms. Staphylococci, streptococci, *P. aeruginosa*, and *Bordetella* elaborate various toxins that cause or contribute to disease, including toxic shock syndrome toxin 1; erythrogenic toxin; exotoxins A, S, T and U; and pertussis toxin. A number of these toxins (e.g., cholera toxin, diphtheria toxin, pertussis toxin, *E. coli* heat-labile toxin, and *P. aeruginosa* exotoxin) have adenosine diphosphate ribosyl transferase activity; i.e., the toxins enzymatically catalyze the transfer of the adenosine diphosphate ribosyl portion of nicotinamide adenine diphosphate to target proteins and inactivate them. The staphylococcal enterotoxins, toxic shock syndrome toxin 1, and the streptococcal pyogenic exotoxins behave as superantigens, stimulating certain T cells to proliferate without processing of the protein toxin by antigen-presenting cells. Part of this process involves stimulation of the antigen-presenting cells to produce IL-1 and TNF-α, which have been implicated in many clinical features of diseases like toxic shock syndrome and scarlet fever. A number of gram-negative pathogens (*Salmonella*, *Yersinia*, and *P. aeruginosa*) can inject toxins directly into host target cells by means of a complex set of proteins referred to as the type III secretion system. Loss or inactivation of this virulence system usually greatly reduces the capacity of a bacterial pathogen to cause disease.

Endotoxin

The lipid A portion of gram-negative LPS has potent biologic activities that cause many of the clinical manifestations of gram-negative bacterial sepsis, including fever, muscle proteolysis, uncontrolled intravascular coagulation, and shock. The effects of lipid A appear to be mediated by the production of potent cytokines due to LPS binding to CD14 and signal transduction via TLRs, particularly TLR4. Cytokines exhibit potent hypothermic activity through effects on the hypothalamus; they also increase vascular permeability, alter the activity of endothelial cells, and induce endothelial-cell procoagulant activity. Numerous therapeutic strategies aimed at neutralizing the effects of endotoxin are under investigation, but so far the results have been disappointing. One drug, activated protein C, was found to reduce mortality rates by ~20% during severe sepsis, a condition that can be induced by endotoxin release during gram-negative bacterial sepsis.

Invasion

Many diseases are caused primarily by pathogens growing in tissue sites that are normally sterile. Pneumococcal pneumonia is mostly attributable to the growth of *S. pneumoniae* in the lung and the attendant host inflammatory response, although specific factors that enhance this process (e.g., pneumolysin) may be responsible for some of the pathogenic potential of the pneumococcus. Disease that follows bacteremia and invasion of the meninges by meningitis-producing bacteria such as *N. meningitidis*, *H. influenzae*, *E. coli* K1, and group B streptococci appears to be due solely to the ability of these organisms to gain access to these tissues, multiply in them, and provoke cytokine production leading to tissue-damaging host inflammation.

Specific molecular mechanisms accounting for tissue invasion by fungal and protozoal pathogens are less well described. Except for studies pointing to factors like capsule and melanin production by *C. neoformans* and possibly levels of cell wall glucans in some pathogenic fungi, the molecular basis for fungal invasiveness is not well defined. Melanism has been shown to protect the fungal cell against death caused by phagocyte factors such as nitric oxide, superoxide, and hypochlorite. Morphogenic variation and production of proteases (e.g., the *Candida* aspartyl proteinase) have been implicated in fungal invasion of host tissues.

If pathogens are effectively to invade host tissues (particularly the blood), they must avoid the major host defenses represented by complement and phagocytic cells. Bacteria most often avoid these defenses through their surface polysaccharides—either capsular polysaccharides or long O-side-chain antigens characteristic of the smooth LPS of gram-negative bacteria. These molecules can prevent the activation and/or deposition of complement opsonins or can limit the access of phagocytic cells with receptors for complement opsonins to these molecules when they are deposited on

the bacterial surface below the capsular layer. Another potential mechanism of microbial virulence is the ability of some organisms to present the capsule as an apparent self antigen through molecular mimicry. For example, the polysialic acid capsule of group B *N. meningitidis* is chemically identical to an oligosaccharide found on human brain cells.

Immunochemical studies of capsular polysaccharides have led to an appreciation of the tremendous chemical diversity that can result from the linking of a few monosaccharides. For example, three hexoses can link up in more than 300 different, potentially serologically distinct ways, while three amino acids have only six possible peptide combinations. Capsular polysaccharides have been used as effective vaccines against meningococcal meningitis as well as against pneumococcal and *H. influenzae* infections and may prove to be of value as vaccines against any organisms that express a nontoxic, immunogenic capsular polysaccharide. In addition, most encapsulated pathogens become virtually avirulent when capsule production is interrupted by genetic manipulation; this observation emphasizes the importance of this structure in pathogenesis.

Host response

The inflammatory response of the host is critical for interruption and resolution of the infectious process but also is often responsible for the signs and symptoms of disease. Infection promotes a complex series of host responses involving the complement, kinin, and coagulation pathways. The production of cytokines such as IL-1, IL-18, TNF-α, and other factors regulated in part by the NF-κB transcription factor leads to fever, muscle proteolysis, and other effects. An inability to kill or contain the microbe usually results in further damage due to the progression of inflammation and infection. For example, in many chronic infections, degranulation of host inflammatory cells can lead to release of host proteases, elastases, histamines, and other toxic substances that can degrade host tissues. Chronic inflammation in any tissue can lead to the destruction of that tissue and to clinical disease associated with loss of organ function, such as sterility from pelvic inflammatory disease caused by chronic infection with *N. gonorrhoeae*.

The nature of the host response elicited by the pathogen often determines the pathology of a particular infection. Local inflammation produces local tissue damage, while systemic inflammation, such as that seen during sepsis, can result in the signs and symptoms of septic shock. The severity of septic shock is associated with the degree of production of host effectors. Disease due to intracellular parasitism results from the formation of granulomas, wherein the host attempts to wall off the parasite inside a fibrotic lesion surrounded by fused epithelial cells that make up so-called multinucleated giant cells. A number of pathogens, particularly anaerobic bacteria, staphylococci, and streptococci, provoke the formation of an abscess, probably because of the presence of zwitterionic surface polysaccharides such as the capsular polysaccharide of *Bacteroides fragilis*. The outcome of an infection depends on the balance between an effective host response that eliminates a pathogen and an excessive inflammatory response that is associated with an inability to eliminate a pathogen and with the resultant tissue damage that leads to disease.

TRANSMISSION TO NEW HOSTS

As part of the pathogenic process, most microbes are shed from the host, often in a form infectious for susceptible individuals. However, the rate of transmissibility may not necessarily be high, even if the disease is severe in the infected individual, as these traits are not linked. Most pathogens exit via the same route by which they entered: respiratory pathogens by aerosols from sneezing or coughing or through salivary spread, gastrointestinal pathogens by fecal-oral spread, sexually transmitted diseases by venereal spread, and vector-borne organisms by either direct contact with the vector through a blood meal or indirect contact with organisms shed into environmental sources such as water. Microbial factors that specifically promote transmission are not well characterized. Respiratory shedding is facilitated by overproduction of mucous secretions, with consequently enhanced sneezing and coughing. Diarrheal toxins such as cholera toxin, *E. coli* heat-labile toxins, and *Shigella* toxins probably facilitate fecal-oral spread of microbial cells in the high volumes of diarrheal fluid produced during infection. The ability to produce phenotypic variants that resist hostile environmental factors (e.g., the highly resistant cysts of *E. histolytica* shed in feces) represents another mechanism of pathogenesis relevant to transmission. Blood parasites such as *Plasmodium* species change phenotype after ingestion by a mosquito—a prerequisite for the continued transmission of this pathogen. Venereally transmitted pathogens may undergo phenotypic variation due to the production of specific factors to facilitate transmission, but shedding of these pathogens into the environment does not result in the formation of infectious foci.

In summary, the molecular mechanisms used by pathogens to colonize, invade, infect, and disrupt the host are numerous and diverse. Each phase of the infectious process involves a variety of microbial and host factors interacting in a manner that can result in disease. Recognition of the coordinated genetic regulation of virulence factor elaboration when organisms move from their natural environment into the mammalian host emphasizes the complex nature of the host-parasite interaction. Fortunately, the need for diverse factors in successful infection and disease implies that a variety of therapeutic strategies may be developed to interrupt this process and thereby prevent and treat microbial infections.

CHAPTER 3

THE HUMAN MICROBIOME

Jeffrey I. Gordon ■ Rob Knight

The words *well-being* and *microbes* typically are not spoken in the same breath. Microbes have a strong negative connotation in contemporary societies and are viewed in a warlike context. Disease-producing or pathogenic microbes are indeed serious threats to human health and have received justifiable attention from the inception of the field of microbiology. The list of known and notorious pathogens is long. However, most human encounters with microbes are not hostile but benign or even beneficial. Advances in DNA sequencing and computational biology now permit comprehensive description of the composition of and the roles played by the microbial communities (*microbiota*) associated with the human body.

Like all animals on the planet, humans have had to adapt to a microbe-dominated biosphere. The number of microbes on Earth is staggering. It has been estimated that 10^{30} microbes live in the ocean, in surface and subsurface terrestrial ecosystems, and on and inside animals and plants. Microbes, which are defined here as microscopic living organisms that belong to any of the three known domains of life on Earth (Bacteria, Archaea, and Eukarya), inhabit the exposed exterior and interior surfaces of the human body (e.g., the skin, mouth, airways, gastrointestinal tract, and vagina). The uterus traditionally has been thought to be microbe-free, although new evidence may prompt a reevaluation of the idea that this ecosystem is completely sterile throughout gestation. Colonization with microbes begins no later than during parturition; in the ensuing years, microbes come to outnumber human cells by an estimated tenfold in the human body. Therefore, a comprehensive view of humans as a life form entails consideration of the body's microbial and *Homo sapiens* cells together as a connected network—a coevolved symbiosis ("living together")—in which various body habitats serve as homes to microbial communities. These habitats harbor microbiota composed of members that function as mutualists (both host and microbe benefit from the other's presence), commensals (one partner benefits, and the other is seemingly unaffected), and potential or overt pathogens (one partner benefits, and the other is harmed).

HUMAN MICROBIOME PROJECTS

Human microbiome projects (HMPs) reflect this view of the human body as an amalgamation of human and microbial cells as well as human and microbial genes. These projects represent a confluence of ongoing technical and computational advances in the genome sciences. The newest generation of massively parallel DNA sequencers can be used to document—with unprecedented speed and economy—which microbes compose a microbiota and to characterize a microbiota's gene content (its *microbiome*). Key terms relevant to HMPs are defined in **Table 3-1**.

Computing power and software tools are evolving rapidly to mine the vast amount of data generated by these sequencers. The coevolution of software development and ever-increasing data-set generation is not surprising. In systems ranging from artificial organisms to bacteria to metazoa, coevolution of predators and prey greatly accelerates the evolutionary rate. Dawkins and Krebs (1979) introduced the concept of an "arms race" in which the predator has a clear advantage in developing better means for consuming its prey and the prey has a clear advantage in developing better means to avoid being eaten. Adaptation to evade a population that is itself adapting proceeds at a far more rapid rate than does adaptation to an environment that can change but cannot evolve in an adaptive way. The same dynamics are apparent in software development: the "consumers" of software produce ever-larger data sets that break the software, in part because the availability of these resources prompts new strategies for exploitation (i.e., the design of experiments that could not have been conceived without the availability of the improved tools). This intimate association between tool users and tool developers is essential for rapid development in terms of what the software can accomplish and what experiments can be conceived and accomplished in HMPs. HMPs also reflect a more ecologic focus of microbiology on the properties and functions of microbial communities; that is, these projects go beyond the properties and functions that individual component species of these

communities exhibit when studied in isolation—i.e., outside their native environments.

The ability to characterize the structures and functions of whole microbial communities without culturing their component members has spawned a new field of science known as *metagenomics* (Table 3-1). Metagenomics involves the sequencing of DNA isolated directly from a microbial community residing in a particular environment; the resulting information permits the application of other systems-level techniques, such as profiling of mRNA and protein products expressed by a microbiome and characterization of a community's metabolic activities. The goal of metagenomics (these allied systemwide characterizations) and of HMPs in general is an understanding of the ecologic principles and the various factors that determine how microbial communities are assembled, are maintained, and operate. The results promise to provide a deeper understanding of how habitats and microbial communities coevolve and, in the case of humans, how these communities vary both compositionally and functionally over time at different anatomic sites within an individual

TABLE 3-1

GLOSSARY OF TERMS USED IN DISCUSSION OF THE HUMAN MICROBIOME

TERM	DEFINITION
Culture-independent analysis	A type of analysis that does not require culture of microbes. Information is extracted directly from environmental samples.
Diversity	The distribution of different kinds of organisms in a specific habitat or habitats. *Alpha* diversity is, broadly speaking, the number of kinds of organisms in a single sample; *beta* diversity describes how the types of organisms are partitioned among samples.
Domains of life	The three major branches of life on Earth: the Eukarya (including humans), the Bacteria, and the Archaea
Gnotobiotics	Rearing of animals under sterile (germ-free) conditions. Animals subsequently can be colonized at various stages of their life cycle with defined collections of microbes.
Human microbiome	In ecology, *biome* refers to a habitat and the organisms in it. In this sense, the human *microbiome* would be defined as the collection of microorganisms associated with the human body. However, the term *microbiome* is also used to refer to the collective genomes and genes present in members of a particular microbiota, and the human *metagenome* is the sum of the human genome and microbial genes (microbiome). A *core* human microbiome is defined as everything shared in a par-ticular body habitat among all or the vast majority of human microbiomes. A core microbiome may include a common set of genomes and genes encoding various protein families and/or metabolic capabilities. Microbial genes that are variably represented in different humans may contribute to distinctive physiologic/metabolic phenotypes.
Metagenomics	An emerging field encompassing culture-independent studies of the structures and functions of microbial communities and their interactions with the habitats they occupy. Metagenomics includes (1) shotgun sequencing of microbial DNA isolated directly from a particular environment and (2) high-throughput screening of expression libraries constructed from cloned community DNA to identify specific functions such as antibiotic resistance (*functional* metagenomics). DNA-level analyses provide the foundation for profiling of mRNAs and proteins produced by a microbiome (*meta-transcriptomics* and *meta-proteomics*) and for identification of a community's metabolic network (*meta-metabolomics*).
Microbiota	A microbial community, including Bacteria, Archaea, Eukarya, and viruses, that occupies a specific habitat
Pangenome	The group of genes found in genomes that make up a particular microbial phylotype, including *core* genes found in all genomes and *dispensable* genes found in a subset of genomes within the phylotype
Phylogenetic analysis	Characterization of the evolutionary relationships between organisms and their gene products
Phylogenetic tree	A "tree" in which organisms are shown according to their relationships to hypothetical common ancestors. When built from molecular sequences, the branch lengths are proportional to the amount of evolutionary change separating each ancestor-descendant pair.
Phylotype	A phylogenetic group of microbes, currently defined by a threshold percentage identity shared among their small subunit rRNA genes (e.g., ≥97% for a species-level phylotype)
Rarefaction	A procedure in which subsampling is used to assess whether all the diversity present in a specific sample or set of samples has been observed at a specific sampling depth and to extrapolate how much additional sampling would be needed to observe all the diversity
Resilience	A community's ability to return to its initial state after a perturbation

and in different groups of people living in different cultural contexts as well as how these communities contribute to human physiologic status, physiologic variation, disease predisposition, and disease pathogenesis.

Furthermore, HMPs address one of the most fundamental questions in genetics: How does environment influence the structure and function of "human genes"? Over a lifetime, each human encounters a unique environment. Part of this personally experienced environment is incorporated into the body habitat–associated microbiota. In this sense, HMPs will expand the conceptualization of "human" genetic potential from a relatively fixed deterministic view in which individuals are seen as inheriting only a defined set of ~20,000 genes from their parents to a view in which each human acquires a microbiome containing a varied assemblage of genes several orders of magnitude larger than the collected *H. sapiens* genes through a process influenced by family, lifestyle, and life experiences as well as by *H. sapiens* genes. International HMPs probably will help determine whether there is a dimension of human evolution that is occurring at the level of the human microbiota and microbiome and—if so—whether, how, and how fast this microbial evolution may be affecting human biology. Finally, these projects probably will raise a number of important questions about personal identity, how to define the origins of health disparities, and issues related to privacy and confidentiality.

A TOOLBOX FOR CULTURE-INDEPENDENT METAGENOMIC ANALYSES OF MICROBIAL COMMUNITIES

Most members of complex microbial communities cannot be cultured by conventional laboratory techniques. The vast microbial diversity that exists inside and on the human body cannot be characterized with culture-based approaches, in large part because the metabolic milieu fashioned by these communities in their native habitats cannot be duplicated in vitro at this time. Therefore, investigators have turned to culture-independent methods to identify which organisms are present in a microbiota and in what abundance. The gene widely used to identify microorganisms and classify their evolutionary relationships encodes the major RNA component of the small subunit (SSU) of ribosomes. The SSU rRNA gene has been highly conserved among all known life forms on Earth. This conservation allows SSU rRNA genes from different organisms to be aligned accurately so that regions of nucleotide sequence variation can be identified readily. Pairwise comparisons of SSU rRNA gene sequences from different microbes allow the construction of a phylogenetic tree that represents an evolutionary map; previously unknown organisms can then be assigned a location (coordinate) on that map. This approach, known as *molecular phylogenetics*, allows each organism to be characterized on the basis of its evolutionary distance from other organisms. Different phylogenetic types (phylotypes) can be viewed as branches on an evolutionary tree.

The most straightforward way to define which microbes are present in microbial communities associated with the human body is to amplify SSU rRNA genes by polymerase chain reaction (PCR), using primers directed at regions with nucleotide sequences that are conserved among all bacteria (or archaea or eukaryota) and that flank more variable regions. These variable regions can be used to discriminate among different kinds of organisms belonging to each of the three domains of life. Because bacteria dominate human microbial communities, most efforts have been devoted to defining bacterial diversity in the microbiota.

The coevolution of high-throughput next-generation DNA sequencing with new software tools has led to an SSU rRNA renaissance that allows simultaneous characterization of the diversity present in hundreds to thousands of microbial communities. Sequencing of a small fragment of the 1500-bp (base pair) bacterial 16S rRNA gene has been found to be sufficient for many types of analysis. For example, 250-base reads encompassing a variable region of the gene are suitable for taxonomic assignments and microbial community comparisons provided that the region is chosen carefully. Primer design for PCR of bacterial 16S rRNA genes is a critical factor: differential annealing with different primer pairs designed to amplify different variable regions can lead to over- or underrepresentation of specific taxonomic groups (*taxa*), and different regions within the gene can have somewhat different patterns of evolution. Therefore, caution must be exercised in comparisons of the relative abundance of taxa in samples characterized in different studies using different methods.

A key innovation has been multiplex sequencing with highly parallel DNA sequencers that can generate large numbers of sequences with read lengths of ≥200 nucleotides. Amplicons generated from each microbial-community DNA sample are tagged by incorporation of a unique oligonucleotide barcode into the primer. Amplicons that harbor these sample-specific barcodes can be pooled together so that multiple samples representing multiple communities can be sequenced simultaneously **(Fig. 3-1)**.

One important choice in multiplex barcoded sequencing involves a trade-off between the number of samples that can be processed simultaneously and the number of sequences per sample, which in turn depends on the expected size of the differences between microbial communities. Differences in the microbiota between individuals or between communities occupying different body habitats in the same individual are large; therefore, relatively few (<1000) SSU rRNA reads are required for discrimination among communities. However, the identification of systematic differences in community ecology that correlate with physiologic or pathophysiologic status is confounded by this immense interpersonal variation. For example, 1000 sequences per sample means that species present at 1% abundance can be identified with reasonable confidence, although this level of coverage will fail to identify many of the rarer species-level phylotypes that may provide critical functions for using specific

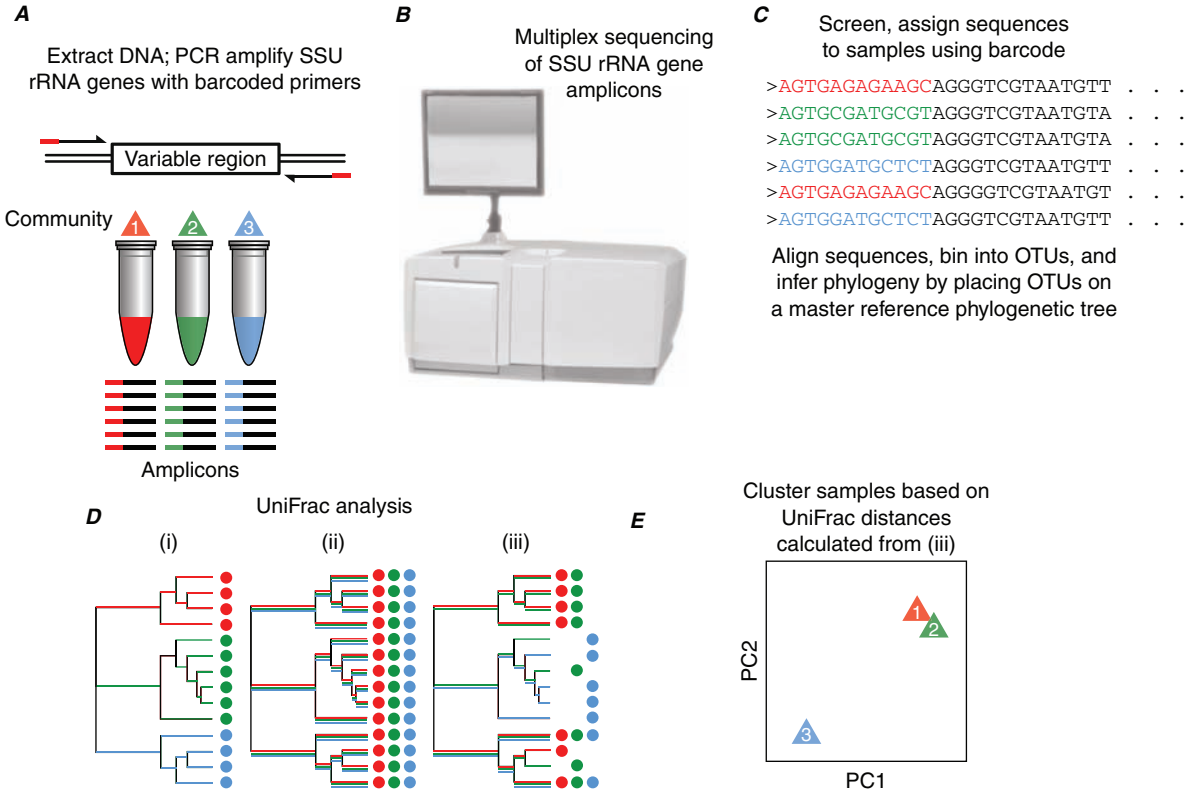


FIGURE 3-1

Pipeline for culture-independent studies of a microbiota. ***(A)*** DNA is extracted directly from a sampled human body habitat–associated microbial community. The precise location of the community and relevant patient meta-data are collected. Polymerase chain reaction (PCR) is used to amplify portions of the bacterial 16S rRNA gene containing one or more variable regions. Primers with sample-specific, error-correcting barcodes are designed to recognize the more conserved regions of the 16S rRNA gene that flank the targeted variable region(s). ***(B)*** Barcoded amplicons from multiple samples (communities 1–3) are pooled and sequenced in batches in a highly parallel next-generation DNA sequencer. ***(C)*** The resulting reads are processed. Barcodes denote which sample the sequence came from. After barcode sequences are removed in silico, reads are aligned and grouped according to a specified level of shared identity; e.g., sequences that share ≥97% nucleotide sequence identity are regarded as representing a species. Once reads are binned in this fashion, they are placed on a phylogenetic tree of all known bacteria to infer their phylogeny. ***(D)*** Communities can be compared to one another by either taxon-based methods, in which phylogeny is not considered and the number of shared taxa is simply scored, or phylogenetic methods, in which community similarity is considered in light of the evolutionary relationships of community members. The UniFrac metric is commonly used for phylogenetic-based comparisons. In the three stylized examples here, communities with varying degrees of similarity are shown. Each circle represents an operational taxonomic unit (OTU), which is colored according to its community of origin and placed on a master phylogenetic tree that includes all lineages from all communities. Branches (*horizontal lines*) are colored with each community that contains members from that branch. Examples (i), (ii), and (iii) vary in the amount of branch length shared between the OTUs from each community. In (i), there is no shared branch length, and the three communities have a similarity score of 0. In (ii), the communities are identical and are assigned a similarity score of 1. In (iii), there is an intermediate level of similarity. Communities represented in red and green share more branch length and thus have a higher similarity score than red versus blue or green versus blue. The amount of shared branch length in each pairwise community comparison provides a distance matrix. ***(E)*** The results of taxon- or phylogenetic-based distance matrices can be displayed by principal coordinates analysis (PCoA), in which each community is plotted spatially such that the largest component of variance is captured on the *x* axis (PC1) and the second largest component of variance is displayed on the *y* axis (PC2). In the example shown, the three communities in (iii) from panel D are compared. Note that for shotgun sequencing of whole-community DNA (microbiome analysis), reads are compared with genes present in the genomes of sequenced cultured microbes and/or with genes that have been annotated by hierarchical classification schemes in various databases, such as KEGG. Communities can then be compared according to the distribution of functional groups in their microbiomes (in a manner analogous to taxon-based methods for 16S rRNA-based comparisons) and the results plotted by PCoA.

nutrients or for triggering immune responses that greatly affect other components of the microbiota.

The capacity to perform multiplex sequencing of bacterial 16S rRNA genes with highly parallel sequencers creates a problem: traditional tools for aligning sequences and defining taxonomic groups by their sequence similarity [a process known as *picking operational taxonomic units* (OTUs)] and traditional methods for phylogenetic analyses cannot handle the vast data sets involved. Emerging tools for performing large-scale alignments and large-scale taxon-based and phylogenetic analyses are starting to resolve this issue.

Both taxon-based methods (analyses based only on the OTUs present regardless of their evolutionary relationships) and phylogenetic methods (compositional analyses considered in light of the evolutionary relationships of community members) can be useful. The advantages of taxon-based methods are that they reveal directly which taxa contribute to the similarities and differences among samples (communities) and do not rely on possibly inaccurate tree reconstructions. The advantages of phylogenetic methods are that, with the same input data, they use a more accurate picture of evolution to provide clearer results than do taxon-based methods. Unlike taxon-based methods, phylogenetic methods do not assume that all taxa are equally related to one another.

UniFrac, a commonly used phylogenetic method that compares the evolutionary history encompassed within different microbial communities, can be used to compare any two communities by noting the degree to which they share branch length on a master tree of microbial life: the more similar communities are to one another, the more branch length they will share (Fig. 3-1). A matrix of UniFrac-based measurements of distances between each pair of communities can be generated and the results graphed by principal coordinates analysis (PCoA), nonmetric multidimensional scaling (NMDS), or other geometric techniques that project a high-dimensional data set down onto a small number of dimensions that can be visualized and analyzed conveniently. The resulting dimensions show, in descending order, orthogonal contributions to variation in the full data set (Fig. 3-1).

Another level of analysis entails estimation of the richness, or diversity, of a microbial community by plotting the number of different types of SSU rRNA sequences at a specific phylogenetic level (e.g., species, genus) that are identified in a sample as a function of the number of sequences collected. Diversity estimates typically are based on rarefaction procedures, which assess how many species (or genera, etc.) would have been observed in a given sample if only 100, 200, 300, or more sequences had been collected.

ASSEMBLING A BACTERIAL 16S RRNA-BASED ATLAS OF THE HUMAN BODY

At several levels, humans are very much alike: their *H. sapiens* genomes are >99% identical, and they have similar collections of human cells. However, microbial communities differ drastically both between people and between habitats within a single human body. The variation is greatest between body sites; for example, the difference between the microbial communities residing in a person's mouth and those residing in that person's gut is comparable to the difference between the communities found in soil and in seawater. Even within a body site, the differences between people are not subtle: both gut and hand communities can differ by 80–90% at the bacterial species level, although the degree of variation in the mouth appears to be somewhat less (see below). The poet John Donne said that "no man is an island"; from a microbial perspective, however, each person consists of not just one isolated island but a whole archipelago of distinct habitats that exchange microbes with one another and with the "outside" at some undetermined level.

As with other ecosystems, human body habitat–associated microbial communities vary over time, and an understanding of this variation is probably essential to a functional understanding of the human microbiota. For example, studies of forests would prove puzzling without an understanding of the succession of events during which plant communities change systematically over time from weedy species colonizing fields to large mature trees. One exciting area opened up by high-throughput sequencing is the potential for tracking multiple body locations in multiple individuals over time, with direct visualization of the flow of microbes among different body habitats and different individuals in the presence or absence of various perturbations, such as antibiotic administration.

International HMPs must address a number of issues during the cataloging of microbial communities that inhabit humans. How many people have to be sampled (breadth) and how extensively (depth) to get a true measure of the extent of microbial diversity in humans? Where and how can investigators consistently sample a defined region of body habitat? In sampling relatively inaccessible microbial communities deep in the interior of the body, how can the risk to the donor be minimized? Defining the spatial features of microbial community structure in the mouth and the skin poses a particularly daunting challenge; for example, there is evidence that each tooth in an individual has a distinctive microbiota and that brushing produces a dramatic, immediate reduction in diversity. How often and over what period should a human being be sampled? What are the effects of gender? What is the impact of a person's relationship to family members who may or may not be sharing living space? What demographic factors should be evaluated (e.g., rural versus urban)? What is the impact of culture, lifestyle, health status, medications, and *H. sapiens* genotype?

Ecologists, who study the macroscopic world of plants and animals, have shown that the composition of a community depends on the order of initial entry of the component species. The same thing is probably true in the microbial world. Studies of bacterial diversity in fecal samples obtained from young adult female mono- and dizygotic twin pairs and their mothers over time have revealed that (1) the communities with the greatest degree of similarity are those derived from the same individual, (2) the similarity in the gut bacterial communities

of adult monozygotic twin pairs is not significantly different in degree from the similarity of those of dizygotic twin pairs, and (3) fecal communities are more similar within family members than between members of different families. These results emphasize that early environmental exposures are a critical determinant of adult-gut microbial ecology. In humans, initial exposures depend on the mode of delivery. Babies sampled within 20 min of birth have relatively undifferentiated microbial communities in the mouth, the skin, and the gut. For vaginally delivered babies, these communities resemble the specific microbial communities found in the mother's vagina; for babies delivered by cesarean section, the communities resemble the mother's skin communities. The infant-gut microbiota changes to resemble the adult-gut community over the first 3 years of life and may continue to change throughout life. The stages at which communities in other body habitats reach their highly differentiated adult forms have not been determined.

An initial integrated view of the spatial and temporal distribution of bacteria in the human body has been obtained from a survey of communities of microbiota occupying 27 sites in a few healthy unrelated men and women. The body habitats sampled (on a given day for 2 consecutive days on two occasions separated by 3 months) included the gut (feces), the oral cavity, the external auditory canals, the inside of the nares, and 18 distinct skin locations **(Fig. 3-2)**. Across all body habitats, members of 22 bacterial phyla were detected, but the vast majority of sequences belonged to only four bacterial phyla: Actinobacteria (37%), Firmicutes (34%), Proteobacteria (12%), and Bacteroidetes (10%). UniFrac-based PCoA revealed strong primary clustering by body habitat; community composition was significantly less varied within than between habitats. Within habitats, the degree of variation was significantly less within individuals sampled over time than between individuals sampled on a specific day. Finally, after habitat and individual had been taken into account, the degree of variation was significantly less over 1 day than over 3 months. People's daily composite "whole-body" communities revealed perfect grouping by host and month, further emphasizing that the personal microbiota signature remains relatively stable over time.

Several surveys have emphasized that the skin harbors communities with predictable, albeit complex, biogeographic features (Fig. 3-2). To determine whether these

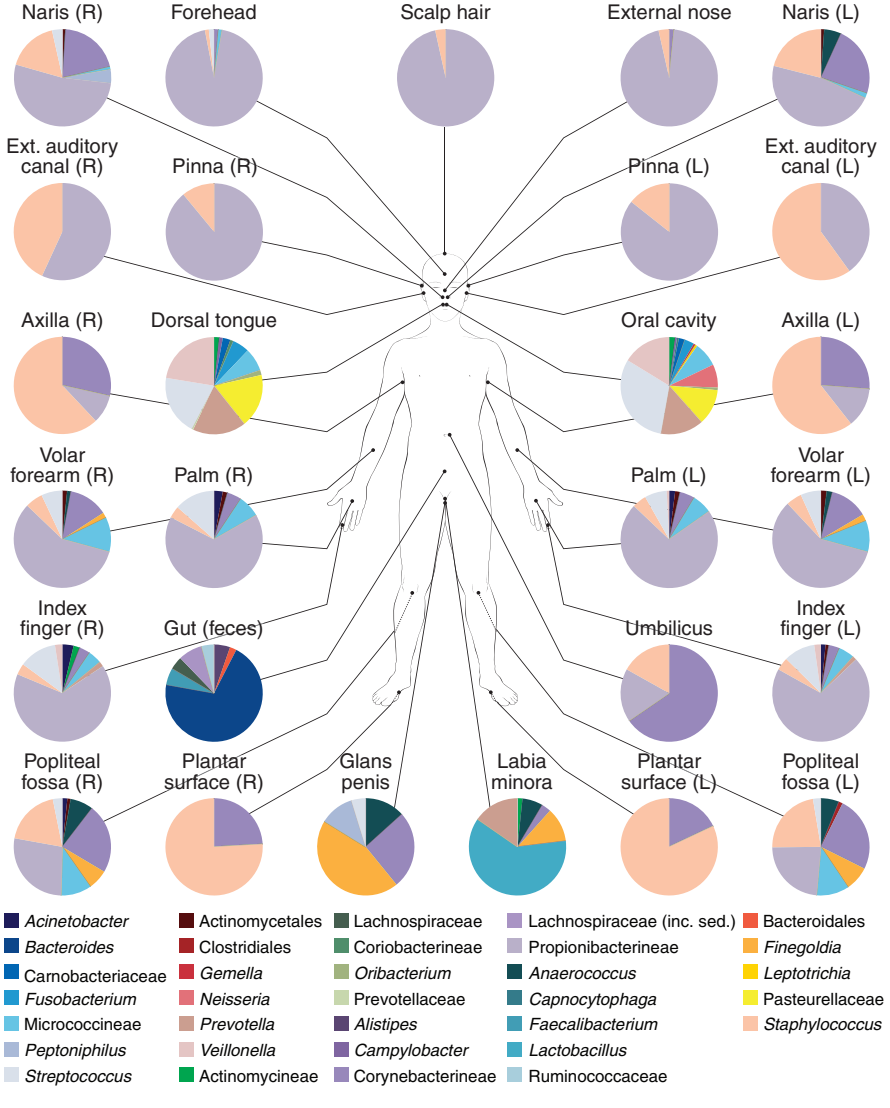


FIGURE 3-2
Results of a 16S rRNA gene sequence–based study of bacterial diversity in 27 body habitats of nine unrelated healthy human adults. The relative proportions of major phylogenetic groups present in the various microbial communities are shown. Note that skin communities occupying comparable positions on the right and left sides of the body are similar. (*Adapted from EK Costello et al: Science 326:1694, 2009.*)

differences reflect differences in local environmental factors, the history of the exposure of a specific site to microbes, or both, reciprocal microbiota transplantation has been performed in which microbial communities from one region of the skin are depleted by treatment with germicidal agents and the region (plot) is inoculated with a "foreign" microbiota harvested from different regions of the skin or from different body habitats from the same person or another individual. Community assembly at the site of transplantation subsequently is tracked over time. Remarkably, assembly proceeds differently at different sites: forearm plots receiving a tongue microbiota remained more similar to tongue communities than to native forearm communities in terms of their composition and diversity. However, forehead plots inoculated with tongue bacteria evolved to become more similar to native forehead communities. Thus, it appears that environmental factors operating at the forehead plot, in addition to the history of exposure to tongue bacteria, shaped community assembly.

These results underscore the need to specify body habitat when conducting microbial surveillance studies designed to examine the flow of normal and pathogenic organisms into and out of different body sites in inpatients and their health care providers. They also tie together several emerging themes from studies of human-associated microbial communities. Notably, there is a high level of *inter*personal variability in every body habitat studied to date. *Intra*personal variation in a specific body habitat is less marked, making longitudinal studies of microbial community ecology in a person before, during, or after a perturbation (e.g., dietary, pharmacologic) an attractive study option.

The resilience of human-associated microbial communities after perturbation has been addressed in several other contexts. One study showed that hand washing led to profound changes in the microbial community, greatly increasing diversity (presumably because of the preferential removal of high-abundance dominant phylotypes such as *Propionibacterium*). Within 6 h, the microbiota had rebounded to resemble the original hand communities. In adults, studies of a few individuals who took a 5-day course of ciprofloxacin showed that restoration of the fecal community after antibiotic administration took several months. Both the nature and the time course of restoration (reconfiguration) varied with the individual. Most previously present taxa returned, although in different proportions. The effects of antibiotics given during the first year of life on the assembly of the microbiota are ill defined. Are these effects transient or persistent? Is the diversity of the adult microbiota affected? Intriguingly, the "hygiene hypothesis" links the development of the human immune system to microbial exposures early in life. Increasing evidence indicates that fewer exposures and less conditioning are associated with an increased risk of allergic disorders such as asthma and various food sensitivities.

Bacterial 16S rRNA–based studies of the midvaginal microbiota in sexually active asymptomatic women have documented significant differences in community configurations among four self-reported ethnic groups (women of white, black, Hispanic, and Asian ancestry). Unlike most other body habitats surveyed, this ecosystem is dominated by a single genus, *Lactobacillus*. Four species of this genus together make up more than one-half the bacteria in most of these communities. Five community groups, designated I–V, have been defined. Four groups are dominated by *L. iners*, *L. crispatus*, *L. gasseri*, or *L. jensii,* whereas the fifth group includes proportionally fewer members of this genus and more anaerobes. The representation of these community categories was very distinctive within each of the four ethnic groups and correlated with vaginal pH and Nugent scores (a biomarker for bacterial vaginosis). Identification of the factors that determine the assembly of these distinct communities within and between ethnic groups as well as their resistance to or resilience after various physiologic or pathologic perturbations will require extensive longitudinal studies within individuals, including assessment of the impact of menstrual cycle, age, pregnancy, vaginal infections, and antibiotic use.

WHO ELSE IS THERE? OTHER BRANCHES OF THE TREE OF LIFE REPRESENTED IN THE HUMAN BODY

Surveys based on SSU rRNA sequencing have focused largely on bacteria, yet the census of "who's there" in human body habitat–associated communities ultimately must take into account the other two domains of life (Archaea and Eukarya) as well as viruses. The representation of the four major Archaea phyla (Euryarchaeota, Crenarchaeota, Nanoarchaeota, and Korarchaeota) in human microbial communities and their contributions to community functions are largely ill defined, in part because of the difficulty in optimizing Archaea-directed primer design. Some archaeons are known to play key roles in community metabolism. For example, methane-producing archaeons (methanogens) make up as many as 10% of all anaerobes in the feces of some humans, yet archaeal diversity in the gut microbiota appears to be low, with *Methanobrevibacter smithii* being the dominant species. Gut methanogens improve the efficiency of dietary polysaccharide degradation and fermentation by preventing the buildup of hydrogen gas, an end product of fermentation. It is not a particularly rewarding job: the task of coupling H_2 oxidation with CO_2 reduction to produce methane (CH_4) is one of the lowest-energy-yielding reactions known in biology.

Culture-independent surveys of eukaryotic diversity in body habitat–associated communities of microbiota have been very limited to date. Information about the representation of members of this domain of life has important implications for defining "normal"; for example, eukaryotic parasites are represented in millions of hosts living in various parts of the world and may be construed as a component of "normal" in these regions. Culture-independent analyses have relied on targeting

eukaryotic SSU rRNA genes that encode 18S rRNA as well as the internal transcribed spacer (ITS) regions of fungal rRNA genes. Metagenomic studies of the fecal microbiota of a few healthy human adults indicate that the degree of eukaryotic diversity is lower than that of bacterial diversity, with prominent representation of members of the genus *Blastocystis*—obligate anaerobes with a wide host range whose role as parasites or pathogens in the human gut ecosystem is not clear. The fecal microbiota of these healthy humans also harbored other fungal genera (*Galactomyces, Paecilomyces*, and *Gloeotinia*). As with bacteria, culture-independent and culture-based surveys provide very different pictures of community composition, with *Candida* species appearing dominant among cultivable fecal eukaryotes.

Viruses are *the* major predators on this microbe-dominated planet, determining which microbial strains survive. Most genetic diversity on Earth is viral: viruses move DNA from microbial host to microbial host, harboring host-derived genes as they evolve. The current view is that there are ~10 virus-like particles (VLPs) per microbial cell in virtually all microbial communities. Sequencing of VLP DNA from purified feces from a group of monozygotic twins and their mothers disclosed that prophages and phages constitute the majority of the virome, with a majority of the phages belonging to the Podoviridae. One survey found that most viral diversity in the distal gut was novel (<20% of VLP sequencing reads exhibited homology to known viruses) and that VLP sequences represented <5% of all fecal microbiome sequences. Time-course studies of the fecal virome revealed that viral populations—like bacterial populations—are most similar within an individual; i.e., interpersonal variation is greater than intrapersonal variation. Unlike bacterial populations, in which community composition is more similar among family members than among unrelated individuals, interpersonal variations in VLP-associated viral populations are not appreciably less pronounced within than between families.

THE MICROBIOME: CONVERGENT FUNCTIONS FROM DIFFERENT SPECIES ASSEMBLAGES

Characterization of the microbiome by shotgun sequencing is important because, unlike SSU rRNA analysis, this method provides a direct readout of the genes that are available to perform particular functions in a specific community. The central issues are (1) to what degree variation in species-level assemblages occupying particular body habitats correlates with variation in community gene content and (2) whether groups of genes are represented in a particular body habitat–associated community in most or all individuals. The neutral theory of community assembly developed by macroecologists posits that most species in a community will have the same general niche (profession) or will adopt the broadest niche possible, endowing the community with functional redundancy. If applicable to the microbial world, neutral community assembly would predict a high level of variation in the types of microbial lineages that occupy a specific body habitat in different individuals (as defined by SSU rRNA sequencing), although the broad functions encoded in the microbiomes of these communities could be quite similar. In addition, chemical food webs are generated when the metabolic product(s) of one type of microbe become the substrate(s) for other microbes. These webs can be incredibly elaborate and can change as microbes adjust their patterns of gene expression and metabolism in response to alterations in nutrient availability. Thus, the sum of all activities of members of a microbial community can be viewed as an emergent rather than a fixed property.

There are several key challenges in dealing with data obtained from shotgun sequencing of microbiomes. The first challenge is to attain a biomass sufficient for DNA recovery. Most human microbiome characterization has used fecal samples because they can be obtained readily in bulk quantities, 50% of the biomass of stool is microbial, and feces are an excellent proxy for depicting interpersonal differences in gut microbial ecology. At present, microbiome-level analyses typically are based on counts of reads assigned to specific taxa or functions. It is challenging to reconstruct metabolic pathways realistically for prediction of symbiotic, syntrophic, or antagonistic relationships among organisms. A number of databases are available for functional assignments; they employ various schemes for hierarchical classification. Unfortunately, the vast majority of these functional assignments are based on the very limited number of cultured organisms that have been subjected to direct experimental analyses.

Shotgun sequencing of the fecal microbiome has revealed that different microbial communities (species assemblages) converge on the same functional state. In other words, there is a group of microbial genes represented in the guts of unrelated as well as related individuals. This "core" microbiome is enriched in functions related to microbial survival in the gut (e.g., translation; nucleotide, carbohydrate, and amino acid metabolism) and in functions that benefit the host (nutrient and energy partitioning from the diet to microbes *and* host). Microbial genes whose proportional representation in gut communities varies among individuals and make up a "variable" microbiome. Pairwise comparisons have shown that family members have functionally more similar gut microbiomes than do unrelated individuals. Thus, intrafamilial transmission of a gut microbiome—which probably contains >100-fold more genes than the human genome—within a specific generation and across multiple generations could shape the biologic features of humans belonging to a kinship. This second dimension of human gene flow (the other occurring at the level of *H. sapiens* genes) could modulate/mediate risks for a variety of pathogenic states.

The generalizability of the observation that vastly different species assemblages converge on similar gene functional

repertoires in human body–associated habitats will have profound implications for an understanding of microbial functions in these different environments and the way these functions shape "human" physiologic and metabolic phenotypes. Issues such as the level of intra- and interpersonal variation in the gene content of the microbiome in various body habitats, the sampling depth required to characterize these differences, and the role of the *H. sapiens* genotype in shaping the microbiome genotype will be critical for informing this understanding.

EARLY EXAMPLES OF ASSOCIATIONS BETWEEN THE HUMAN MICROBIOTA AND DISEASE STATES

HMPs probably will expand the scientific view of what constitutes a pathogenic microbe. Pathogens currently are viewed as discrete phylotypes that are able to elicit disease in susceptible hosts; this attribution is, in the best circumstances, based on satisfying Koch's postulates. A more ecologic view is that pathogens do not function in isolation; rather, their invasions and/or emergence as well as their effects on the host reflect interactions with other members of a microbiota. An even more expansive view is that a number of co-occurring organisms can "conspire" to produce pathogenic effects in certain host and environmental contexts, forming a "pathologic community."

The relationships of microbiota and microbiome composition and their function to human diseases are being investigated in many HMPs. The rationale for hypotheses invoking a disease–microbiota/microbiome relationship in many cases emanates from gnotobiotic mouse models (i.e., mice raised in germ-free environments—with no exposure to microbes—and then colonized at specific stages of life with different microbial communities). Germ-free animals are compared with conventionally raised animals of similar genotype or with germ-free mice that have received a microbiota from a conventionally raised mouse donor with a defined phenotype. These comparisons have shown that the gut microbiota plays a key role in the maturation of the innate as well as the adaptive components of the immune system, that the microbiota is a key trigger in the development of inflammatory bowel disease (IBD) in animals that harbor mutations in genes associated with disease risk in humans, and that surface components of certain members of the gut microbiota can specifically modify the activity of the immune system to mitigate or prevent IBD. The risk of development of type 1 diabetes in genetically susceptible mice is modified by the gut microbiota; this fact provides additional evidence for the role of this microbial community in the pathogenesis of certain types of autoimmune disorders.

Gnotobiotic mice provide an excellent system for controlling host genotype, microbial community composition, diet, and housing conditions. Microbial communities harvested from donor mice of defined genotypes and physiologic phenotypes can be used to determine the impact of these communities on formerly germ-free recipients as well as the effect of the recipient on the transplanted microbiota and its microbiome. In this respect, gnotobiotic mice provide an opportunity to combine comparative metagenomic studies of donor communities with functional assays of community properties. Studies of gnotobiotic mice also have revealed that the gut microbiota plays a role in regulating the efficiency of energy and nutrient harvest from the diet; it does so not only by processing otherwise indigestible components of the diet (e.g., polysaccharides) but also by regulating host genes that affect energy storage in adipocytes. The microbiota influences the rate of epithelial turnover in the gut (the rate is slower in germ-free animals), modulates the development of the elaborate microvasculature that underlies the epithelium (capillary network density is markedly reduced in adult germ-free animals but can be restored to normal levels within 2 weeks after gut microbiota transplantation), is a key determinant of whether radiation enteritis follows abdominal or whole-body irradiation (germ-free mice are resistant), and influences gut motility. The impact of the gut microbiota extends beyond the gastrointestinal tract. Heart weight, whether measured echocardiographically or as wet mass and normalized to tibial length or lean body weight, is reduced significantly in germ-free mice; this difference is eliminated within 2 weeks after colonization with a gut microbiota. The presence or absence of a gut microbiota influences certain aspects of behavior, including locomotor activity. This observation raises the question of whether in this coevolved relationship microbes have developed strategies for manipulating certain features of host behavior that are mutually beneficial. For example, it is intriguing that plasma levels of serotonin are several-fold higher in conventionally raised mice than in germ-free mice.

Initial metagenomic studies of relatively small numbers of humans have provided insights into bacterial communities associated with several diseases, offering, for example, new ways to classify bacterial vaginosis, identifying alterations in the cutaneous bacterial communities of patients with psoriatic lesions, demonstrating shifts in the representation of various bacterial taxa in IBD, and revealing differences in the composition of the microbiota and microbiome in obese versus lean individuals as well as before and after bariatric surgery. The challenge provided by such observations is not only to expand the level of sampling to different populations of individuals but also to determine whether these associations are causal or only side effects of other processes.

Ongoing studies are exploring the impact of the microbiota on nutritional status, the development of *Clostridium difficile* colitis and its risk of relapse, the occurrence of necrotizing enterocolitis in premature newborns, the pathogenesis of diabetes, and various other metabolic phenotypes (*metabotypes*). These studies include assessment of the impact of the microbiota on drug metabolism. Comparisons of metabolites in the blood of germ-free and conventionally raised mice by nontargeted mass spectrometry have disclosed hundreds of compounds that are detectable in one but not

the other type of animal and whose concentrations are affected markedly by the microbiota. These include compounds that are conjugated with sulfate, glycine, glucuronide, or other charged adducts that also modify xenobiotics, potentially altering the capacity of the host to metabolize these foreign molecules. Analogous events are being observed in humans. For example, metabolism of the analgesic acetaminophen to either sulfonated or glucuronidated forms is associated with predose levels of *p*-cresol, a microbial tyrosine metabolite that competes with acetaminophen for its sulfonate donor and the relevant sulfotransferase enzyme. Higher levels of *p*-cresol correlate with decreased sulfonation and increased glucuronidation of acetaminophen.

An additional series of metagenomic studies is exploring antibiotic resistance reservoirs in human microbial communities. To this end, a recent study of fecal samples used expression cloning: taking random fragments of the microbiome, placing them in expression vectors in a bacterial host, and screening for antibiotic resistance phenotypes. A related study demonstrated that bacteria subsisting on antibiotics are widely distributed in the environment. Capable of degrading a variety of antibiotics, these organisms are extensively drug resistant, phylogenetically diverse, and in many cases related to pathogens; they also harbor many resistance genes identical to those in clinical pathogens.

The role of microbes in therapeutics extends to clinical trials of the impact of probiotics—most recovered from fermented dairy products—on various forms of IBD [pouchitis that occurs in both ileoanal (pull-through) pouches and continent ileostomies or in recurrent *C. difficile* colitis]. A number of questions raised about probiotics typify the issues that surround studies of the role of the microbiota and microbiome in disease pathogenesis and therapeutics. Is there a consistent configuration of the microbiota definable in the study population that is associated with a particular disease state? The answer has diagnostic and mechanistic implications. How is the configuration affected by the intervention? Is there an identifiable reconfiguration? If so, how does it proceed? Are there many routes? Are the pathways related to the initial pretreatment state? If a reconfiguration does occur, is it sustained after cessation of treatment? How is host biology related to the configuration or reconfiguration? As with all studies involving human microbial ecology, the issue of what constitutes a suitable reference control is extremely important: the person himself or herself? family members? age- and sex-matched individuals living in the same locale with similar cultural traditions?

IMPACT OF HMPs ON GENETIC DETERMINISM, PERSONAL IDENTITY, CULTURAL TRADITIONS, AND PERSONALIZED MEDICINE

Sets of mono- and dizygotic twins and their family members will be an extremely valuable resource for initially teasing out relationships between environmental exposures, *H. sapiens* genotype, and human microbial ecology. Similarly, monozygotic twins discordant for certain disease states represent a powerful paradigm that enhances the ability to determine whether various diseases (e.g., asthma, IBD, metabolic disorders) can be linked to a person's microbiota and microbiome. It will be important to explore microbial ecology in groups of individuals living in developing countries that are undergoing rapid transformations in lifestyle and experiencing the emergence of a variety of Western diseases. Birth cohort studies (including studies of twins) that are initiated every 10 years in these countries may capture the impact of changes in lifestyle, including diet, on human microbial ecology.

Defining the human metagenome (the genes embedded in the *H. sapiens* genome plus the microbiome) will provide an entirely new level of refinement to the human description of self as well as a potential microbial legacy of personal lifestyle choices. Although this information may promote an appreciation of the origins of certain health disparities, care must be taken to avoid stigmatization of individuals or groups of individuals who have different cultural norms or express different behaviors. Metagenomics is a new field through which to view the influence of cultural traditions on lifestyles and choices that in turn affect human microbial ecology. Cultural anthropologists must examine the impact of this field on the ways in which study volunteers who live in various cultural settings view the natural world that envelops them and the ways this field and their cultural traditions interact to influence their perceptions of forces that affect their lives or their connections to one another within the context of a family or community. The union of metagenomics and cultural anthropology can help reveal how cultural traditions (e.g., the way infants are handled and cared for in early life) influence the flow of microbes between generations of humans, thus shaping the physiologic and genetic features of a kinship.

Finally, although microbiome-directed/related diagnostics and therapeutics would represent a new and different dimension of personalized medicine, sensitivity to the societal impact of this work is essential. This field is changing the human sense of personal identity, relationships with the world, and genetic determinism. Studies of human microbiomes promise to uncover new gene and protein families and probably will reveal novel biotransformations by microbial communities that could have commercial and therapeutic implications. Assessing the microbiome's capacity to metabolize orally administered drugs may be highly instructive for the pharmaceutical industry as it investigates new and more accurate ways to predict drug bioavailability and toxicity. The chemical entities that human microbial communities synthesize to support mutually beneficial relationships with the host may become new classes of drugs; the human genes that these chemical entities target (manipulate) may represent new targets for drug discovery. Microbial strains harvested from the microbiota of people living in various parts of the world with varied diets and lifestyles could expand the repertoire of probiotic strains, including

strains that could be added to food to enhance its nutrient value. Microbes, microbial genes, and microbial products may serve as new and valuable biomarkers of physiologic status and distinctive biological properties. Thus, a microbial ecology scan may become a standard component of regular health examinations or a tool for forensic scientists. All these speculations raise questions about how microbial strains and whole microbial communities obtained from volunteers should be archived and distributed as well as about who owns these reagents and discoveries emanating from them.

SUMMARY

HMPs are an important manifestation of progress in the genome sciences, a timely step in the quest to achieve a better understanding of the place of humans in the natural world, and a reflection of the evolving focus of twenty-first-century medicine on disease prevention, new definitions of health, new ways to determine the origins of individual biological differences, and new approaches to elucidate how changes in lifestyle and biosphere affect human biology.

CHAPTER 4

IMMUNIZATION PRINCIPLES AND VACCINE USE

Anne Schuchat ■ Lisa A. Jackson

Few medical interventions of the past century can rival the effect that immunization has had on longevity, economic savings, and quality of life. Seventeen diseases are now preventable through vaccines routinely administered to children and adults in the United States (Table 4-1), and most vaccine-preventable diseases of childhood are at historically low levels (Table 4-2). Health care providers deliver the vast majority of vaccines in the United States in the course of providing routine health services and therefore play an integral role in the nation's public health system.

VACCINE IMPACT

Direct and indirect effects

Immunizations against specific infectious diseases protect individuals against infection and thereby prevent symptomatic illnesses. Specific vaccines may blunt the severity of clinical illness (e.g., rotavirus vaccines and severe gastroenteritis) or reduce complications (e.g., zoster vaccines and postherpetic neuralgia). Some immunizations also reduce transmission of infectious disease agents from immunized people to others, thereby reducing the impact of infection spread. This indirect impact is known as *herd immunity*. The level of immunization in a population that is required to achieve indirect protection of unimmunized people varies substantially with the specific vaccine.

Since childhood vaccines have become widely available in the United States, major declines in rates of vaccine-preventable diseases among both children and adults have become evident (Table 4-2). For example, vaccination of children <5 years of age against seven types of *Streptococcus pneumoniae* led to a >90% overall reduction in invasive disease caused by those types. A series of vaccines targeting 10 vaccine-preventable childhood diseases in a single birth cohort leads to prevention of 33,000 premature deaths and 14 million illnesses and saves $42 billion (U.S.): $9 billion in direct medical savings and $33 billion in indirect societal savings.

Control, elimination, and eradication of vaccine-preventable diseases

Immunization programs are associated with the goals of controlling, eliminating, or eradicating a disease. *Control* of a vaccine-preventable disease reduces illness outcomes and often limits the disruptive impacts associated with

TABLE 4-1

DISEASES THAT ARE NOW PREVENTABLE WITH VACCINES ROUTINELY ADMINISTERED IN THE UNITED STATES TO CHILDREN AND/OR ADULTS

CONDITION	TARGET POPULATION(S) FOR ROUTINE USE
Pertussis	Children, adolescents, adults
Diphtheria	Children, adolescents, adults
Tetanus	Children, adolescents, adults
Poliomyelitis	Children
Measles	Children
Mumps	Children
Rubella, congenital rubella syndrome	Children
Hepatitis B	Children
Haemophilus influenzae type b infection	Children
Hepatitis A	Children
Influenza	Children, adolescents, adults
Varicella	Children
Invasive pneumococcal disease	Children, older adults
Meningococcal disease	Children, adolescents
Rotavirus infection	Infants
Human papillomavirus infection, cervical cancer	Adolescent girls and women
Zoster	Older adults

TABLE 4-2

DECLINE IN VACCINE-PREVENTABLE DISEASES IN THE UNITED STATES FOLLOWING WIDESPREAD IMPLEMENTATION OF NATIONAL VACCINE RECOMMENDATIONS

CONDITION	ANNUAL NO. OF PREVACCINE CASES (AVERAGE)	NO. OF CASES REPORTED IN 2010[a]	REDUCTION (%) IN CASES AFTER WIDESPREAD VACCINATION
Smallpox	29,005	0	100
Diphtheria	21,053	0	100
Measles	530,217	61	≥99
Mumps	162,344	2,528	98
Pertussis	200,752	21,291	89
Polio (paralytic)	16,316	0	100
Rubella	47,745	6	>99
Congenital rubella syndrome	152	0	100
Tetanus	580	8	99
Haemophilus influenzae type b infection	20,000	270[b]	99
Hepatitis A	117,333	11,049	91
Hepatitis B (acute)	66,232	11,269	83
Invasive pneumococcal infection: all ages	63,067	44,000[c]	30
Invasive pneumococcal infection: <5 years of age	16,069	4,167[c]	74
Varicella	4,085,120	449,363	89.0

[a]Except for cases of hepatitis A, hepatitis B, and pneumococcal infection, for which 2008 figures are shown.
[b]Includes 16 type b infections and 254 infections caused by unknown types (<5 years of age).
[c]Data are from the CDC's Active Bacterial Core Surveillance Report; *www.cdc.gov/abcs/survreports/spneu08.pdf.*
Source: Adapted from SW Roush et al: JAMA 298:2155, 2007, with permission.

outbreaks of disease in communities, schools, and institutions. Control programs can also reduce absences from work for ill persons and for parents caring for sick children, decrease absences from school, and limit health care utilization associated with treatment visits.

Elimination of a disease is a more demanding goal than control, usually requiring the reduction to zero of cases in a defined geographic area but sometimes defined as reduction in the indigenous sustained transmission of an infection in a geographic area. As of 2010, the United States had eliminated indigenous transmission of measles, rubella, poliomyelitis, and diphtheria. Importation of pathogens from other parts of the world continues to be important, and public health efforts are intended to react promptly to such cases and to limit forward spread of the infectious agent.

Eradication of a disease is achieved when its elimination can be sustained without ongoing interventions. The only vaccine-preventable disease that has been globally eradicated thus far is smallpox. Although smallpox vaccine is no longer given routinely, the disease has not naturally reemerged because all chains of human transmission were interrupted through earlier vaccination efforts and humans were the only natural reservoir of the virus. Currently, a major health initiative is targeting the global eradication of polio. Sustained transmission of polio has been eliminated from most nations but has never been interrupted in four countries: Afghanistan, India, Nigeria, and Pakistan. Detection of a case of disease that has been targeted for eradication or elimination is considered a sentinel event that could permit the infectious agent to become reestablished in the community or region. Hence, such episodes must be promptly reported to public health authorities.

Outbreak detection and control

Clusters of cases of a vaccine-preventable disease detected in an institution, a medical practice, or a community may signal important changes in the pathogen, vaccine, or environment. Several factors can give rise to increases in vaccine-preventable disease, including (1) low rates of immunization that result in an accumulation of susceptible people (e.g., measles resurgence among vaccination abstainers); (2) changes in the infectious agent that permit it to escape vaccine-induced protection (e.g., nonvaccine-type pneumococci); (3) waning of vaccine-induced immunity (e.g., pertussis among adolescents and adults vaccinated in early childhood); and (4) point-source introductions of large inocula (e.g., food-borne exposure to hepatitis A virus). Reporting episodes of outbreak-prone diseases to public health authorities can facilitate recognition of clusters that require further interventions.

Public health reporting

Recognition of suspected cases of diseases targeted for elimination or eradication—along with other diseases that require urgent public health interventions, such as contact tracing, administration of chemo- or immunoprophylaxis, or epidemiologic investigation for common- source exposure)—is typically associated with special reporting requirements. Many diseases against which vaccines are routinely used, including measles, pertussis, *Haemophilus influenzae* invasive disease, and varicella, are nationally notifiable. Clinicians and laboratory staff have a responsibility to report some vaccine-preventable disease occurrences to local or state public health authorities according to specific case-definition criteria. All providers should be aware of state or city disease-reporting requirements and the best ways to contact public health authorities. A prompt response to vaccine-preventable disease outbreaks can greatly enhance the effectiveness of control measures.

Global considerations

Several international health initiatives currently focus on reducing vaccine-preventable diseases in regions throughout the world. These efforts include improving access to new and underutilized vaccines, such as pneumococcal conjugate, rotavirus, human papillomavirus (HPV), and meningococcal A conjugate vaccines. The American Red Cross, the World Health Organization (WHO), the United Nations Foundation, the United Nations Children's Fund (UNICEF), and the Centers for Disease Control and Prevention (CDC) are partners in the Measles Initiative, which targeted reduction of worldwide measles deaths by 90% from 2000 to 2010. During 2000–2008, global measles mortality rates declined by 78%—i.e., from an estimated 733,000 deaths in 2000 to 164,000 deaths in 2008. Rotary International, UNICEF, the CDC, and the WHO are leading partners in the global eradication of polio, an endeavor that reduced the annual number of paralytic polio cases from 350,000 in 1988 to <2000 in 2009. The GAVI Alliance and the Bill and Melinda Gates Foundation have brought substantial momentum to global efforts to reduce vaccine-preventable diseases, expanding on earlier efforts by the WHO, UNICEF, and governments in developed and developing countries.

Enhancing immunization in adults

Although immunization has become a centerpiece of routine pediatric medical visits, it has not been as well integrated into routine health care visits for adults. This chapter focuses on immunization principles and vaccine use in adults.Accumulating evidence suggests that immunization coverage can be increased through efforts directed at consumer-, provider-, institution-, and system-level factors. The literature suggests that the application of multiple strategies is more effective at raising coverage rates than is the use of any single strategy.

Recommendations for adult immunizations

The CDC's Advisory Committee on Immunization Practices (ACIP) is the main source of recommendations for use of vaccines licensed by the U.S. Food and Drug Administration (FDA) for children and adults in the U.S. civilian population. The ACIP is a federal advisory committee that consists of 15 voting members (experts in fields associated with immunization) appointed by the Secretary of the U.S. Department of

Health and Human Services; 8 ex officio members representing federal agencies; and 26 nonvoting representatives of various liaison organizations, including major medical societies and managed-care organizations. The ACIP recommendations are available at *www.cdc.gov/vaccines/pubs/ACIP-list.htm*. These recommendations are harmonized to the greatest extent possible with vaccine recommendations made by other organizations, including the American College of Obstetricians and Gynecologists, the American Academy of Family Physicians, and the American College of Physicians.

Adult immunization schedules

Immunization schedules for adults in the United States are updated annually and can be found online (*www.cdc.gov/vaccines/recs/schedules/adult-schedule.htm*). In January, the schedules are published in *American Family Physician*, the *Annals of Internal Medicine*, and *Morbidity and Mortality Weekly Report* (*www.cdc.gov/mmwr*). The adult immunization schedules for 2011 are summarized in **Fig. 4-1**. Additional information and specifications are contained in the footnotes to these schedules. In the time between annual publications, additions and changes to schedules are published as Notices to Readers in *Morbidity and Mortality Weekly Report*.

IMMUNIZATION PRACTICE STANDARDS

Administering immunizations to adults involves a number of processes, such as deciding whom to vaccinate, assessing vaccine contraindications and precautions, providing vaccine information statements (VISs), ensuring appropriate storage and handling of vaccines, administering vaccines, and maintaining vaccine records. In addition, provider reporting of adverse events that follow vaccination is an essential component of the vaccine safety monitoring system.

Deciding whom to vaccinate

Every effort should be made to ensure that adults receive all indicated vaccines as expeditiously as possible. When adults present for care, their immunization history should be assessed and recorded, and this information should be used to identify needed vaccinations according to the most current version of the adult immunization schedule. Decision-support tools incorporated into electronic health records can provide prompts for needed vaccinations. Standing orders, which are often used for routinely indicated vaccines (e.g., influenza and pneumococcal vaccines), permit a nurse or another approved licensed practitioner to administer vaccines without a specific physician order, thus lowering barriers to adult immunization.

Assessing contraindications and regulations

Before vaccination, all patients should be screened for contraindications and precautions. A *contraindication* is a condition that is believed to substantially increase the risk of a serious adverse reaction to vaccination. A vaccine should not be administered when a contraindication is documented. For example, a history of an anaphylactic reaction to a dose of vaccine or to a vaccine component is a contraindication for further doses. A *precaution* is a condition that may increase the risk of an adverse event or that may compromise the ability of the vaccine to evoke immunity (e.g., administering measles vaccine to a person who has recently received a blood transfusion and may consequently have transient passive immunity to measles). Normally, a vaccine is not administered when a precaution is noted. However, situations may arise when the benefits of vaccination outweigh the estimated risk of an adverse event, and the provider may decide to vaccinate the patient despite the precaution.

In some cases, contraindications and precautions are temporary and may lead to mere deferral of vaccination until a later time. For example, moderate or severe febrile illnesses are generally considered transient precautions to vaccination and result in postponement of vaccine administration until the acute phase has resolved; thus the superimposition of adverse effects of vaccination on the underlying illness and the mistaken attribution of a manifestation of the underlying illness to the vaccine are avoided. Contraindications and precautions to vaccines licensed in the United States for use in civilian adults are summarized in **Table 4-3**. It is important to recognize conditions that are *not* contraindications in order not to miss opportunities for vaccination. For example, in most cases, mild acute illness (with or without low-grade fever), a history of a mild to moderate local reaction to a previous dose of the vaccine, and breastfeeding are not contraindications to vaccination.

History of immediate hypersensitivity to a vaccine component

A severe allergic reaction (e.g., anaphylaxis) to a previous dose of a vaccine or to one of its components is a contraindication to vaccination. While most vaccines have many components, substances to which individuals are most likely to have had a severe allergic reaction include egg protein, gelatin, and yeast. In addition, although natural rubber (latex) is not a vaccine component, some vaccines are supplied in vials or syringes that contain natural rubber. These vaccines can be identified by the product insert and should not be administered to persons who report a severe (anaphylactic) allergy to latex. The much more common local or contact hypersensitivity to latex is *not* a contraindication to administration of a vaccine supplied in a vial or syringe that contains latex. Vaccines that, as of April 2009, were sometimes supplied in a vial or syringe containing natural rubber included Havrix hepatitis A vaccine (syringe), Vaqta hepatitis A vaccine (vial and syringe), Engerix-B hepatitis B vaccine (syringe), Recombivax HB hepatitis B vaccine (vial), Boostrix Tdap vaccine (syringe), and Menomune meningococcal polysaccharide vaccine (vial).

Pregnancy

Live-virus vaccines are contraindicated during pregnancy because of the possibility that vaccine virus

Recommended Adult Immunization Schedule
UNITED STATES - 2011

Note: These recommendations *must* be read with the footnotes that follow containing number of doses, intervals between doses, and other important information.

Recommended adult immunization schedule, by vaccine and age group

VACCINE / AGE GROUP	19–26 years	27–49 years	50–59 years	60–64 years	≥65 years
Influenza[1,*]	1 dose annually				
Tetanus, diphtheria, pertussis (Td/Tdap)[2,*]	Substitute 1-time dose of Tdap for Td booster; then boost with Td every 10 yrs				Td booster every 10 yrs
Varicella[3,*]	2 doses				
Human papillomavirus (PHV)[4,*]	3 doses (females)				
Zoster[5]				1 dose	
Measles, mumps, rubella (MMR)[6,*]	1 or 2 doses		1 dose		
Pneumococcal (polysaccharide)[7,8]	1 or 2 doses				1 dose
Meningococcal[9,*]	1 or more doses				
Hepatitis A[10,*]	2 doses				
Hepatitis B[11,*]	3 doses				

*Covered by the Vaccine Injury Compensation Program.

For all persons in this category who meet the age requirements and who lack evidence of immunity (e.g., lack documentation of vaccination or have no evidence of previous infection)

Recommended if some other risk factor is present (e.g., based on medical, occupational, lifestyle, or other indications)

No recommendation

Report all clinically significant postvaccination reactions to the Vaccine Adverse Event Reporting System (VAERS). Reporting forms and instructions on filing a VAERS report are available at http://www.vaers.hhs.gov or by telephone, 800-822-7967.

Information on how to file a Vaccine Injury Compensation Program claim is available at http://www.hrsa.gov/vaccinecompensation or by telephone, 800-338-2382. Information about filing a claim for vaccine injury is available through the U.S. Court of Federal Claims, 717 Madison Place, N.W., Washington, D.C. 20005; telephone, 202-357-6400.

Additional information about the vaccines in this schedule, extent of available data, and contraindications for vaccination also is available at http://www.cdc.gov/vaccines or from the CDC-INFO Contact Center at 800-CDC- INFO (800-232-4636) in English and Spanish, 24 hours a day, 7 days a week.

Vaccines that might be indicated for adults based on medical and other indications

VACCINE / INDICATION	Pregnancy	Immuno-compromising conditions (excluding human immunodeficiency virus [HIV])[3,5,6,13]	HIV infection[3,6,12,13] CD4+ T lympho-cyte count <200 cells/µL	HIV infection[3,6,12,13] CD4+ T lympho-cyte count ≥200 cells/µL	Diabetes, heart disease, chronic lung disease, chronic alcoholism	Asplenia[12] (including elective splenectomy) and persistent complement component deficiencies	Chronic liver disease	Kidney failure, end-stage renal disease, receipt of hemodialysis	Healthcare personnel
Influenza[1,*]	1 dose TIV annually								1 dose TIV or LAIV annually
Tetanus, diphtheria, pertussis (Td/Tdap)[2,*]	Td	Substitute 1-time dose of Tdap for Td booster; then boost with Td every 10 yrs							
Varicella[3,*]	Contraindicated		2 doses						
Human papillomavirus (HPV)[4,*]		3 doses through age 26 yrs							
Zoster[5]	Contraindicated			1 dose					
Measles, mumps, rubella (MMR)[6,*]	Contraindicated		1 or 2 doses						
Pneumococcal (polysaccharide)[7,8]		1 or 2 doses							
Meningococcal[9,*]	1 or more doses								
Hepatitis A[10,*]	2 doses								
Hepatitis B[11,*]				3 doses					

*Covered by the Vaccine Injury Compensation Program.

For all persons in this category who meet the age requirements and who lack evidence of immunity (e.g., lack documentation of vaccination or have no evidence of previous infection)

Recommended if some other risk factor is present (e.g., on the basis of medical, occupational, lifestyle, or other indications)

No recommendation

These schedules indicate the recommended age groups and medical indications for which administration of currently licensed vaccines is commonly indicated for adults ages 19 years and older, as of February 4, 2011. For all vaccines being recommended on the adult immunization schedule, a vaccine series does not need to be restarted, regardless of the time that has elapsed between doses. Licensed combination vaccines may be used whenever any components of the combination are indicated and when the vaccine's other components are not contraindicated. For detailed recommendations on all vaccines, including those used primarily for travelers or that are issued during the year, consult the manufacturers' package inserts and the complete statements from the Advisory Committee on Immunization Practices (http:// www.cdc.gov/vaccines/pubs/acip-list.htm).

The recommendations in this schedule were approved by the Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP), the American Academy of Family Physicians (AAFP), the American College of Obstetricians and Gynecologists (ACOG), and the American College of Physicians (ACP).

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION

CDC

FIGURE 4-1

Recommended adult immunization schedules, United States, 2011. For complete statements by the Advisory Committee on Immunization Practices (ACIP), visit *www.cdc.gov/vaccines/pubs/ACIP-list.htm*.

1. Influenza vaccination Annual vaccination against influenza is recommended for all persons aged 6 months and older, including all adults. Healthy, nonpregnant adults aged less than 50 years without high-risk medical conditions can receive either intranasally administered live, attenuated influenza vaccine (FluMist), or inactivated vaccine. Other persons should receive the inactivated vaccine. Adults aged 65 years and older can receive the standard influenza vaccine or the high-dose (Fluzone) influenza vaccine. Additional information about influenza vaccination is available at *http://www.cdc.gov/vaccines/vpd-vac/flu/default.htm*.

2. Tetanus, diphtheria, and acellular pertussis (Td/Tdap) vaccination Administer a one-time dose of Tdap to adults aged less than 65 years who have not received Tdap previously or for whom vaccine status is unknown to replace one of the 10-year Td boosters, and as soon as feasible to all 1) postpartum women, 2) close contacts of infants younger than age 12 months (e.g., grandparents and child-care providers), and 3) healthcare personnel with direct patient contact. Adults aged 65 years and older who have not previously received Tdap and who have close contact with an infant aged less than 12 months also should be vaccinated. Other adults aged 65 years and older may receive Tdap. Tdap can be administered regardless of interval since the most recent tetanus or diphtheria-containing vaccine.

Adults with uncertain or incomplete history of completing a 3-dose primary vaccination series with Td-containing vaccines should begin or complete a primary vaccination series. For unvaccinated adults, administer the first 2 doses at least 4 weeks apart and the third dose 6–12 months after the second. If incompletely vaccinated (i.e., less than 3 doses), administer remaining doses. Substitute a one-time dose of Tdap for one of the doses of Td, either in the primary series or for the routine booster, whichever comes first.

If a woman is pregnant and received the most recent Td vaccination 10 or more years previously, administer Td during the second or third trimester. If the woman received the most recent Td vaccination less than 10 years previously, administer Tdap during the immediate postpartum period. At the clinician's discretion, Td may be deferred during pregnancy and Tdap substituted in the immediate postpartum period, or Tdap may be administered instead of Td to a pregnant woman after an informed discussion with the woman.

The ACIP statement for recommendations for administering Td as prophylaxis in wound management is available at *http://www.cdc.gov/vaccines/pubs/acip-list.htm.*

3. Varicella vaccination All adults without evidence of immunity to varicella should receive 2 doses of single-antigen varicella vaccine if not previously vaccinated or a second dose if they have received only 1 dose, unless they have a medical contraindication. Special consideration should be given to those who 1) have close contact with persons at high risk for severe disease (e.g., healthcare personnel and family contacts of persons with immunocompromising conditions) or 2) are at high risk for exposure or transmission (e.g., teachers; child-care employees; residents and staff members of institutional settings, including correctional institutions; college students; military personnel; adolescents and adults living in households with children; nonpregnant women of childbearing age; and international travelers).

Evidence of immunity to varicella in adults includes any of the following: 1) documentation of 2 doses of varicella vaccine at least 4 weeks apart; 2) U.S.-born before 1980 (although for healthcare personnel and pregnant women, birth before 1980 should not be considered evidence of immunity); 3) history of varicella based on diagnosis or verification of varicella by a healthcare provider (for a patient reporting a history of or having an atypical case, a mild case, or both, healthcare providers should seek either an epidemiologic link with a typical varicella case or to a laboratory-confirmed case or evidence of laboratory confirmation, if it was performed at the time of acute disease); 4) history of herpes zoster based on diagnosis or verification of herpes zoster by a healthcare provider; or 5) laboratory evidence of immunity or laboratory confirmation of disease.

Pregnant women should be assessed for evidence of varicella immunity. Women who do not have evidence of immunity should receive the first dose of varicella vaccine upon completion or termination of pregnancy and before discharge from the healthcare facility. The second dose should be administered 4–8 weeks after the first dose.

4. Human papillomavirus (HPV) vaccination HPV vaccination with either quadrivalent (HPV4) vaccine or bivalent vaccine (HPV2) is recommended for females at age 11 or 12 years and catch-up vaccination for females aged 13 through 26 years.

Ideally, vaccine should be administered before potential exposure to HPV through sexual activity; however, females who are sexually active should still be vaccinated consistent with age-based recommendations. Sexually active females who have not been infected with any of the four HPV vaccine types (types 6, 11, 16, and 18, all of which HPV4 prevents) or any of the two HPV vaccine types (types 16 and 18, both of which HPV2 prevents) receive the full benefit of the vaccination. Vaccination is less beneficial for females who have already been infected with one or more of the HPV vaccine types. HPV4 or HPV2 can be administered to persons with a history of genital warts, abnormal Papanicolaou test, or positive HPV DNA test, because these conditions are not evidence of previous infection with all vaccine HPV types.

HPV4 may be administered to males aged 9 through 26 years to reduce their likelihood of genital warts. HPV4 would be most effective when administered before exposure to HPV through sexual contact.

A complete series for either HPV4 or HPV2 consists of 3 doses. The second dose should be administered 1–2 months after the first dose; the third dose should be administered 6 months after the first dose.

Although HPV vaccination is not specifically recommended for persons with the medical indications described in the lower panel ("Vaccines that might be indicated for adults based on medical and other indications"), it may be administered to these persons because the HPV vaccine is not a live-virus vaccine. However, the immune response and vaccine efficacy might be less for persons with the medical indications described in the lower panel than in persons who do not have the medical indications described or who are immunocompetent.

(*continued*)

FIGURE 4-1 (*Continued*)

5. Herpes zoster vaccination A single dose of zoster vaccine is recommended for adults aged 60 years and older regardless of whether they report a previous episode of herpes zoster. Persons with chronic medical conditions may be vaccinated unless their condition constitutes a contraindication.

6. Measles, mumps, rubella (MMR) vaccination Adults born before 1957 generally are considered immune to measles and mumps. All adults born in 1957 or later should have documentation of 1 or more doses of MMR vaccine unless they have a medical contraindication to the vaccine, laboratory evidence of immunity to each of the three diseases, or documentation of provider-diagnosed measles or mumps disease. For rubella, documentation of provider-diagnosed disease is not considered acceptable evidence of immunity.

Measles component: A second dose of MMR vaccine, administered a minimum of 28 days after the first dose, is recommended for adults who 1) have been recently exposed to measles or are in an outbreak setting; 2) are students in postsecondary educational institutions; 3) work in a healthcare facility; or 4) plan to travel internationally. Persons who received inactivated (killed) measles vaccine or measles vaccine of unknown type during 1963–1967 should be revaccinated with 2 doses of MMR vaccine.

Mumps component: A second dose of MMR vaccine, administered a minimum of 28 days after the first dose, is recommended for adults who 1) live in a community experiencing a mumps outbreak and are in an affected age group; 2) are students in postsecondary educational institutions; 3) work in a healthcare facility; or 4) plan to travel internationally. Persons vaccinated before 1979 with either killed mumps vaccine or mumps vaccine of unknown type who are at high risk for mumps infection (e.g. persons who are working in a healthcare facility) should be revaccinated with 2 doses of MMR vaccine.

Rubella component: For women of childbearing age, regardless of birth year, rubella immunity should be determined. If there is no evidence of immunity, women who are not pregnant should be vaccinated. Pregnant women who do not have evidence of immunity should receive MMR vaccine upon completion or termination of pregnancy and before discharge from the healthcare facility.

Healthcare personnel born before 1957: For unvaccinated healthcare personnel born before 1957 who lack laboratory evidence of measles, mumps, and/or rubella immunity or laboratory confirmation of disease, healthcare facilities should 1) consider routinely vaccinating personnel with 2 doses of MMR vaccine at the appropriate interval (for measles and mumps) and 1 dose of MMR vaccine (for rubella), and 2) recommend 2 doses of MMR vaccine at the appropriate interval during an outbreak of measles or mumps, and 1 dose during an outbreak of rubella. Complete information about evidence of immunity is available at *http://www.cdc.gov/vaccines/recs/provisional/default.htm.*

7. Pneumococcal polysaccharide (PPSV) vaccination Vaccinate all persons with the following indications:

Medical: Chronic lung disease (including asthma); chronic cardiovascular diseases; diabetes mellitus; chronic liver diseases; cirrhosis; chronic alcoholism; functional or anatomic asplenia (e.g., sickle cell disease or splenectomy [if elective splenectomy is planned, vaccinate at least 2 weeks before surgery]); immunocompromising conditions (including chronic renal failure or nephrotic syndrome); and cochlear implants and cerebrospinal fluid leaks. Vaccinate as close to HIV diagnosis as possible.

Other: Residents of nursing homes or long-term care facilities and persons who smoke cigarettes. Routine use of PPSV is not recommended for American Indians/Alaska Natives or persons aged less than 65 years unless they have underlying medical conditions that are PPSV indications. However, public health authorities may consider recommending PPSV for American Indians/Alaska Natives and persons aged 50 through 64 years who are living in areas where the risk for invasive pneumococcal disease is increased.

8. Revaccination with PPSV One-time revaccination after 5 years is recommended for persons aged 19 through 64 years with chronic renal failure or nephrotic syndrome; functional or anatomic asplenia (e.g., sickle cell disease or splenectomy); and for persons with immunocompromising conditions. For persons aged 65 years and older, one-time revaccination is recommended if they were vaccinated 5 or more years previously and were aged less than 65 years at the time of primary vaccination.

9. Meningococcal vaccination Meningococcal vaccine should be administered to persons with the following indications:

Medical: A 2-dose series of meningococcal conjugate vaccine is recommended for adults with anatomic or functional asplenia, or persistent complement component deficiencies. Adults with HIV infection who are vaccinated should also receive a routine 2-dose series. The 2 doses should be administered at 0 and 2 months.

Other: A single dose of meningococcal vaccine is recommended for unvaccinated first-year college students living in dormitories; microbiologists routinely exposed to isolates of *Neisseria meningitidis*; military recruits; and persons who travel to or live in countries in which meningococcal disease is hyperendemic or epidemic (e.g., the "meningitis belt" of sub-Saharan Africa during the dry season [December through June]), particularly if their contact with local populations will be prolonged. Vaccination is required by the government of Saudi Arabia for all travelers to Mecca during the annual Hajj.

Meningococcal conjugate vaccine, quadrivalent (MCV4) is preferred for adults with any of the preceding indications who are aged 55 years and younger; meningococcal polysaccharide vaccine (MPSV4) is preferred for adults aged 56 years and older. Revaccination with MCV4 every 5 years is recommended for adults previously vaccinated with MCV4 or MPSV4 who remain at increased risk for infection (e.g., adults with anatomic or functional asplenia, or persistent complement component deficiencies).

10. Hepatitis A vaccination Vaccinate persons with any of the following indications and any person seeking protection from hepatitis A virus (HAV) infection:

Behavioral: Men who have sex with men and persons who use injection drugs.

Occupational: Persons working with HAV-infected primates or with HAV in a research laboratory setting.

Medical: Persons with chronic liver disease and persons who receive clotting factor concentrates.

Other: Persons traveling to or working in countries that have high or intermediate endemicity of hepatitis A (a list of countries is available at *http://wwwn.cdc.gov/travel/content-diseases.aspx*).

(*continued*)

FIGURE 4-1 (*Continued*)

Unvaccinated persons who anticipate close personal contact (e.g., household or regular babysitting) with an international adoptee during the first 60 days after arrival in the United States from a country with high or intermediate endemicity should be vaccinated. The first dose of the 2-dose hepatitis A vaccine series should be administered as soon as adoption is planned, ideally 2 or more weeks before the arrival of the adoptee.

Single-antigen vaccine formulations should be administered in a 2-dose schedule at either 0 and 6–12 months (Havrix), or 0 and 6–18 months (Vaqta). If the combined hepatitis A and hepatitis B vaccine (Twinrix) is used, administer 3 doses at 0, 1, and 6 months; alternatively, a 4-dose schedule may be used, administered on days 0, 7, and 21–30, followed by a booster dose at month 12.

11. Hepatitis B vaccination Vaccinate persons with any of the following indications and any person seeking protection from hepatitis B virus (HBV) infection:

Behavioral: Sexually active persons who are not in a long-term, mutually monogamous relationship (e.g., persons with more than one sex partner during the previous 6 months); persons seeking evaluation or treatment for a sexually transmitted disease (STD); current or recent injection-drug users; and men who have sex with men.

Occupational: Healthcare personnel and public-safety workers who are exposed to blood or other potentially infectious body fluids.

Medical: Persons with end-stage renal disease, including patients receiving hemodialysis; persons with HIV infection; and persons with chronic liver disease.

Other: Household contacts and sex partners of persons with chronic HBV infection; clients and staff members of institutions for persons with developmental disabilities; and international travelers to countries with high or intermediate prevalence of chronic HBV infection (a list of countries is available at *http://wwwn.cdc.gov/travel/contentdiseases.aspx*).

Hepatitis B vaccination is recommended for all adults in the following settings: STD treatment facilities; HIV testing and treatment facilities; facilities providing drug-abuse treatment and prevention services; healthcare settings targeting services to injection-drug users or men who have sex with men; correctional facilities; end-stage renal disease programs and facilities for chronic hemodialysis patients; and institutions and nonresidential day-care facilities for persons with developmental disabilities.

Administer missing doses to complete a 3-dose series of hepatitis B vaccine to those persons not vaccinated or not completely vaccinated. The second dose should be administered 1 month after the first dose; the third dose should be given at least 2 months after the second dose (and at least 4 months after the first dose). If the combined hepatitis A and hepatitis B vaccine (Twinrix) is used, administer 3 doses at 0, 1, and 6 months; alternatively, a 4-dose Twinrix schedule, administered on days 0, 7, and 21 to 30, followed by a booster dose at month 12 may be used.

Adult patients receiving hemodialysis or with other immunocompromising conditions should receive 1 dose of 40 μg/mL (Recombivax HB) administered on a 3-dose schedule or 2 doses of 20 μg/mL (Engerix-B) administered simultaneously on a 4-dose schedule at 0, 1, 2, and 6 months.

12. Selected conditions for which *Haemophilus influenzae* type b (Hib) vaccine may be used 1 dose of Hib vaccine should be considered for persons who have sickle cell disease, leukemia, or HIV infection, or who have had a splenectomy, if they have not previously received Hib vaccine.

13. Immunocompromising conditions Inactivated vaccines generally are acceptable (e.g., pneumococcal, meningococcal, influenza [inactivated influenza vaccine]) and live vaccines generally are avoided in persons with immune deficiencies or immunocompromising conditions. Information on specific conditions is available at *http://www.cdc.gov/vaccines/pubs/acip-list.htm*.

replication will cause congenital infection or have other adverse effects on the fetus. Most live-virus vaccines, including varicella vaccine, are not secreted in breast milk; therefore, breast-feeding is not a contraindication for live-virus or other vaccines. Pregnancy is not a contraindication to administration of inactivated vaccines, but most are avoided during pregnancy because relevant safety data are limited. The only vaccine routinely recommended for women in the United States who are or will be pregnant during influenza season is trivalent inactivated influenza vaccine. Some other vaccines, such as tetanus and diphtheria toxoid (Td) vaccine and tetanus and diphtheria toxoid and acellular pertussis (Tdap) vaccine, may be given to pregnant women in certain circumstances. Resurgence of pertussis in some areas has prompted greater use of Tdap in pregnancy.

Immunosuppression

Live-virus vaccines elicit an immune response due to replication of the attenuated (weakened) vaccine virus that is contained by the recipient's immune system. In persons with compromised immune function, enhanced replication of vaccine viruses is possible and could lead to disseminated infection with the vaccine virus. For this reason, live-virus vaccines are contraindicated for persons with severe immunosuppression, defined according to the specific vaccine on the basis—at least in part—of differences in the prevalence of conditions causing immunosuppression at the time of vaccine recommendation issuance. Severe immunosuppression may be caused by many disease conditions, including HIV infection and hematologic or generalized malignancy. In some of these conditions, all affected persons are severely immunocompromised. In others (e.g., HIV infection), the degree to which the immune system is compromised depends on the severity of the condition, which in turn depends on the stage of disease or treatment. Severe immunosuppression may also be due to therapy with immunosuppressive agents, including high-dose glucocorticoids. In this situation, the dose, duration, and route of administration may influence the degree of immunosuppression.

The definition of severe immunosuppression that is a contraindication to zoster vaccine—the most recently licensed live-virus vaccine for adults—may be used as

TABLE 4-3

CONTRAINDICATIONS AND PRECAUTIONS FOR COMMONLY USED VACCINES IN ADULTS

VACCINE FORMULATION	CONTRAINDICATIONS AND PRECAUTIONS
All vaccines	**Contraindication** Severe allergic reaction (e.g., anaphylaxis) after a previous vaccine dose or to a vaccine component **Precaution** Moderate or severe acute illness with or without fever; defer vaccination until illness resolves
Td	**Precautions** GBS within 6 weeks after a previous dose of TT-containing vaccine History of Arthus-type hypersensitivity reactions after a previous dose of TT-containing vaccine; defer vaccination until at least 10 years have elapsed since the last dose
Tdap	**Contraindication** History of encephalopathy (e.g., coma or prolonged seizures) not attributable to another identifiable cause within 7 days of administration of a vaccine with pertussis components, such as DTaP or Tdap **Precautions** GBS within 6 weeks after a previous dose of TT-containing vaccine Unstable neurologic condition (e.g., cerebrovascular events and acute encephalopathic conditions) History of Arthus-type hypersensitivity reactions after a previous dose of TT-containing and/or DT-containing vaccine, including MCV4; defer vaccination until at least 10 years have elapsed since the last dose Pregnancy
HPV	**Contraindication** History of immediate hypersensitivity to yeast (for Gardasil) **Precaution** Pregnancy. If a woman is found to be pregnant after initiation of the vaccination series, the remainder of the 3-dose regimen should be delayed until after completion of the pregnancy. If a vaccine dose has been administered during pregnancy, no intervention is needed. A vaccine-in-pregnancy registry has been established for Gardasil; patients and health care providers should report any exposure to quadrivalent HPV vaccine during pregnancy (telephone: 800-986-8999).
MMR	**Contraindications** History of immediate hypersensitivity reaction to gelatin[a] or neomycin Pregnancy Known severe immunodeficiency (e.g., hematologic and solid tumors; chemotherapy; congenital immunodeficiency; long-term immunosuppressive therapy; severe immunocompromise due to HIV infection) **Precaution** Recent (within 11 months) receipt of antibody-containing blood product
Varicella	**Contraindications** Pregnancy Known severe immunodeficiency History of immediate hypersensitivity reaction to gelatin[a] or neomycin **Precaution** Recent (within 11 months) receipt of antibody-containing blood product
Influenza, injectable, trivalent	**Contraindication** History of immediate hypersensitivity reaction to eggs[b] **Precautions** History of GBS within 6 weeks after a previous influenza vaccine dose Pregnancy is *not* a contraindication or precaution. This vaccine is recommended for women who will be pregnant during influenza season.
Influenza, live attenuated	**Contraindications** History of immediate hypersensitivity reaction to eggs[b] Age ≥50 years Pregnancy Immunosuppression, including that caused by medications or by HIV infection; known severe immunodeficiency (e.g., hematologic and solid tumors; chemotherapy; congenital immunodeficiency; long-term immunosuppressive therapy; severe immunocompromise due to HIV infection) Certain chronic medical conditions, such as diabetes mellitus; chronic pulmonary disease (including asthma); chronic cardiovascular disease (except hypertension); renal, hepatic, neurologic/neuromuscular, hematologic, or metabolic disorders

(*continued*)

TABLE 4-3

CONTRAINDICATIONS AND PRECAUTIONS FOR COMMONLY USED VACCINES IN ADULTS (*CONTINUED*)

VACCINE FORMULATION	CONTRAINDICATIONS AND PRECAUTIONS
	Close contact with severely immunosuppressed persons who require a protected environment, such as isolation in a bone marrow transplantation unit Close contact with persons with lesser degrees of immunosuppression (e.g., persons receiving chemotherapy or radiation therapy who are not being cared for in a protective environment; persons with HIV infection) is *not* a contraindication or precaution. **Precaution** History of GBS within 6 weeks of a previous influenza vaccine dose
Pneumococcal polysaccharide	None
Hepatitis A	**Precaution** Pregnancy
Hepatitis B	**Contraindication** History of immediate hypersensitivity to yeast
Meningococcal conjugate	**Contraindications** Age >55 years (licensed for use only among persons 2–55 years of age) History of severe allergic reaction to dry natural rubber (latex) or to DT-containing vaccines **Precaution** History of GBS
Meningococcal polysaccharide	**Contraindication** History of severe allergic reaction to dry natural rubber (latex)
Zoster	**Contraindications** Age <60 years Pregnancy Known severe immunodeficiency History of immediate hypersensitivity reaction to gelatin[a] or neomycin

[a]Extreme caution must be exercised in administering MMR, varicella, or zoster vaccine to persons with a history of an anaphylactic reaction to gelatin or gelatin-containing products. Before administration, skin testing for sensitivity to gelatin can be considered. However, no specific protocols for this purpose have been published.
[b]Protocols have been published for safely administering influenza vaccine to persons with egg allergies. See references 222–224 in Fiore AE et al: MMWR 57:1, 2008.
Abbreviations: DT, diphtheria toxoid; GBS, Guillain-Barré syndrome; HPV, human papillomavirus; MMR, measles, mumps, and rubella; Td, tetanus and diphtheria toxoids; Tdap, tetanus and diphtheria toxoids and acellular pertussis; TT, tetanus toxoid.

a guide to conditions that are also contraindications to other live-virus vaccines. Recommendations state that zoster vaccine should not be administered to persons with primary or acquired immunodeficiency, including the following:

1. Persons with leukemia, lymphomas, or other malignant neoplasms affecting the bone marrow or lymphatic system. However, patients whose leukemia is in remission and who have not received chemotherapy (e.g., alkylating drugs or antimetabolites) or radiation therapy for at least 3 months can receive zoster vaccine.
2. Persons with AIDS or other clinical manifestations of HIV infection, including persons with CD4+ T lymphocyte counts of ≤200/μL or ≤15% of total lymphocytes.
3. Persons receiving immunosuppressive therapy, including high-dose glucocorticoids (≥20 mg of prednisone per day or the equivalent) for ≥2 weeks. Zoster vaccination should be deferred for at least 1 month after discontinuation of such therapy. Short-term glucocorticoid therapy (<14 days); low to moderate glucocorticoid dosage (<20 mg of prednisone per day or the equivalent); topically applied glucocorticoids (e.g., those applied directly to the nose or skin or inhaled); intraarticular, bursal, or tendon glucocorticoid injections; and long-term alternate-day treatment with low to moderate doses of short-acting systemic glucocorticoids are not considered sufficiently immunosuppressive to cause concerns about vaccine safety and should not preclude the administration of zoster vaccine. Low doses of methotrexate (≤0.4 mg/kg per week), azathioprine (≤3.0 mg/kg per day), or 6-mercaptopurine (≤1.5 mg/kg per day) for treatment of rheumatoid arthritis, psoriasis, polymyositis, sarcoidosis,

inflammatory bowel disease, and other conditions likewise do not constitute a contraindication.

4. Persons with clinical or laboratory evidence of other unspecified cellular immunodeficiency. However, persons with impaired humoral immunity (e.g., hypogammaglobulinemia or dysgammaglobulinemia) can receive zoster vaccine.
5. Persons undergoing hematopoietic stem cell transplantation. The experience of these patients with varicella-zoster virus–containing vaccines (e.g., zoster vaccine) is limited. Physicians should assess the immune status of the recipient on a case-by-case basis to determine the relevant risks. If a decision is made to administer zoster vaccine, vaccination should take place no sooner than 24 months after transplantation.
6. Persons receiving recombinant human immune mediators and immune modulators, especially the anti–tumor necrosis factor agents adalimumab, infliximab, and etanercept. The safety and efficacy of zoster vaccine administered concurrently with these agents is unknown. If it is not possible to administer zoster vaccine to patients before initiation of therapy, physicians should assess immune status on a case-by-case basis to determine the relevant risks and benefits. Otherwise, vaccination should be deferred for at least 1 month after discontinuation of such therapy.

VACCINE INFORMATION STATEMENTS

A VIS is a one-page (two-sided) information sheet produced by the CDC that informs vaccine recipients (or their parents or legal representatives) about the benefits and risks of a vaccine. VISs are mandated by the National Childhood Vaccine Injury Act (NCVIA) of 1986 and—whether the vaccine recipient is a child or an adult—must be provided for any vaccine covered by the Vaccine Injury Compensation Program. As of June 2009, vaccines that are covered by the NCVIA and that are licensed for use in adults include Td, Tdap, hepatitis A, hepatitis B, HPV, inactivated influenza, live intranasal influenza, measles/mumps/rubella (MMR), meningococcal, polio, and varicella vaccines. When combination vaccines for which no separate VIS exists are given (e.g., hepatitis A and B combination vaccine), all relevant VISs should be provided. VISs also exist for some vaccines not covered by the NCVIA, such as pneumococcal polysaccharide, Japanese encephalitis, rabies, zoster, typhoid, and yellow fever vaccines. The use of these VISs is encouraged but is not mandated.

All current VISs are available on the internet at two websites: the CDC's Vaccines & Immunizations site *(www.cdc.gov/vaccines)* and the Immunization Action Coalition's site *(www.immunize.org/vis/)*. (The latter site also includes translations of the VISs.) VISs from these sites can be downloaded and printed.

STORAGE AND HANDLING

Injectable vaccines are packaged in multidose vials, single-dose vials, or manufacturer-filled single-dose syringes. The live attenuated nasal-spray influenza vaccine is packaged in single-dose sprayers. Oral typhoid vaccine is packaged in capsules. Some vaccines, such as MMR, varicella, zoster, and meningococcal polysaccharide vaccines, come as lyophilized (freeze-dried) powders that must be reconstituted (i.e., mixed with a liquid diluent) before use. The lyophilized powder and the diluent come in separate vials. Diluents are not interchangeable but rather are specifically formulated for each type of vaccine; only the specific diluent provided by the manufacturer for each type of vaccine should be used. Once lyophilized vaccines have been reconstituted, their shelf-life is limited and they must be stored under appropriate temperature and light conditions. For example, varicella and zoster vaccines must be protected from light and administered within 30 minutes of reconstitution; MMR vaccine likewise must be protected from light but can be used up to 8 h after reconstitution. Single-dose vials of meningococcal polysaccharide vaccine must be used within 30 minutes of reconstitution, while multidose vials must be used within 35 days.

Vaccines are stored either at refrigerator temperature (2–8°C) or at freezer temperature (–15°C or colder). In general, inactivated vaccines (e.g., inactivated influenza, pneumococcal polysaccharide, and meningococcal conjugate vaccines) are stored at refrigerator temperature, while vials of lyophilized-powder live-virus vaccines (e.g., varicella, zoster, and MMR vaccines) are stored at freezer temperature. Diluents for lyophilized vaccines may be stored at refrigerator or room temperature. Live attenuated influenza vaccine—a live-virus liquid formulation administered by nasal spray—is stored at refrigerator temperature.

To avoid temperature fluctuations, vaccines should be placed in the body of a refrigerator and not in the door, in vegetable bins, on the floor, next to the wall, or next to the freezer—locations where temperatures may differ significantly. Frequent opening of a refrigerator door to retrieve food items can adversely affect the internal temperature of the unit and damage vaccines; thus, food and drink should not be stored in the same refrigerator as vaccines. Frozen vaccines must be stored in the body (not the door) of a freezer that has its own external door separate from the refrigerator. They should not be stored in small "dormitory-style" refrigerators. The temperature of refrigerators and freezers used for vaccine storage must be monitored and the temperature recorded at least twice a day. Ideally, continuous thermometers are used that measure and record temperature all day and all night.

ADMINISTRATION OF VACCINES

Parenteral vaccines recommended for routine administration to adults in the United States are given by either the IM or the SC route. Most parenteral vaccines are given to adults by the IM route. Vaccines given by the SC route include live-virus vaccines such as varicella,

zoster, and MMR vaccines as well as the inactivated meningococcal polysaccharide vaccine. The 23-valent pneumococcal polysaccharide vaccine may be given by either of these routes, but IM administration is preferred because it is associated with a lower risk of injection-site reactions.

Vaccines given to adults by the SC route are administered with a 5/8-inch needle into the upper outer-triceps area **(Fig. 4-2)**. Vaccines administered to adults by the IM route are injected into the deltoid muscle (Fig. 4-2) with a needle whose length should be selected on the basis of the recipient's sex and weight to ensure adequate penetration into the muscle. Current guidelines indicate that, for men and women weighing <130 lbs (<60 kg), a 5/8-inch needle is sufficient; for women weighing 130–200 lbs (60–90 kg) and men weighing 130–260 lbs (60–118 kg), a 1- to 1.5-inch needle is needed; and for women weighing >200 lbs (>90 kg) and men weighing >260 lbs (>118 kg), a 1.5-inch needle is required.

Aspiration is the process of pulling back on the plunger of the syringe after skin penetration but prior to injection to ensure that the contents of the syringe are not injected into a blood vessel. Although this practice is advocated by some experts, aspiration is not required because of the lack of large blood vessels at the recommended vaccine injection sites.

Multiple vaccines can be administered at the same visit; indeed, administration of all needed vaccines at one visit is encouraged. Studies have shown that vaccines are as effective when administered simultaneously as they are individually, and simultaneous administration of multiple vaccines is not associated with an increased risk of adverse effects. If more than one vaccine must be administered in the same limb, the injection sites should be separated by 1–2 inches so that any local reactions can be differentiated. If a vaccine and an immune globulin preparation are administered simultaneously (e.g., Td vaccine and tetanus immune globulin), a separate anatomic site should be used for each injection.

For certain vaccines (e.g., HPV vaccine and hepatitis B vaccine), multiple doses are required for an adequate and persistent antibody response. The recommended vaccination schedule specifies the interval between doses. Many adults who receive the first dose in a multiple-dose vaccine series do not complete the series or do not receive subsequent doses within the recommended interval; in these circumstances, vaccine efficacy and/or the duration of protection may be compromised. Providers should implement recall systems that will prompt patients to return for subsequent doses in a vaccination series at the appropriate intervals. With the exception of oral typhoid vaccination, an interruption in the schedule does not require restarting of the entire series or the addition of extra doses.

Syncope may follow vaccination, especially with adolescents and young adults. Serious injuries, including head trauma and motor vehicle accidents, have occurred. Vaccine administration procedures that minimize the impact

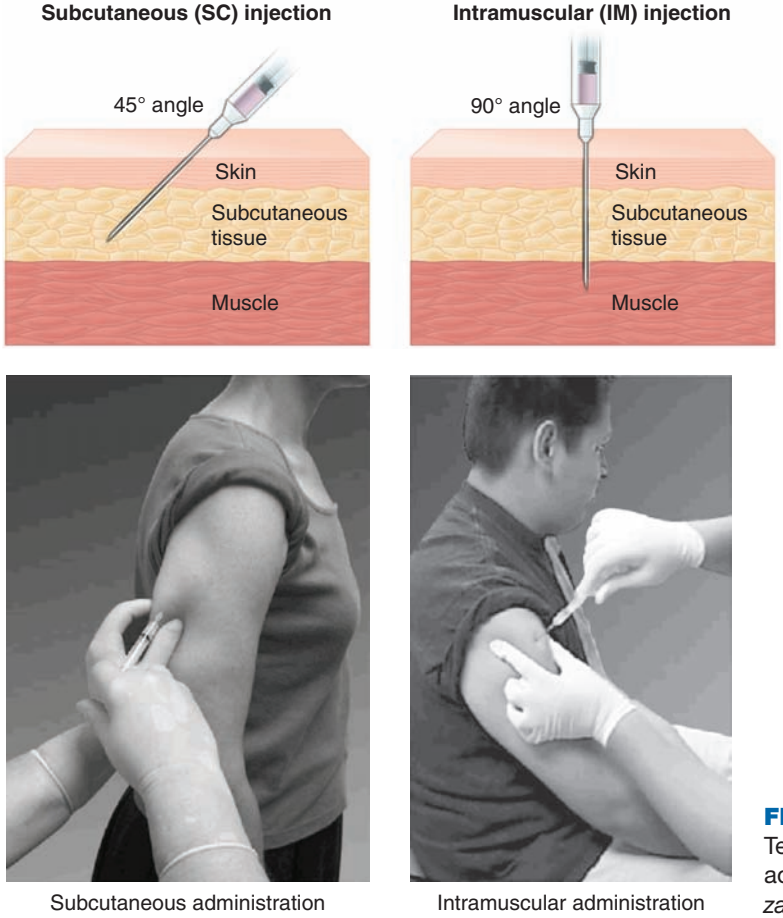


FIGURE 4-2
Techniques for SC and IM administration of vaccines to adults. (*Adapted from materials provided by the Immunization Action Coalition; www.immunize.org.*)

of postvaccination syncope should be used. To avoid trauma when syncope does occur, patients should be seated during vaccination. The ACIP recommends that vaccine providers strongly consider observing patients for 15 minutes after they are vaccinated. If syncope develops, patients should be observed until the symptoms resolve.

Anaphylaxis is a rare complication of vaccination. All facilities providing immunizations should have an emergency kit containing aqueous epinephrine for administration in the event of a systemic anaphylactic reaction.

VACCINE SAFETY MONITORING AND ADVERSE EVENT REPORTING

Prelicensure evaluations of vaccine safety

Before vaccines are licensed by the FDA, they are evaluated in clinical trials with volunteers. These trials are conducted in three progressive phases. Phase 1 trials are small, usually involving fewer than 100 volunteers. Their purposes are to provide a basic evaluation of safety and to identify common adverse events. Phase 2 trials, which are larger and may involve several hundred participants, collect additional information on safety and are usually designed to evaluate immunogenicity as well. Data gained from phase 2 trials can be used to determine the composition of the vaccine, the number of doses required, and a profile of common adverse events. Vaccines that appear promising are evaluated in phase 3 trials, which typically involve several hundred to several thousand volunteers and are generally designed to demonstrate vaccine efficacy and provide additional information on vaccine safety.

Postlicensure monitoring of vaccine safety

After licensure, a vaccine's safety is assessed by several mechanisms. The NCVIA of 1986 requires health care providers to report certain adverse events that follow vaccination of children. As a mechanism for that reporting, the Vaccine Adverse Event Reporting System (VAERS) was established in 1990 and is jointly managed by the CDC and the FDA. This safety surveillance system collects reports of adverse events associated with vaccines currently licensed in the United States. *Adverse events* are defined as health effects that occur after immunization and that may or may not be related to the vaccine. While VAERS was established in response to the NCVIA, any adverse event following vaccination—whether in a child or an adult, and whether or not it is believed to have been caused by vaccination—may be reported through VAERS. In 2008, VAERS received >25,000 reports of adverse events following vaccination. Of those, 9.5% were reportedly serious, causing disability, hospitalization, life-threatening illness, or death.

Anyone can file a VAERS report, including health care providers, manufacturers, and vaccine recipients or their parents or guardians. VAERS reports may be submitted online (*http://vaers.hhs.gov/esub/index*) or by completing a paper form requested online, by phone (800-822-7967), or by fax (877-721-0366). The VAERS form asks for the following information: the type of vaccine received; the timing of vaccination; the time of onset of the adverse event; and the recipient's current illnesses or medications, history of adverse events following vaccination, and demographic characteristics (e.g., age and gender). This information is entered into a database. The individual who reported the adverse event then receives a confirmation letter by mail with a VAERS identification number that can be used if additional information is submitted later. In selected cases of serious adverse reaction, the patient's recovery status may be followed up at 60 days and 1 year after vaccination. The FDA and the CDC have access to VAERS data and use this information to monitor vaccine safety and conduct research studies. VAERS data (minus personal information) are also available to the public.

While the VAERS provides useful information on vaccine safety, this passive reporting system has important limitations. One is that it only collects information about events following vaccination; it does not assess whether a given type of event occurs more often than expected after vaccination. A second is that event reporting is incomplete and is biased toward events that are believed to be more likely to be due to vaccination and that occur relatively soon after vaccination. To obtain more systematic information on adverse events occurring in both vaccinated and unvaccinated persons, the Vaccine Safety Datalink project was initiated in 1991. Directed by the CDC, this project includes eight managed-care organizations in the United States; member databases include information on immunizations, medical conditions, demographics, laboratory results, and medication prescriptions. The Department of Defense oversees a similar system monitoring the safety of immunizations among active-duty military personnel. In addition, postlicensure evaluations of vaccine safety may be conducted by the vaccine manufacturer. In fact, such evaluations are often required by the FDA as a condition of vaccine licensure.

Maintenance of vaccine records

All vaccines administered should be fully documented in the patient's permanent medical record. Documentation should include the date of administration, the name or common abbreviation of the vaccine, the vaccine lot number and manufacturer, the administration site, the VIS edition, the date the VIS was provided, and the name of the person who administered the vaccine.

CONSUMER ACCESS TO AND DEMAND FOR IMMUNIZATION

By removing barriers to the consumer or patient, providers and health care institutions can improve vaccine use. Financial barriers have traditionally been important

constraints, particularly among uninsured adults. Even for insured adults, out-of-pocket costs associated with newer, more expensive adult vaccines (e.g., zoster vaccine) are an obstacle to be overcome. After influenza vaccine was included by Medicare for all beneficiaries in 1993, coverage among persons ≥65 years of age doubled (from ~30% in 1989 to >60% in 1997; **Fig. 4-3**). Other strategies that enhance patients' access to vaccination include extended office hours (e.g., evening and weekend hours) and scheduled vaccination-only clinics where waiting times are reduced. Provision of vaccines outside the "medical home" (e.g., through occupational clinics, universities, and retail settings) can expand access for adults who do not make medical visits frequently. Increasing proportions of nonelderly adults are being vaccinated in these settings.

Health promotion efforts aimed at increasing the demand for immunization are common. Direct-to-consumer advertising by pharmaceutical companies has been used for some newer adolescent and adult vaccines. Efforts to raise consumer demand for vaccines have not increased immunization rates unless implemented in conjunction with other strategies that target strengthening of provider practices or reduction of consumer barriers. Attitudes and beliefs related to vaccination can be considerable impediments to consumer demand. Many adults view vaccines as important for children but are less familiar with vaccinations targeting disease prevention in adults. Several vaccines are recommended for adults with certain medical risk factors, but self-identification as a high-risk individual is relatively rare. Communication research suggests that many adults with chronic diseases may be more motivated to receive a vaccine by a desire to protect their family members rather than to reduce their own risk. Some vaccines are explicitly recommended for persons at relatively low risk of serious complications, with the goal of reducing the risk of transmission to higher-risk contacts. For example, for parents and caretakers of newborns, vaccinations against influenza and pertussis are recommended.

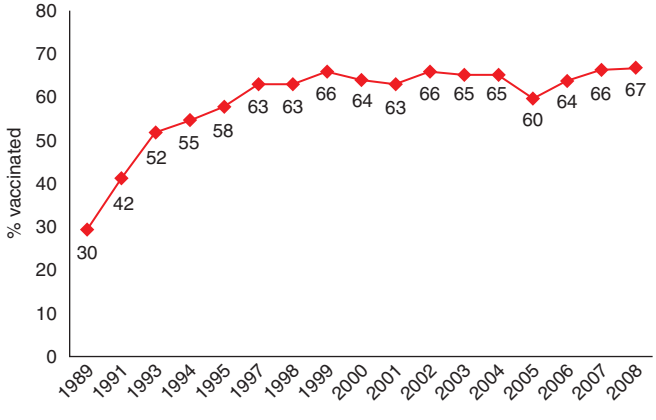


FIGURE 4-3
Influenza vaccination coverage among adults ≥65 years of age, United States, 1989–2008. (*From http://www.cdc.gov/FLU/PROFESSIONALS/VACCINATION/pdf/NHIS89_08fluvaxtrendtab.pdf.*)

STRATEGIES FOR PROVIDERS AND HEALTH CARE FACILITIES

Recommendation from the provider

Health care providers can have great influence on patients with regard to immunization. A recommendation from a doctor or nurse carries more weight than do recommendations from professional societies or endorsements by celebrities. Providers should be well informed about vaccine risks and benefits so that they can address patients' common concerns. The CDC, the American College of Physicians, and the American Academy of Family Physicians review and update the schedule for adult immunization on an annual basis and also have developed educational materials to facilitate provider–patient discussions about vaccination (*www.cdc.gov/vaccines*).

System supports

Medical offices can incorporate a variety of methods to ensure that providers consistently offer specific immunizations to patients with indications for specific vaccines. Decision-support tools have been incorporated into some electronic health records to alert the provider when specific vaccines are indicated. Manual or automated reminders and standing orders have been discussed (see "Deciding Whom to Vaccinate," discussed earlier) and have consistently improved vaccination coverage in both office and hospital settings. Most clinicians' estimates of their own performance diverge from objective measurements of their patients' immunization coverage; quantitative assessment and feedback have been shown in pediatric practice to increase immunization performance significantly. Some health plans have instituted incentives for providers with high rates of immunization coverage. Specialty providers, including obstetrician–gynecologists, may be the only providers serving high-risk patients with indications for selected vaccines (e.g., HPV, influenza, or pneumococcal polysaccharide vaccine).

Immunization requirements

Vaccination against selected communicable diseases is required for attendance at many universities and colleges as well as for service in the U.S. military or in some occupational settings (e.g., child care, laboratory, veterinary, and health care). Immunizations are recommended and sometimes required for travel to certain countries (see Chap. 5).

Vaccination of health care staff

A particular area of focus for medical settings is vaccination of health care workers, including those with and without direct patient-care responsibilities. The Joint Commission (which accredits health care organizations), the CDC's Healthcare Infection Control Practices Advisory Committee, and the ACIP all recommend influenza vaccination of all health care personnel; new recommendations focus on requiring documentation

of declination for providers that do not accept annual influenza vaccination. Some institutions and jurisdictions have added mandates on influenza vaccination of health care workers and have expanded on earlier requirements related to vaccination or proof of immunity for hepatitis B, measles, mumps, rubella, and varicella.

VACCINATION IN NONMEDICAL SETTINGS

Rates of vaccination in medical offices are highest among young children and adults ≥65 years of age. People in these age groups make more office visits and are more likely to receive care in a consistent "medical home" than older children, adolescents, and nonelderly adults. Vaccination outside the medical home can expand access to those whose health care visits are limited and reduce the burden on busy clinical practices. In some locations, financial constraints related to inventory and storage requirements have led providers to stock few or no vaccines. Outside private office and hospital settings, vaccination may also occur at health department venues, workplaces, retail sites (including pharmacies and supermarkets), and schools or colleges.

When vaccines are given in nonmedical settings, it remains important for standards of immunization practice to be followed. Consumers should be provided with information on how to report adverse events (e.g., via provision of a VIS), and procedures should ensure that documentation of vaccine administration is forwarded to the primary care provider and the state or city public health immunization registry. Detailed documentation may be required for employment, school attendance, and travel. Personalized health records can help consumers keep track of their immunizations, and some occupational health clinics have incorporated automated immunization reports that help employees stay up-to-date with recommended vaccinations.

PERFORMANCE MONITORING

Tracking of immunization coverage at national, state, institution, and practice levels can yield feedback to practitioners and programs and facilitate quality improvement. Healthcare Effectiveness Data and Information Set (HEDIS) measures related to adult immunization facilitate comparison of health plans. The CDC's National Immunization Survey and National Health Interview Survey provide selected information on immunization coverage among adults and track progress toward achievement of Healthy People 2020 targets for coverage among persons ≥65 years of age as well as among younger adults with conditions that increase risk. Influenza and pneumococcal vaccine coverage rates have been higher among persons ≥65 years of age (60–70%) than among high-risk 18- to 64-year-olds. Figures on state-specific immunization coverage with pneumococcal polysaccharide and influenza vaccines (as measured through the CDC's Behavioral Risk Factor Surveillance System) reveal substantial geographic variation in coverage. There are persistent disparities in adult immunization coverage rates between whites and racial and ethnic minorities. In contrast, racial and economic disparities in immunization of young children have been dramatically reduced during the past decade. Much of this progress is attributed to the Vaccines for Children Program, which since 1994 has entitled uninsured children to receive free vaccines. Approximately 70% of African-American and Hispanic children are eligible for this program.

FUTURE TRENDS

Although most vaccines developed in the twentieth century targeted common acute infectious diseases of childhood, more recently developed vaccines prevent chronic conditions prevalent among adults. Hepatitis B vaccine prevents hepatitis B–related cirrhosis and hepatocellular carcinoma, zoster vaccine prevents shingles and postherpetic neuralgia, and HPV vaccine prevents some types of cervical cancer as well as genital warts and anogenital cancers. New targets of vaccine development and research may further broaden the definition of vaccine-preventable disease. Research is ongoing on vaccines to prevent insulin-dependent diabetes mellitus, nicotine addiction, and Alzheimer's disease. Expanding strategies for vaccine development are incorporating molecular approaches such as DNA, vector, and peptide vaccines. New technologies, such as the use of transdermal and other needle-less routes of administration, are being applied to vaccine delivery.

CHAPTER 5

HEALTH RECOMMENDATIONS FOR INTERNATIONAL TRAVEL

Jay S. Keystone ■ Phyllis E. Kozarsky

According to the World Tourism Organization, international tourist arrivals grew exponentially from 25 million in 1950 to >900 million in 2008. Not only are more people traveling; travelers are seeking more exotic and remote destinations. Travel from industrialized to developing regions has been increasing, with Asia and the Pacific, Africa, and the Middle East now emerging destinations. **Figure 5-1** summarizes the monthly incidence of health problems during travel in developing countries. Studies show that 50–75% of short-term travelers to the tropics or subtropics report some health impairment. Most of these health problems are minor: only 5% require medical attention, and <1% require hospitalization. Although infectious agents contribute substantially to morbidity among travelers, these pathogens account for only ~1% of deaths in this population. Cardiovascular disease and injuries are the most frequent causes of death among travelers from the United States, accounting for 49% and 22% of deaths, respectively. Age-specific rates of death due to cardiovascular disease are similar among travelers and nontravelers. In contrast, rates of death due to injury (the majority from motor vehicle, drowning, or aircraft accidents) are several times higher among travelers. If one excludes mortality due to cardiovascular disease and preexisting illness, motor vehicle accidents account for >40% of the remaining deaths.

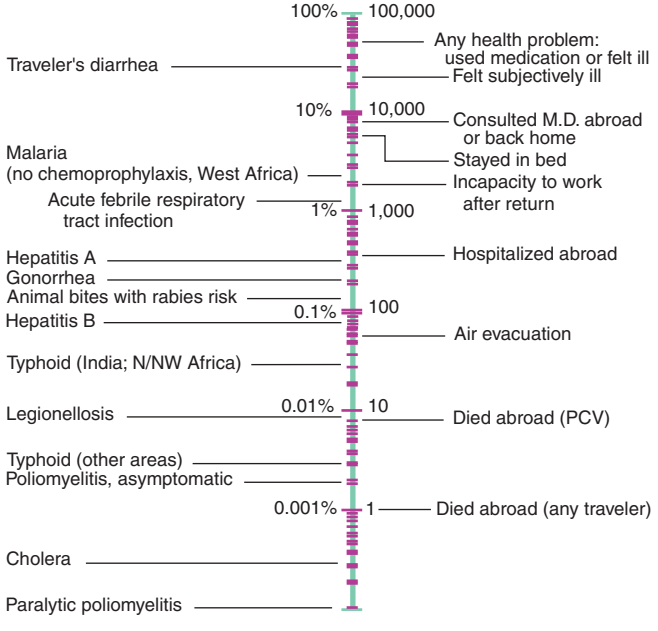


FIGURE 5-1
Incidence rate, per month, of health problems during a stay in developing countries. PCV, Peace Corps volunteer. (*From R Steffen, HO Lobel: Epidemiologic basis for the practice of travel medicine. J Wilderness Med 5:56, 1994. Reprinted with permission from Chapman and Hall, New York.*)

GENERAL ADVICE

Health maintenance recommendations are based not only on the traveler's destination but also on assessment of risk, which is determined by such variables as health status, specific itinerary, purpose of travel, season, and lifestyle during travel. Detailed information regarding country-specific risks and recommendations may be obtained from the Centers for Disease Control and Prevention (CDC) publication *Health Information for International Travel* (available at *wwwnc.cdc.gov/travel/*).

Fitness for travel is an issue of growing concern in view of the increased numbers of elderly and chronically ill individuals journeying to exotic destinations (see "Travel and Special Hosts," discussed later). Since most commercial aircraft are pressurized to 2500 m (8000 ft) above sea level (corresponding to a Pa_{o_2} of ~55 mmHg), individuals with serious cardiopulmonary problems or anemia should be evaluated before travel. In addition, those who have recently had surgery, a myocardial infarction, a cerebrovascular accident, or a deep vein thrombosis may be at high risk for adverse events during flight. A summary of current recommendations regarding fitness to fly has been published by the Aerospace Medical

Association Air Transport Medicine Committee (*www.asma.org/publications/*). A pretravel health assessment maybe advisable for individuals considering particularly adventurous recreational activities, such as mountain climbing and scuba diving.

IMMUNIZATIONS FOR TRAVEL

Immunizations for travel fall into three broad categories: *routine* (childhood/adult boosters that are necessary regardless of travel), *required* (immunizations that are mandated by international regulations for entry into certain areas or for border crossings), and *recommended* (immunizations that are desirable because of travel-related risks). Required and recommended vaccines commonly given to travelers are listed in **Table 5-1**.

Routine immunizations

Diphtheria, tetanus, and polio

Diphtheria (Chap. 42) continues to be a problem worldwide. Large outbreaks have occurred in countries that have reduced their public vaccination programs. Serologic surveys show that tetanus (Chap. 44) antitoxin is lacking in many North Americans, especially in women over the age of 50. The risk of polio (Chap. 97) to the international traveler is extremely low, and wild-type poliovirus has been eradicated from the Western Hemisphere and Europe. However, studies in the United States suggest that 12% of adult travelers are unprotected against at least one poliovirus serogroup. Foreign travel offers an ideal opportunity to have these immunizations updated. With the recent increase in pertussis among adults, the diphtheria–tetanus–acellular pertussis (Tdap) combination is now recommended for adults as a once-only replacement for the 10-year Td booster.

Measles

Measles (rubeola) continues to be a major cause of morbidity and death in the developing world (Chap. 98). Several outbreaks of measles in the United States have been linked to imported cases. The group at highest risk consists of persons born after 1956 and vaccinated before 1980, in many of whom primary vaccination failed.

Influenza

Influenza—possibly the most common vaccine-preventable infection in travelers—occurs year-round in the tropics and during the summer months in the Southern

TABLE 5-1

VACCINES COMMONLY USED FOR TRAVEL

VACCINE	PRIMARY SERIES	BOOSTER INTERVAL
Cholera, live oral (CVD 103 - HgR)	1 dose	6 months
Hepatitis A (Havrix), 1440 enzyme immunoassay U/mL	2 doses, 6–12 months apart, IM	None required
Hepatitis A (VAQTA, AVAXIM, EPAXAL)	2 doses, 6–12 months apart, IM	None required
Hepatitis A/B combined (Twinrix)	3 doses at 0, 1, and 6–12 months *or* 0, 7, and 21 days plus booster at 1 year, IM	None required *except* 12 months (once only, for accelerated schedule)
Hepatitis B (Engerix B): accelerated schedule	3 doses at 0, 1, and 2 months *or* 0, 7, and 21 days plus booster at 1 year, IM	12 months, once only
Hepatitis B (Engerix B or Recombivax): standard schedule	3 doses at 0, 1, and 6 months, IM	None required
Immune globulin (hepatitis A prevention)	1 dose IM	Intervals of 3–5 months, depending on initial dose
Japanese encephalitis (JE-VAX)	3 doses, 1 week apart, SC	12–18 months (first booster), then 4 years
Japanese encephalitis (Ixiaro)	2 doses, 1 month apart, SC	Optimal booster schedule not yet determined
Meningococcus, quadrivalent [Menimmune (polysaccharide), Menactra, Menveo (conjugate)]	1 dose SC	>3 years (optimal booster schedule not yet determined)
Rabies (HDCV), rabies vaccine absorbed (RVA), or purified chick embryo cell vaccine (PCEC)	3 doses at 0, 7, and 21 or 28 days, IM	None required except with exposure
Typhoid Ty21a, oral live attenuated (Vivotif)	1 capsule every other day × 4 doses	5 years
Typhoid Vi capsular polysaccharide, injectable (Typhim Vi)	1 dose IM	2 years
Yellow fever	1 dose SC	10 years

Hemisphere (coinciding with the winter months in the Northern Hemisphere). One prospective study showed that influenza developed in 1% of travelers to Southeast Asia per month of stay. Vaccination should be considered for all travelers to these regions, particularly those who are elderly or chronically ill. Travel-related influenza continues to occur during summer months in Alaska and the Northwest Territories of Canada among cruise-ship passengers and staff (Chap. 92). The speed of global spread of the pandemic H1N1 virus once again illustrates why influenza immunization is so important for travelers.

Pneumococcal infection

Regardless of travel, pneumococcal vaccine should be administered routinely to the elderly and to persons at high risk of serious infection, including those with chronic heart, lung, or kidney disease and those who have been splenectomized or have sickle cell disease (Chap. 37).

Required immunizations

Yellow fever

Documentation of vaccination against yellow fever (Chap. 102) may be required as a condition of entry into or passage through countries of sub-Saharan Africa and equatorial South America, where the disease is endemic or epidemic, or for entry into countries at risk of having the infection introduced. This vaccine is given only by state-authorized yellow fever centers, and its administration must be documented on an official International Certificate of Vaccination. A registry of U.S. clinics that provide the vaccine is available from the CDC (*wwwnc.cdc.gov/travel/*). Recent data suggest that fewer than 50% of travelers entering areas endemic for yellow fever are immunized. Severe adverse events associated with this vaccine have recently increased in incidence. First-time vaccine recipients may present with a syndrome characterized as either neurotropic (1 case per 125,000 doses) or viscerotropic (1 case per 250,000 doses; among persons 60–69 years of age, 1 case per 100,000 doses; and among persons ≥70 years of age, 1 case per 40,000 doses). Immunosuppression and thymic disease increase the risk of these adverse events (*www.cdc.gov/vaccines/pubs/vis/downloads/vis-yf.pdf*).

Meningococcal meningitis

Protection against meningitis (using one of the quadrivalent vaccines) is required for entry into Saudi Arabia during the Hajj (Chap. 48).

Influenza

Both seasonal and pandemic H1N1 vaccines (the latter, where available) were required for entry into Saudi Arabia during the Hajj in 2009.

Recommended immunizations

Hepatitis A and B

Hepatitis A (Chap. 95) is one of the most common vaccine-preventable infections of travelers. The risk is six times greater for travelers who stray from the usual tourist routes. The mortality rate for hepatitis A increases with age, reaching almost 3% among individuals over age 50. Of the four hepatitis A vaccines currently available in North America (two in the United States), all are interchangeable and have an efficacy rate of >95%.

Long-stay overseas workers appear to be at considerable risk for hepatitis B infection (Chap. 95). The recommendation that all travelers be immunized against hepatitis B before departure is supported by two studies showing that 17% of the assessed travelers who received health care abroad had some type of injection; according to the World Health Organization, nonsterile equipment is used for up to 75% of all injections given in the developing world. A 3-week accelerated schedule of the combined hepatitis A and B vaccine has been approved in the United States. Virtually all travelers to less developed countries should be immunized against hepatitis A and B.

Typhoid fever

The attack rate for typhoid fever (Chap. 58) is 1 case per 30,000 travelers per month of travel to the developing world. However, the attack rates in India, Senegal, and North Africa are tenfold higher and are especially high among travelers to relatively remote destinations and among VFRs (immigrants and their families returning to their homelands to visit friends or relatives). Between 1999 and 2006 in the United States, 66% of imported cases involved the latter group. Both of the available vaccines—one oral (live) and the other injectable (polysaccharide)—have efficacy rates of ~70%. In some countries, a combined hepatitis A/typhoid vaccine is available.

Meningococcal meningitis

Although the risk of meningococcal disease among travelers has not been quantified, it is likely to be higher among travelers who live with poor indigenous populations in overcrowded conditions (Chap. 48). Because of its enhanced ability to prevent nasal carriage (compared with the older polysaccharide vaccine), a quadrivalent conjugate vaccine is the product of choice for immunization of persons traveling to sub-Saharan Africa during the dry season or to areas of the world where there are epidemics. The vaccine, which protects against serogroups A, C, Y, and W-135, has an efficacy rate of >90%.

Japanese encephalitis

The risk of Japanese encephalitis (Chap. 102), an infection transmitted by mosquitoes in rural Asia and Southeast Asia, is ~1 case per 5000 travelers per month of stay in an endemic area. Most symptomatic infections among U.S. residents have involved military personnel or their families. The vaccine efficacy rate is >90%. The vaccine is recommended for persons staying>1 month in rural endemic areas or for shorter periods if their activities (e.g., camping, bicycling, hiking) in these areas will increase exposure risk. A new Vero cell vaccine is now available in the United States.

Cholera

The risk of cholera (Chap. 61) is extremely low, with ~1 case per 500,000 journeys to endemic areas. Cholera vaccine, no longer available in the United States,

was rarely recommended but was considered for aid and health care workers in refugee camps or in disaster-stricken/war-torn areas. A more effective oral cholera vaccine is available in other countries.

Rabies

Domestic animals, primarily dogs, are the major transmitters of rabies in developing countries (Chap. 101). Several studies have shown that the risk of rabies posed by a dog bite in an endemic area translates into 1–3.6 cases per 1000 travelers per month of stay. Countries where canine rabies is highly endemic include Mexico, the Philippines, Sri Lanka, India, Thailand, and Vietnam. The three vaccines available in the United States provide >90% protection. Rabies vaccine is recommended for long-stay travelers, particularly children, and persons who may be occupationally exposed to rabies in endemic areas; however, in a large-scale study, almost 50% of potential exposures occurred within the first month of travel. Even after receipt of a preexposure rabies vaccine series, two postexposure doses are required. Travelers who have had the preexposure series do not require rabies immune globulin (which is often unavailable in developing countries) if they are exposed to the disease.

PREVENTION OF MALARIA AND OTHER INSECT-BORNE DISEASES

It is estimated that more than 30,000 American and European travelers develop malaria each year (Chap. 119). The risk to travelers is highest in Oceania and sub-Saharan Africa (estimated at 1:5 and 1:50 per month of stay, respectively, among persons not using chemoprophylaxis); intermediate in malarious areas on the Indian subcontinent and in Southeast Asia (1:250–1:1000 per month); and low in South and Central America (1:2500–1:10,000 per month). Of the more than 1000 cases of malaria reported annually in the United States, 90% of those due to *Plasmodium falciparum* occur in travelers returning or immigrating from Africa and Oceania. VFRs are at the highest risk of acquiring malaria. With the worldwide increase in chloroquine- and multidrug-resistant falciparum malaria, decisions about chemoprophylaxis have become more difficult. In addition, the spread of malaria due to primaquine- and chloroquine-resistant strains of *Plasmodium vivax* has added to the complexity of treatment, as has the recently described "monkey malaria" of humans, which is caused by *P. knowlesi*. The case-fatality rate of falciparum malaria in the United States is 4%; however, *in only one-third of patients who die is the diagnosis of malaria considered before death.*

Several studies indicate that fewer than 50% of travelers adhere to basic recommendations for malaria prevention. Keys to the prevention of malaria include both personal protection measures against mosquito bites (especially between dusk and dawn) and malaria chemoprophylaxis. The former measures include the use of DEET-containing insect repellents, permethrin-impregnated bed-nets and clothing, screened sleeping accommodations, and protective clothing. Thus, in regions where infections such as malaria are transmitted, DEET products (25–50%) are recommended, even for children and infants at birth. Studies suggest that concentrations of DEET above ~50% do not offer a marked increase in protection time against mosquitoes. The CDC also recommends picaridin (icaridin), oil of lemon eucalyptus (PMD, para-menthane-3,8-diol), and IR3535 (ethyl butylacetylaminopropionate). In general, higher concentrations of active ingredient provide longer duration of protection, regardless of the active ingredient. Personal protection measures also help prevent other insect-transmitted illnesses, such as dengue fever (Chap. 102). Over the past decade, the incidence of dengue has increased, particularly in the Caribbean region, Latin America, and Southeast Asia. Both dengue and chikungunya viruses are transmitted by an urban-dwelling mosquito that bites primarily at dawn and dusk.

Table 5-2 lists the currently recommended drugs of choice for prophylaxis of malaria, by destination.

PREVENTION OF GASTROINTESTINAL ILLNESS

Diarrhea, the leading cause of illness in travelers (Chap. 26), is usually a short-lived, self-limited condition; however, 40% of affected individuals need to alter their scheduled activities, and another 20% are confined to bed. The most important determinant of risk is the destination. Incidence rates per 2-week stay have been reported to

TABLE 5-2

MALARIA CHEMOSUPPRESSIVE REGIMENS, ACCORDING TO GEOGRAPHIC AREA[a]

GEOGRAPHIC AREA	DRUG OF CHOICE	ALTERNATIVES
Central America (north of Panama), Iraq, Turkey, northern Argentina, and Paraguay	Chloroquine	Atovaquone-proguanil[b] Doxycycline Mefloquine Primaquine (except Honduras)
South America, including Haiti, Dominican Republic, and Panama but not northern Argentina or Paraguay; Asia, including Southeast Asia; Africa; and Oceania	Doxycycline Atovaquone-proguanil Mefloquine	
Thai-Myanmar and Thai-Cambodian borders and central Vietnam	Atovaquone-proguanil Doxycycline	

[a]See CDC's *Health Information for International Travel 2010*.
[b]Malarone.
Note: See also Chap. 119.

be as low as 8% in industrialized countries and as high as 55% in parts of Africa, Central and South America, and Southeast Asia. Infants and young adults are at particularly high risk. Recent reviews suggested that there is little correlation between dietary indiscretions and the occurrence of travelers' diarrhea. Earlier studies of U.S. students in Mexico showed that eating meals in restaurants and cafeterias or consuming food from street vendors was associated with increased risk.

Etiology

(See also Table 26-3) The most frequently identified pathogens causing travelers' diarrhea are toxigenic *Escherichia coli* and enteroaggregative *E. coli* (Chap. 54), although in some parts of the world (notably northern Africa and Southeast Asia) *Campylobacter* infections (Chap. 60) appear to predominate. Other common causative organisms include *Salmonella* (Chap. 58), *Shigella* (Chap. 59), rotavirus (Chap. 94), and norovirus (Chap. 94). The latter virus has caused numerous outbreaks on cruise ships. Except for giardiasis (Chap. 125), parasitic infections are uncommon causes of travelers' diarrhea. A growing problem for travelers is the development of antibiotic resistance among many bacterial pathogens. Examples include strains of *Campylobacter* resistant to quinolones and strains of *E. coli*, *Shigella*, and *Salmonella* resistant to trimethoprim-sulfamethoxazole.

Precautions

General food and water precautions include eating foods piping hot; avoiding foods that are raw, poorly cooked, or sold by street vendors; and drinking only boiled or commercially bottled beverages, particularly those that are carbonated. Heating kills diarrhea-causing organisms, whereas freezing does not; therefore, ice cubes made from unpurified water should be avoided. In spite of these recommendations, the literature has repeatedly documented dietary indiscretions by 98% of travelers within the first 72 h after arrival at their destination. The maxim "Boil it, cook it, peel it, or forget it!" is easy to remember but apparently difficult to follow.

Self-treatment

(See also Table 26-5) As travelers' diarrhea often occurs despite rigorous food and water precautions, travelers should carry medications for self-treatment. An antibiotic is useful in reducing the frequency of bowel movements and duration of illness in moderate to severe diarrhea. The standard regimen is a 3-day course of a quinolone taken twice daily (or, in the case of some newer formulations, once daily). However, studies have shown that a single double dose of a quinolone may be equally effective. For diarrhea acquired in areas such as Thailand, where >90% of *Campylobacter* infections are quinolone resistant, azithromycin may be a better alternative. Rifaximin, a poorly absorbed rifampin derivative, is highly effective against noninvasive bacterial pathogens such as toxigenic and enteroaggregative *E. coli*. The current approach to self-treatment of travelers' diarrhea is for the traveler to carry three once-daily doses of an antibiotic and to use as many doses as necessary to resolve the illness. If neither high fever nor blood in the stool accompanies the diarrhea, loperamide should be taken in combination with the antibiotic; studies have shown that this combination is more effective than an antibiotic alone.

Prophylaxis

Prophylaxis of travelers' diarrhea with bismuth subsalicylate is widely used but only ~60% effective. For certain individuals (e.g., athletes, persons with a repeated history of travelers' diarrhea, and persons with chronic diseases), a single daily dose of a quinolone, azithromycin, or rifaximin during travel of <1 month's duration is 75–90% efficacious in preventing travelers' diarrhea. Probiotics have been only ~20% effective as prophylaxis. In Europe and Canada, an oral subunit cholera vaccine that cross-protects against enterotoxigenic *E. coli* has been shown to provide 30–50% protection against travelers' diarrhea.

Illness after return

Although extremely common, acute travelers' diarrhea is usually self-limited or amenable to antibiotic therapy. Persistent bowel problems after the traveler returns home have a less well-defined etiology and may require medical attention from a specialist. Infectious agents (e.g., *Giardia lamblia*, *Cyclospora cayetanensis*, *Entamoeba histolytica*) appear to be responsible for only a small proportion of cases with persistent bowel symptoms. By far the most common causes of persistent diarrhea after travel are postinfectious sequelae such as lactose intolerance or irritable bowel syndrome. A meta-analysis showed that postinfectious irritable bowel syndrome lasting months to years may occur in as many as 4–13% of cases. When no infectious etiology can be identified, a trial of metronidazole therapy for presumed giardiasis, a strict lactose-free diet for 1 week, or a several-week trial of high-dose hydrophilic mucilloid (plus an osmotic laxative such as lactulose or PEG 3350 for persons with alternating diarrhea and constipation) relieves the symptoms of many patients.

PREVENTION OF OTHER TRAVEL-RELATED PROBLEMS

Travelers are at high risk for *sexually transmitted diseases* (Chap. 30). Surveys have shown that large numbers engage in casual sex, and there is a reluctance to use condoms consistently. An increasing number of travelers are being diagnosed with *schistosomiasis* (Chap. 129). Travelers should be cautioned to avoid bathing, swimming, or wading in freshwater lakes, streams, or rivers in parts of northeastern South America, the Caribbean, Africa, and Southeast Asia. Prevention of *travel-associated injury* depends mostly on common-sense precautions. Riding on motorcycles (especially without helmets) and

in overcrowded public vehicles is not recommended; in developing countries, individuals should not travel by road in rural areas after dark. In addition to its association with motor vehicle accidents, excessive alcohol use has been a significant factor in drownings, assaults, and injuries. Travelers are cautioned to avoid walking barefoot because of the risk of hookworm and *Strongyloides* infections (Chap. 127) and snakebites (Chap. 131).

THE TRAVELER'S MEDICAL KIT

A traveler's medical kit is strongly advisable. The contents may vary widely, depending on the itinerary, duration of stay, style of travel, and local medical facilities. While many medications are available abroad (often over the counter), directions for their use may be nonexistent or in a foreign language, or a product may be outdated or counterfeit. For example, a multicountry study in Southeast Asia showed that a mean of 53% (range, 21–92%) of antimalarial products were counterfeit or contained inadequate amounts of active drug. In the medical kit, the short-term traveler should consider carrying an analgesic; an antidiarrheal agent and an antibiotic for self-treatment of travelers' diarrhea; antihistamines; a laxative; oral rehydration salts; a sunscreen with a skin-protection factor of at least 30; a DEET-containing or equivalent insect repellent for the skin; an insecticide for clothing (permethrin); and, if necessary, an antimalarial drug. To these medications, the long-stay traveler might add a broad-spectrum general-purpose antibiotic (levofloxacin or azithromycin), an antibacterial eye and skin ointment, and a topical antifungal cream. Regardless of the duration of travel, a first-aid kit containing such items as scissors, tweezers, and bandages should be considered. A practical approach to self-treatment of infections in the long-stay traveler who carries a once-daily dose of antibiotics (e.g., levofloxacin) is to use 3 tablets "below the waist" (bowel and bladder infections) and 6 tablets "above the waist" (skin and respiratory infections).

TRAVEL AND SPECIAL HOSTS

PREGNANCY AND TRAVEL

A woman's medical history and itinerary, the quality of medical care at her destinations, and her degree of flexibility determine whether travel is wise during pregnancy. According to the American College of Obstetrics and Gynecology, the safest part of pregnancy in which to travel is between 18 and 24 weeks, when there is the least danger of spontaneous abortion or premature labor. Some obstetricians prefer that women stay within a few hundred miles of home after the 28th week of pregnancy in case problems arise. In general, however, healthy women may be advised that it is acceptable to travel.

Relative contraindications to international travel during pregnancy include a history of miscarriage, premature labor, incompetent cervix, or toxemia. General medical problems such as diabetes, heart failure, severe anemia, or a history of thromboembolic disease should also prompt the pregnant woman to postpone her travels. Finally, regions in which the pregnant woman and her fetus may be at excessive risk (e.g., those at high altitudes, those where live-virus vaccines are required, and those where multidrug-resistant malaria is endemic) are not ideal destinations during any trimester.

Malaria

Malaria during pregnancy carries a significant risk of morbidity and death. Levels of parasitemia are highest and failure to clear the parasites after treatment is most frequent among primigravidae. Severe disease, with complications such as cerebral malaria, massive hemolysis, and renal failure, is especially likely in pregnancy. Fetal sequelae include spontaneous abortion, stillbirth, preterm delivery, and congenital infection.

Enteric infections

Pregnant travelers must be extremely cautious regarding their food and beverage intake. Dehydration due to travelers' diarrhea can lead to inadequate placental blood flow. Infections such as toxoplasmosis, hepatitis E, and listeriosis can also cause serious sequelae in pregnancy.

The mainstay of therapy for travelers' diarrhea is rehydration. Loperamide may be used if necessary. For self-treatment, azithromycin may be the best option. Although quinolones are increasingly being used safely during pregnancy and rifaximin is poorly absorbed from the gastrointestinal tract, these drugs are not approved for this indication.

Because of the serious problems encountered when infants are given local foods and beverages, women are strongly encouraged to breast-feed when traveling with a neonate. A nursing mother with travelers' diarrhea should not stop breast-feeding but should increase her fluid intake.

Air travel and high-altitude destinations

Commercial air travel is not a risk to the healthy pregnant woman or to the fetus. The higher radiation levels reported at altitudes of >10,500 m (>35,000 ft) should pose no problem for the healthy pregnant traveler. Since each airline has a policy regarding pregnancy and flying, it is best to check with the specific carrier when booking reservations. Domestic air travel is usually permitted until the 36th week, whereas international air travel is generally curtailed after the 32nd week.

There are no known risks for pregnant women who travel to high-altitude destinations and stay for short periods. However, there are likewise no data on the safety of pregnant women at altitudes of >4500 m (15,000 ft).

THE HIV-INFECTED TRAVELER

(See also Chap. 93) The HIV-infected traveler is at special risk of serious infections due to a number of

pathogens that may be more prevalent at travel destinations than at home. However, the degree of risk depends primarily on the state of the immune system at the time of travel. For persons whose CD4+ T cell counts are normal or >500/μL, data suggest no greater risk during travel than for persons without HIV infection. Individuals with AIDS (CD4+ T cell counts of <200/μL) and others who are symptomatic need special counseling and should visit a travel medicine practitioner before departure, especially when traveling to the developing world.

Several countries now routinely deny entry to HIV-positive individuals for prolonged stay, even though these restrictions do not appear to decrease rates of transmission of the virus. In general, HIV testing is required for individuals who wish to stay abroad >3 months or who intend to work or study abroad. Some countries will accept an HIV serologic test done within 6 months of departure, whereas others will not accept a blood test done at any time in the traveler's home country. Border officials often have the authority to make inquiries of individuals entering a country and to check the medications they are carrying. If antiretroviral drugs are identified, the person may be barred from entering the country. Information on testing requirements for specific countries is available from consular offices but is subject to frequent change.

Immunizations

All of the HIV-infected traveler's routine immunizations should be up to date (Chap. 4). The response to immunization may be impaired at CD4+ T cell counts of <200/μL and in some cases at even higher counts. Thus HIV-infected persons should be vaccinated as early as possible to ensure adequate immune responses to all vaccines. For patients receiving antiretroviral therapy, at least 3 months must elapse before regenerated CD4+ T cells can be considered fully functional; therefore, vaccination of these patients should be delayed. However, when the risk of illness is high or the sequelae of illness are serious, immunization is recommended. In certain circumstances, it may be prudent to check the adequacy of the serum antibody response before departure.

Because of the increased risk of infections due to *Streptococcus pneumoniae* and other bacterial pathogens that cause pneumonia following influenza, pneumococcal polysaccharide and influenza vaccines should be administered. The estimated rates of response to influenza vaccine are >80% among persons with asymptomatic HIV infection and <50% among those with AIDS.

In general, live attenuated vaccines are contraindicated for persons with immune dysfunction. Because measles (rubeola) can be a severe or lethal infection in HIV-positive patients, these patients should receive the measles vaccine (or the combination measles-mumps-rubella vaccine) unless the CD4+ T cell count is <200/μL. Between 18% and 58% of symptomatic HIV-infected vaccinees develop adequate antibody titers, and 50–100% of asymptomatic HIV-infected persons seroconvert.

It is recommended that the live yellow fever vaccine not be given to HIV-infected travelers. Although the potential adverse effects of a live vaccine in an HIV-infected individual are always a consideration, there appear to have been no reported cases of illness in those who have inadvertently received this vaccine. Nonetheless, if the CD4+ T cell count is <200/μL, an alternative itinerary that poses no risk of exposure to yellow fever is recommended. If the traveler is passing through or traveling to an area where the vaccine is required but the disease risk is low, a physician's waiver should be issued.

A transient increase in HIV viremia (lasting days to weeks) has been demonstrated in HIV-infected individuals following immunization against influenza, pneumococcal infection, and tetanus (Chap. 93). However, there is no evidence at this point that this transient increase is detrimental.

Gastrointestinal illness

Decreased levels of gastric acid, abnormal gastrointestinal mucosal immunity, other complications of HIV infection, and medications taken by HIV-infected patients make travelers' diarrhea especially problematic in these individuals. Travelers' diarrhea is likely to occur more frequently, be more severe, be accompanied by bacteremia, and be more difficult to treat. *Cryptosporidium, Isospora belli*, and *Microsporidium* infections, although uncommon, are associated with increased morbidity and mortality rates in AIDS patients.

The HIV-infected traveler must be careful to consume only appropriately prepared foods and beverages and may benefit from antibiotic prophylaxis for travelers' diarrhea. Sulfonamides (as used to prevent pneumocystosis) are ineffective because of widespread resistance.

Other travel-related infections

Data are lacking on the severity of many vector-borne diseases in HIV-infected individuals. Malaria is especially severe in asplenic persons and in those with AIDS. The HIV load doubles during malaria, with subsidence in ~8–9 weeks; the significance of this increase in viral load is unknown.

Visceral leishmaniasis (Chap. 122) has been reported in numerous HIV-infected travelers. Diagnosis may be difficult, given that splenomegaly and hyperglobulinemia are often lacking and serologic results are frequently negative. Sandfly bites may be prevented by evening use of insect repellents.

Certain respiratory illnesses, such as histoplasmosis and coccidioidomycosis, cause greater morbidity and mortality among patients with AIDS. Although tuberculosis is common among HIV-infected persons (especially in developing countries), its acquisition by the short-term HIV-infected traveler has not been reported as a major problem. From a prospective study, it is estimated that for nonmedical travelers the risk of tuberculosis infection is ~3% per year of travel.

Medications

Adverse events due to medications and drug interactions are common and raise complex issues for HIV-infected persons. Rates of cutaneous reaction (e.g., increased cutaneous sensitivity to sulfonamides) are unusually high among patients with AIDS. Since zidovudine is metabolized by hepatic glucuronidation, inhibitors of this process may elevate serum levels of the drug. Concomitant administration of the antimalarial drug mefloquine and the antiretroviral agent ritonavir may result in decreased plasma levels of ritonavir. In contrast, no significant influence of concomitant mefloquine administration on plasma levels of indinavir or nelfinavir was detected in two HIV-infected travelers. There is a strong theoretical concern that the antimalarial drugs lumefantrine (combined with artemisinin in Coartem) and halofantrine may interact with HIV protease inhibitors and nonnucleoside reverse transcriptase inhibitors since the latter are known to be potent inhibitors of cytochrome P450.

CHRONIC ILLNESS, DISABILITY, AND TRAVEL

Chronic health problems need not prevent travel, but special measures can make the journey safer and more comfortable.

Heart disease

Cardiovascular events are the main cause of deaths among travelers and of in-flight emergencies on commercial aircraft. Extra supplies of all medications should be kept in carry-on luggage, along with a copy of a recent electrocardiogram and the name and telephone number of the traveler's physician at home. Pacemakers are not affected by airport security devices, although electronic telephone checks of pacemaker function cannot be transmitted by international satellites. Travelers with electronic defibrillators should carry a note to that effect and ask for hand screening. A traveler may benefit from supplemental oxygen; since oxygen delivery systems are not standard, supplementary oxygen should be ordered by the traveler's physician well before flight time. Travelers may benefit from aisle seating and should walk, perform stretching and flexing exercises, consider wearing support hose, and remain hydrated during the flight to prevent venous thrombosis and pulmonary embolism.

Chronic lung disease

Chronic obstructive pulmonary disease is one of the most common diagnoses in patients who require emergency-department evaluation for symptoms occurring during airline flights. The best predictor of the development of in-flight problems is the sea-level Pa_{o_2}. A Pa_{o_2} of at least 72 mmHg corresponds to an in-flight arterial Pa_{o_2} of ~55 mmHg when the cabin is pressurized to 2500 m (8000 ft). If the traveler's baseline Pa_{o_2} is <72 mmHg, the provision of supplemental oxygen should be considered. Contraindications to flight include active bronchospasm, lower respiratory infection, lower-limb deep vein phlebitis, pulmonary hypertension, and recent thoracic surgery (within the preceding 3 weeks) or pneumothorax. Decreased outdoor activity at the destination should be considered if air pollution is excessive.

Diabetes mellitus

Alterations in glucose control and changes in insulin requirements are common problems among patients with diabetes who travel. Changes in time zone, in the amount and timing of food intake, and in physical activity demand vigilant assessment of metabolic control. The traveler with diabetes should pack medication (including a bottle of regular insulin for emergencies), insulin syringes and needles, equipment and supplies for glucose monitoring, and snacks in carry-on luggage. Insulin is stable for ~3 months at room temperature but should be kept as cool as possible. The name and telephone number of the home physician and a card and bracelet listing the patient's medical problems and the type and dose of insulin used should accompany the traveler. In traveling eastward (e.g., from the United States to Europe), the morning insulin dose on arrival may need to be decreased. The blood glucose can then be checked during the day to determine whether additional insulin is required. For flights westward, with lengthening of the day, an additional dose of regular insulin may be required.

Other special groups

Other groups for whom special travel measures are encouraged include patients undergoing dialysis, those with transplants, and those with other disabilities. Up to 13% of travelers have some disability, but few advocacy groups and tour companies dedicate themselves to this growing population. Medication interactions are a source of serious concern for these travelers, and appropriate medical information should be carried, along with the home physician's name and telephone number. Some travelers taking glucocorticoids carry stress doses in case they become ill. Immunization of these immunocompromised travelers may result in less than adequate protection. Thus the traveler and the physician must carefully consider which destinations are appropriate.

MEDICAL TOURISM

Travel for the purpose of obtaining health care abroad has recently received a great deal of attention in the medical literature and the media. According to the annual U.S. Department of Commerce in-flight survey, there were ~500,000 overseas trips during 2006 in which health treatment was at least one purpose of travel. Lower cost is usually cited as the motivation for this type of tourism, and an entire industry has flourished as a result of this phenomenon. However, the

quality of facilities, assistance services, and care is neither uniform nor regulated; thus, in most instances, responsibility for assessing the suitability of an individual program or facility lies solely with the traveler. Persons considering this option must recognize that they are almost always at a disadvantage when being treated in a foreign country, particularly if there are complications. Concerns to be addressed include the quality of the health care facility and its staff; language and cultural differences that may impede accurate interpretation of both verbal and nonverbal communication; religious and ethical differences that may be encountered over issues such as efforts to preserve life and limb or care of the terminally ill; lack of familiarity with the local medical system; limited access of the care provider to the patient's medical history; the use of unfamiliar drugs and medicines; the relative difficulty of arranging follow-up care back in the United States; and the possibility that such follow-up care may be fraught with problems should there be complications. If serious issues arise, legal recourse may be difficult or impossible.

Patients planning to travel abroad to obtain health care, particularly when surgery is involved, should be immunized for hepatitis B and should consider having baseline hepatitis C and HIV tests preoperatively. Prevalence rates of hepatitis B and C and HIV infection vary considerably around the world and are generally higher in developing regions than in the United States and Western Europe. The latest information available on the safety of the blood supply outside the United States is the World Health Organization's Global Database on Blood Safety based on data from 2004–2005 (*www.who.int/bloodsafety/global_database/en*). Persons researching accreditation status of overseas facilities should note that, although these facilities may be part of a chain, they are surveyed and accredited individually. Accreditation resources include (1) the Joint Commission International (*www.jointcommissioninternational.org*), (2) the Australian Council for Healthcare Standards International (*www.achs.org.au/ACHSI*), and (3) the Canadian Council on Health Services (*www.cchsa.ca*).

PROBLEMS AFTER RETURN

The most common medical problems encountered by travelers after their return home are diarrhea, fever, respiratory illnesses, and skin diseases **(Fig. 5-2)**. Frequently ignored problems are fatigue and emotional stress, especially in long-stay travelers. The approach to diagnosis requires some knowledge of geographic medicine, in particular the epidemiology and clinical presentation of infectious disorders. A geographic history should focus on the traveler's exact itinerary, including dates of arrival and departure; exposure history (food indiscretions, drinking-water sources, freshwater contact, sexual activity, animal contact, insect bites); location and style of travel (urban vs. rural, first-class hotel accommodation vs. camping); immunization history; and use of antimalarial chemosuppression.

DIARRHEA

See "Prevention of Gastrointestinal Illness," discussed earlier in the chapter.

FEVER

Fever in a traveler who has returned from a malarious area should be considered a medical emergency because death from *P. falciparum* malaria can follow an illness of only several days' duration. Although "fever from the tropics" does not always have a tropical cause, malaria should be the first diagnosis considered. The risk of *P. falciparum* malaria is highest among travelers returning from Africa or Oceania and among those who become symptomatic within the first 2 months after return. Other important causes of fever after travel include viral hepatitis (hepatitis A and E), typhoid fever, bacterial enteritis, arboviral infections (e.g., dengue fever), rickettsial infections (including tick and scrub typhus and Q fever), and—in rare instances—leptospirosis, acute HIV infection, and amebic liver abscess. A cooperative study by GeoSentinel (an emerging infectious disease surveillance group established by the CDC and the International Society of Travel Medicine) showed that, among 3907 febrile returned travelers, malaria was acquired most often from Africa, dengue from Southeast Asia and the Caribbean, typhoid fever from southern Asia, and rickettsial infections (tick typhus) from southern Africa **(Table 5-3)**. In at least 25% of cases, no etiology can be found, and the fever resolves spontaneously. Clinicians should keep in mind that no present-day antimalarial agent guarantees protection from malaria and that some immunizations (notably, that against typhoid fever) are only partially protective.

When no specific diagnosis is forthcoming, the following investigations, where applicable, are suggested: complete blood count, liver function tests, thick/thin blood films or rapid diagnostic testing for malaria (repeated twice if necessary), urinalysis, urine and blood cultures (repeated once), chest x-ray, and collection of an acute-phase serum sample to be held for subsequent examination along with a paired convalescent-phase serum sample.

SKIN DISEASES

Pyodermas, sunburn, insect bites, skin ulcers, and cutaneous larva migrans are the most common skin conditions affecting travelers after their return home. In those with persistent skin ulcers, a diagnosis of cutaneous leishmaniasis, mycobacterial infection, or fungal infection should be considered. Careful, complete inspection of the skin is important in detecting the rickettsial eschar in a febrile patient or the central breathing hole in a "boil" due to myiasis.

EMERGING INFECTIOUS DISEASES

In recent years, travel and commerce have fostered the worldwide spread of HIV infection, led to the

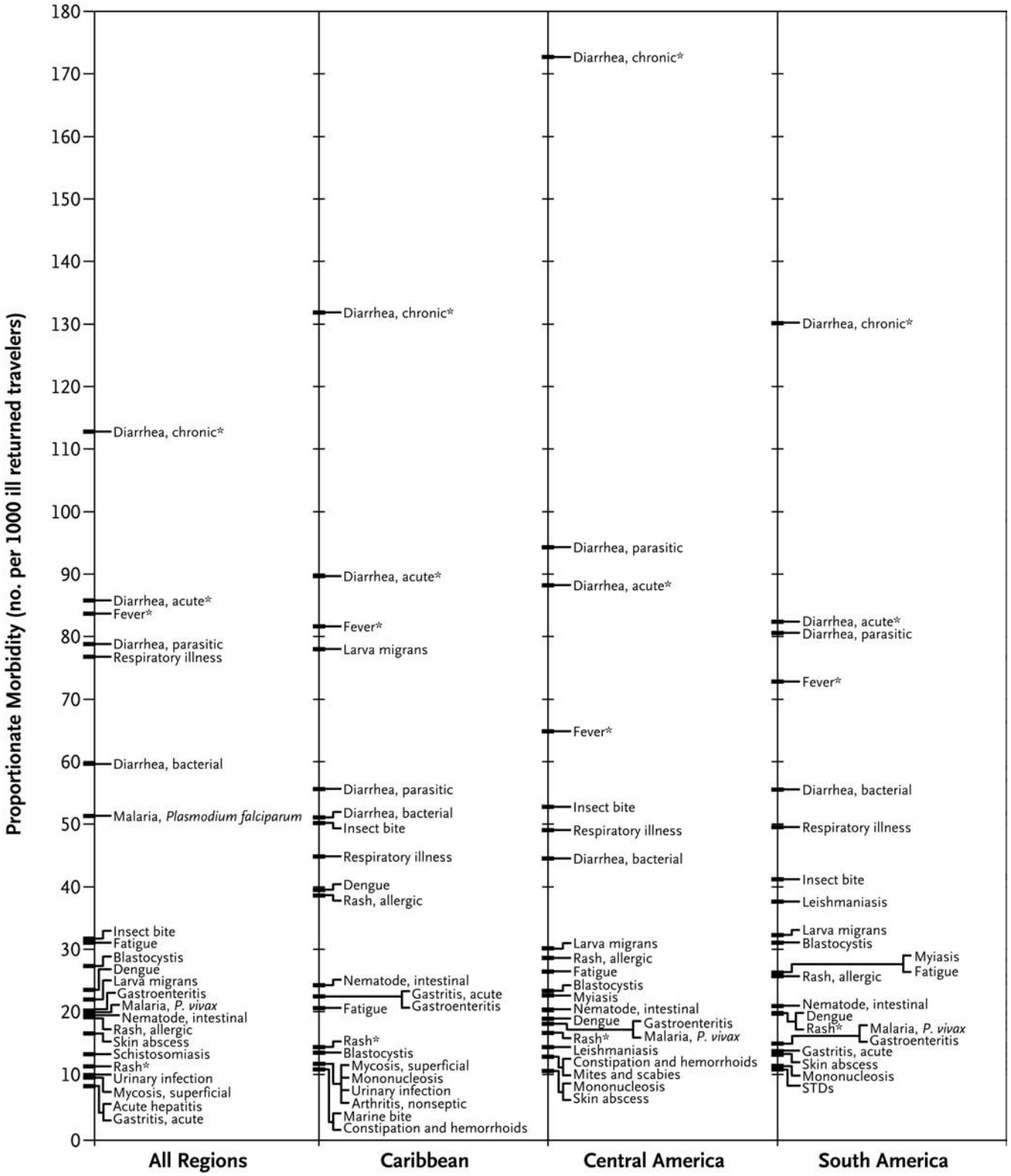


FIGURE 5-2

Proportionate morbidity among ill travelers returning from the developing world, according to region of travel. The proportions (not incidence rates) are shown for each of the top 22 specific diagnoses among all ill returned travelers within each region. STDs, sexually transmitted diseases. Asterisks indicate syndromic diagnoses for which specific etiologies could not be assigned. (*Reprinted with permission from DO Freedman et al: N Engl J Med 354:119, 2006. © 2006 Massachusetts Medical Society.*)

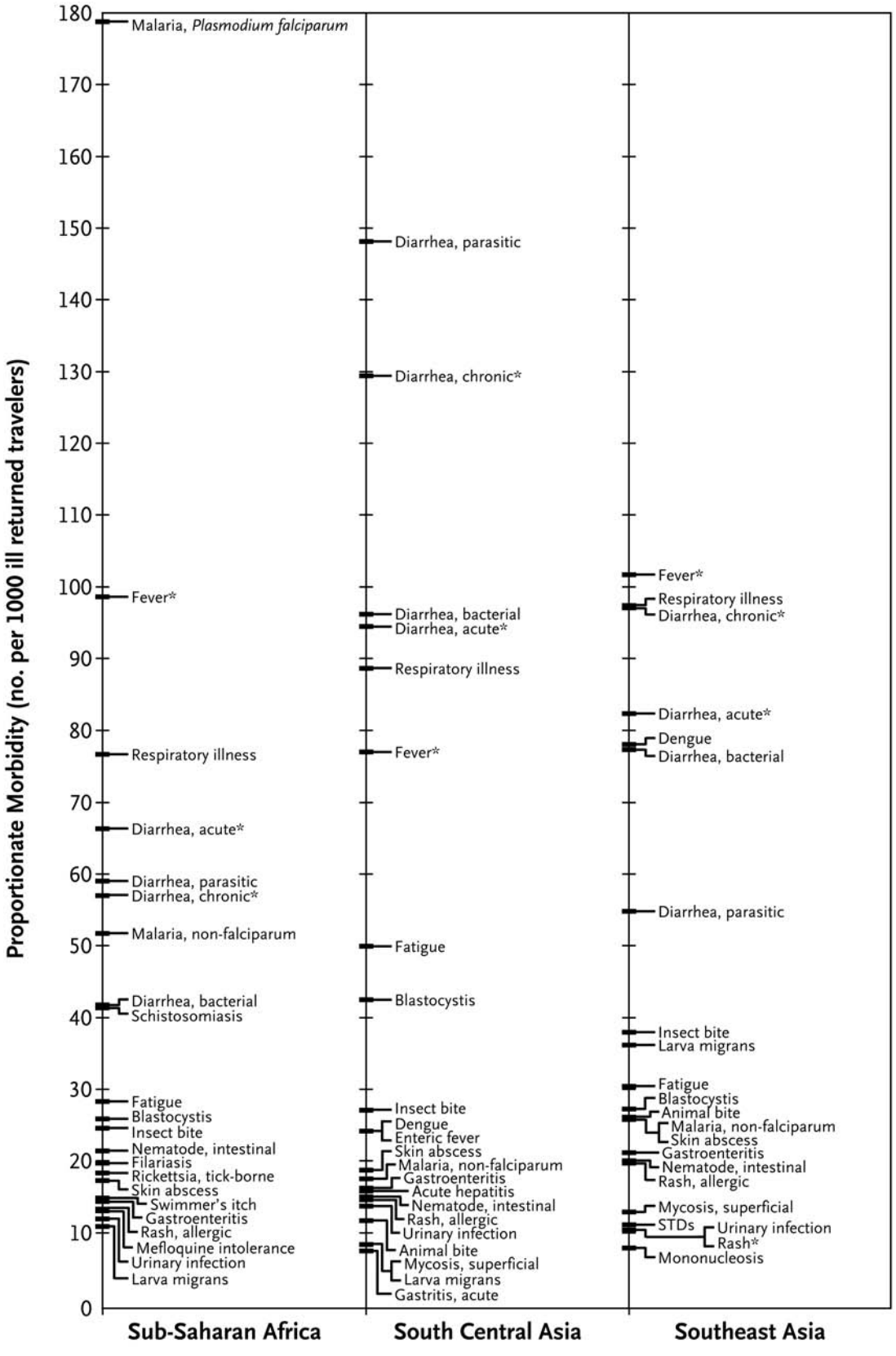


FIGURE 5-2 (*Continued*)

TABLE 5-3

ETIOLOGY AND GEOGRAPHIC DISTRIBUTION OF SYSTEMIC FEBRILE ILLNESS IN RETURNED TRAVELERS (N = 3907)

	PERCENTAGE OF CASES					
ETIOLOGY	**CARIB**	**CAm**	**SAm**	**SSA**	**SCA**	**SEA**
Malaria	<1	13	13	**62**	14	13
Dengue	**23**	12	14	<1	14	**32**
Mononucleosis	7	7	8	1	2	3
Rickettsia	0	0	0	**6**	1	2
Salmonella	2	3	2	<1	**14**	3

Note: Carib, Caribbean; CAm, Central America; SAm, South America; SSA, sub-Saharan Africa; SCA, south-central Asia; SEA, Southeast Asia. Bold type is for emphasis only.
Source: Revised from Table 2 in DO Freedman et al: N Engl J Med 354:119, 2006. Used with permission from the Massachusetts Medical Society.

reemergence of cholera as a global health threat, and created considerable fear about the possible spread of severe acute respiratory syndrome (SARS) and avian influenza (H5N1). For travelers, there are more realistic concerns. One of the largest outbreaks of dengue fever ever documented is now raging in Latin America; chikungunya virus has spread rapidly from Africa to southern Asia and recently to southern Europe; schistosomiasis is being described in previously unaffected lakes in Africa; and antibiotic-resistant strains of sexually transmitted and enteric pathogens are emerging at an alarming rate in the developing world. In addition, concerns have been raised about the potential for bioterrorism involving not only standard strains of unusual agents but mutant strains as well. Time will tell whether travelers (as well as persons at home) will routinely be vaccinated against diseases such as anthrax and smallpox. As Nobel laureate Dr. Joshua Lederberg pointed out, "The microbe that felled one child in a distant continent yesterday can reach yours today and seed a global pandemic tomorrow." The vigilant clinician understands that the importance of a thorough travel history cannot be overemphasized.

CHAPTER 6

LABORATORY DIAGNOSIS OF INFECTIOUS DISEASES

Alexander J. McAdam ■ Andrew B. Onderdonk

The laboratory diagnosis of infection requires the demonstration—either direct or indirect—of viral, bacterial, fungal, or parasitic agents in tissues, fluids, or excreta of the host. Clinical microbiology laboratories are responsible for processing these specimens and also for determining the antibiotic susceptibility of bacterial and fungal pathogens. Traditionally, detection of pathogenic agents has relied largely on either the microscopic visualization of pathogens in clinical material or the growth of microorganisms in the laboratory. Identification generally is based on phenotypic characteristics such as fermentation profiles for bacteria, cytopathic effects in

tissue culture for viral agents, and microscopic morphology for fungi and parasites. These techniques are reliable but are often time-consuming. Increasingly, the use of nucleic acid probes is becoming a standard method for detection, quantitation, and/or identification in the clinical microbiology laboratory, gradually replacing phenotypic characterization and microscopic visualization methods.

DETECTION METHODS

Reappraisal of the methods employed in the clinical microbiology laboratory has led to the development of strategies for detection of pathogenic agents through nonvisual biologic signal detection systems. Much of this methodology is based on the use of either electronic detection systems involving relatively inexpensive but sophisticated computers or nucleic acid probes directed at specific DNA or RNA targets. This chapter discusses both the methods that are currently available and those that are being developed.

BIOLOGIC SIGNALS

A *biologic signal* is a material that can be reproducibly differentiated from other substances present in the same physical environment. Key issues in the use of a biologic (or electronic) signal are distinguishing it from background noise and translating it into meaningful information. Examples of biologic signals applicable to clinical microbiology include structural components of bacteria, fungi, and viruses; specific antigens; metabolic end products; unique DNA or RNA base sequences; enzymes; toxins or other proteins; and surface polysaccharides.

DETECTION SYSTEMS

A detector is used to sense a signal and discriminate between that signal and background noise. Detection systems range from the trained eyes of a technologist assessing morphologic variations to sensitive electronic instruments such as gas-liquid chromatographs coupled to computer systems for signal analysis. The sensitivity with which signals can be detected varies widely. It is essential to use a detection system that discerns small amounts of signal even when biologic background noise is present—i.e., that is both sensitive and specific. Common detection systems include immunofluorescence; chemiluminescence for DNA/RNA probes; flame ionization detection of short- or long-chain fatty acids; and detection of substrate utilization or end-product formation as color changes, of enzyme activity as a change in light absorbance, of turbidity changes as a measure of growth, of cytopathic effects in cell lines, and of particle agglutination as a measure of antigen presence.

AMPLIFICATION

Amplification enhances the sensitivity with which weak signals can be detected. The most common microbiologic amplification technique is growth of a single bacterium into a discrete colony on an agar plate or into a suspension containing many identical organisms. The advantage of growth as an amplification method is that it requires only an appropriate growth medium; the disadvantage is the amount of time required. More rapid specific amplification of biologic signals can be achieved with techniques such as polymerase chain reaction (PCR), ligase chain reaction (LCR), and transcription-mediated amplification (TMA), all of which target the pathogen's DNA/RNA; enzyme immunoassays (EIAs, for antigens and antibodies); electronic amplification (for gas-liquid chromatography assays); antibody capture methods (for concentration and/or separation); and selective filtration or centrifugation. Although a variety of methods are available for the amplification and detection of biologic signals in research, thorough testing is required before these methods are validated as diagnostic assays.

DIRECT DETECTION

MICROSCOPY

The field of microbiology has been defined largely by the development and use of the microscope. The examination of specimens by microscopic methods rapidly provides useful diagnostic information. Staining techniques permit organisms to be seen more clearly.

The simplest method for microscopic evaluation is the wet mount, which is used, for example, to examine cerebrospinal fluid (CSF) for the presence of *Cryptococcus neoformans*, with India ink as a background against which to visualize large-capsuled yeast cells. Wet mounts with dark-field illumination also are used to detect spirochetes from genital lesions and to reveal *Borrelia* or *Leptospira* in blood. Skin scrapings and hair samples can be examined with the use of either 10% KOH wet-mount preparations or the Calcofluor white method and ultraviolet illumination to detect fungal elements as fluorescing structures. Staining of wet mounts—e.g., with lactophenol cotton blue stain for fungal elements—often is used for morphologic identification. These techniques enhance signal detection and decrease the background, making it easier to identify specific fungal structures.

STAINING

Gram's stain

Without staining, bacteria are difficult to see at the magnifications (400× to 1000×) used for their detection. Although simple one-step stains can be used, differential stains are more common. Gram's stain differentiates between organisms with thick peptidoglycan cell walls (gram-positive) and those with thin peptidoglycan cell walls and outer membranes that can be dissolved with alcohol or acetone (gram-negative). Cellular morphology and Gram's stain characteristics often can be used to categorize stained organisms into groups such as streptococci, staphylococci, and clostridia **(Fig. 6-1)**.

Gram-Negative Organisms

	GRx only	Oxidase +	Oxidase –	Fastidious	Anaerobic	Curved
Rod		*Pseudomonas* *Aeromonas* *Pasteurella* Others	Enterobacteriaceae Others	*Haemophilus* *Legionella* *Bordetella* *Brucella* *Francisella* Others	*Bacteroides* *Prevotella* *Fusobacterium* Others	*Vibrio* *Campylobacter*
Coccus	*Neisseria* *Branhamella*				*Veillonella* *Acidaminococcus* *Megasphaera*	

Gram-Positive Organisms

	Branching	Spores	Acid-Fast	Catalase +	Catalase –
Rod	*Nocardia* *Actinomyces* *Bifidobacterium*	*Clostridium* *Bacillus*	*Mycobacterium*	*Corynebacterium* *Listeria* Others	*Lactobacillus* Others
Coccus				*Staphylococcus* *Micrococcus* Others	*Streptococcus*

FIGURE 6-1
Interpretation of Gram's stain.

Gram's stain is particularly useful for examining sputum for polymorphonuclear leukocytes (PMNs) and bacteria. Sputum specimens from immunocompetent patients with ≥25 PMNs and <10 epithelial cells per low-power field often provide clinically useful information. However, the presence in "sputum" samples of >10 epithelial cells per low-power field and of multiple bacterial types suggests contamination with oral microflora. Despite the difficulty of discriminating between normal microflora and pathogens, Gram's stain may prove useful for specimens from areas with a large resident microflora if a useful biologic marker (signal) is available. Gram's staining of vaginal swab specimens can be used to detect epithelial cells covered with gram-positive bacteria in the absence of lactobacilli and the presence of gram-negative rods—a scenario regarded as a sign of bacterial vaginosis. Similarly, examination of stained stool specimens for leukocytes is useful as a screening procedure before testing for *Clostridium difficile* toxin or other enteric pathogens.

The examination of CSF and joint, pleural, or peritoneal fluid with Gram's stain is useful for determining whether bacteria and/or PMNs are present. The sensitivity is such that $>10^4$ bacteria per milliliter should be detected. Centrifugation often is performed before staining to concentrate specimens thought to contain low numbers of organisms. The pellet is examined after staining. This simple method is particularly useful for examination of CSF for bacteria and white blood cells or examination of sputum for mycobacteria.

Acid-fast stain

The acid-fast stain identifies organisms that retain carbol fuchsin dye after acid/organic solvent disruption (e.g., *Mycobacterium* spp.). Modifications of this procedure allow the differentiation of *Actinomyces* from *Nocardia* or other weakly (or partially) acid-fast organisms. The acid-fast stain is applied to sputum, other fluids, and tissue samples when acid-fast bacilli (AFB, e.g., *Mycobacterium* species) are suspected. Because few AFB may be detected in an entire smear, even when the specimen has been concentrated by centrifugation, identification of the pink/red AFB against the blue background of the counterstain requires a trained eye. An alternative method is the auramine-rhodamine combination fluorescent dye technique.

Fluorochrome stains

Fluorochrome stains such as acridine orange are used to identify white blood cells, yeasts, and bacteria in body fluids. Other specialized stains, such as Dappe's stain, may be used for the detection of mycoplasmas in cell cultures. Capsular, flagellar, and spore stains are used for identification or demonstration of characteristic structures.

Immunofluorescent stains

The *direct* immunofluorescent antibody technique uses antibody coupled to a fluorescent compound (e.g., fluorescein) and directed at a specific antigenic target to visualize organisms or subcellular structures. When samples are examined under appropriate conditions, the fluorescing compound absorbs ultraviolet light and reemits light at a higher wavelength that is visible to the human eye. In the *indirect* immunofluorescent antibody technique, an unlabeled (target) antibody binds a specific antigen. The specimen is then stained with fluorescein-labeled polyclonal antibody directed at the target antibody. Because each unlabeled target antibody

attached to the appropriate antigen has multiple sites for attachment of the second antibody, the visual signal can be intensified (i.e., amplified). This form of staining is called *indirect* because a two-antibody system is used to generate the signal for detection of the antigen. Both direct and indirect methods detect viral antigens (e.g., cytomegalovirus, herpes simplex virus, and respiratory viruses) within cultured cells or clinical specimens as well as many difficult-to-grow bacterial agents (e.g., *Legionella pneumophila*) in clinical specimens.

MACROSCOPIC ANTIGEN DETECTION

Latex agglutination assays and EIAs are rapid and inexpensive methods for identifying organisms, extracellular toxins, and viral agents by means of protein and polysaccharide antigens. Such assays may be performed directly on clinical samples or after growth of organisms on agar plates or in viral cell cultures. The biologic signal in each case is the antigen to be detected. Monoclonal or polyclonal antibodies coupled to a reporter (such as latex particles or an enzyme) are used for detection of antibody-antigen binding reactions.

Techniques such as direct agglutination of bacterial cells with specific antibody are simple but relatively insensitive; latex agglutination and EIAs are more sensitive. Some cell-associated antigens, such as capsular polysaccharides and lipopolysaccharides, can be detected by agglutination of a suspension of bacterial cells when antibody is added; this method is useful for typing of the somatic antigens of *Shigella* and *Salmonella*. In systems such as EIAs, which employ antibodies coupled to an enzyme, an antigen-antibody reaction results in the conversion of a colorless substrate to a colored product. Because the coupling of an enzyme to the antibody can amplify a weak biologic signal, the sensitivity of such assays is often high. In each instance, the basis for antigen detection is antigen-antibody binding, with the detection system changed to accommodate the biologic signal. Most of these assays provide information about whether antigen is present but do not quantify the antigen. EIAs are also useful for detecting bacterial toxins—e.g., *C. difficile* toxins A and B in stool.

Rapid and simple immunoassays for antigens of group A *Streptococcus*, influenza virus, and respiratory syncytial virus can be used in the clinical setting without a specialized diagnostic laboratory. Such tests are usually reasonably specific but may have only modest sensitivity.

DETECTION OF PATHOGENIC AGENTS BY CULTURE

SPECIMEN COLLECTION AND TRANSPORT

To culture bacterial, fungal, or viral pathogens, an appropriate sample must be placed into the proper medium for growth (amplification). The success of efforts to identify a specific pathogen often depends on the collection and transport process coupled to a laboratory-processing algorithm suitable for the specific sample/agent. In some instances, it is better for specimens to be plated at the time of collection rather than first being transported to the laboratory (e.g., urethral swabs being cultured for *Neisseria gonorrhoeae* or sputum specimens for pneumococci). In general, the more rapidly a specimen is plated onto appropriate media, the better the chance is for isolating bacterial pathogens. Deep tissue or fluid (pus) samples are more likely to give useful culture results than are superficial swab specimens. **Table 6-1** lists procedures for collection and transport of common specimens. Because there are many pathogen-specific paradigms for these procedures, it is important to seek advice from the microbiology laboratory when in doubt about a particular situation.

ISOLATION OF BACTERIAL PATHOGENS

Isolation of suspect pathogens from clinical material relies on the use of artificial media that support bacterial growth in vitro. Such media are composed of agar, which is not metabolized by bacteria; nutrients to support the growth of the species of interest; and sometimes substances to inhibit the growth of other bacteria. Broth is employed for growth (amplification) of organisms from specimens with few bacteria, such as peritoneal dialysis fluid, CSF, or samples in which anaerobes or other fastidious organisms may be present. The general use of liquid medium for all specimens is not worthwhile.

Two basic strategies are used to isolate pathogenic bacteria. The first is to employ enriched media that support the growth of any bacteria that may be present in a sample, such as blood or CSF, that contains no bacteria under normal conditions. Broths that allow the growth of small numbers of organisms may be subcultured to solid media when growth is detected. The second strategy is to use selective media to isolate (amplify) specific bacterial species from stool, genital tract secretions, or sputum—sites that contain many bacteria under normal conditions. Antimicrobial agents or other inhibitory substances are incorporated into the agar medium to inhibit growth of all but the bacteria of interest. After incubation, organisms that grow on such media are characterized further to determine whether they are pathogens. Selection for organisms that may be pathogens from the normal microflora shortens the time required for diagnosis **(Fig. 6-2)**.

ISOLATION OF VIRAL AGENTS

(See also Chap. 82) Pathogenic viral agents are often sought by culture when the presence of serum antibody is not a criterion for active infection, when serologic diagnosis is not practical, or when immunoassays have inadequate sensitivity. The biologic signal, virus, is amplified to a detectable level. Although a number of techniques for viral culture are available, an essential element is a monolayer of cultured mammalian cells sensitive to infection with the suspected virus. These cells serve as the amplification system by allowing the

TABLE 6-1

INSTRUCTIONS FOR COLLECTION AND TRANSPORT OF SPECIMENS FOR CULTURE

Note: It is absolutely essential that the microbiology laboratory be informed of the site of origin of the sample to be cultured and the infections that are suspected. This information determines the selection of culture media and the length of culture time.

TYPE OF CULTURE (SYNONYMS)	SPECIMEN	MINIMAL VOLUME	CONTAINER	OTHER CONSIDERATIONS
Blood				
Blood, routine (blood culture for aerobes, anaerobes, and yeasts)	Whole blood	10 mL in each of 2 bottles for adults and children; 5 mL, if possible, in aerobic bottles for infants; less for neonates	See below.[a]	See below.[b]
Blood for fungi, *Mycobacterium* spp.	Whole blood	10 mL in each of 2 bottles, as for routine blood cultures, or in Isolator tube requested from laboratory	Same as for routine blood culture	Specify "hold for extended incubation," since fungal agents may require 4 weeks to grow.
Blood, Isolator (lysis centrifugation)	Whole blood	10 mL	Isolator tubes	Use mainly for isolation of fungi, *Mycobacterium*, and other fastidious aerobes and for elimination of antibiotics from cultured blood in which organisms are concentrated by centrifugation.
Respiratory tract				
Nose	Swab from nares	1 swab	Sterile culturette or similar transport system containing holding medium	Swabs made of calcium alginate may be used.
Throat	Swab of posterior pharynx, ulcerations, or areas of suspected purulence	1 swab	Sterile culturette or similar swab specimen collection system containing holding medium	See below.[c]
Sputum	Fresh sputum (not saliva)	2 mL	Commercially available sputum collection system or similar sterile container with screw cap	*Cause for rejection:* Care must be taken to ensure that the specimen is sputum and not saliva. Examination of Gram's stain, with number of epithelial cells and polymorphonuclear leukocytes (PMNs) noted, can be an important part of the evaluation process. Induced sputum specimens should not be rejected.
Bronchial aspirates	Transtracheal aspirate, bronchoscopy specimen, or bronchial aspirate	1 mL of aspirate or brush in transport medium	Sterile aspirate or bronchoscopy tube, bronchoscopy brush in a separate sterile container	Special precautions may be required, depending on diagnostic considerations (e.g., *Pneumocystis*).

(*continued*)

TABLE 6-1

INSTRUCTIONS FOR COLLECTION AND TRANSPORT OF SPECIMENS FOR CULTURE (*CONTINUED*)

TYPE OF CULTURE (SYNONYMS)	SPECIMEN	MINIMAL VOLUME	CONTAINER	OTHER CONSIDERATIONS
Stool				
Stool for routine culture; stool for *Salmonella, Shigella*, and *Campylobacter*	Rectal swab or (preferably) fresh, randomly collected stool	1 g of stool or 2 rectal swabs	Plastic-coated cardboard cup or plastic cup with tight-fitting lid. Other leakproof containers are also acceptable.	If *Vibrio* spp. are suspected, the laboratory must be notified, and appropriate collection/transport methods should be used.
Stool for *Yersinia, Escherichia coli* O157	Fresh, randomly collected stool	1 g	Plastic-coated cardboard cup or plastic cup with tight-fitting lid	*Limitations:* Procedure requires enrichment techniques.
Stool for *Aeromonas* and *Plesiomonas*	Fresh, randomly collected stool	1 g	Plastic-coated cardboard cup or plastic cup with tight-fitting lid	*Limitations:* Stool should not be cultured for these organisms unless also cultured for other enteric pathogens.
Urogenital tract				
Urine	Clean-voided urine specimen or urine collected by catheter	0.5 mL	Sterile, leak-proof container with screw cap or special urine transfer tube	See below.[d]
Urogenital secretions	Vaginal or urethral secretions, cervical swabs, uterine fluid, prostatic fluid, etc.	1 swab or 0.5 mL of fluid	Vaginal and rectal swabs transported in Amies transport medium or similar holding medium for group B *Streptococcus;* direct inoculation preferred for *Neisseria gonorrhoeae*	Vaginal swab samples for "routine culture" should be discouraged whenever possible unless a particular pathogen is suspected. For detection of multiple organisms (e.g., group B *Streptococcus, Trichomonas, Chlamydia*, or *Candida* spp.), 1 swab per test should be obtained.
Body fluids, aspirates, and tissues				
Cerebrospinal fluid (lumbar puncture)	Spinal fluid	1 mL for routine cultures; ≥5 mL for *Mycobacterium*	Sterile tube with tight-fitting cap	Do not refrigerate; transfer to laboratory as soon as possible.
Body fluids	Aseptically aspirated body fluids	1 mL for routine cultures	Sterile tube with tight-fitting cap. Specimen may be left in syringe used for collection if the syringe is capped before transport.	For some body fluids (e.g., peritoneal lavage samples), increased volumes are helpful for isolation of small numbers of bacteria.
Biopsy and aspirated materials	Tissue removed at surgery, bone, anticoagulated bone marrow, biopsy samples, or other specimens from normally sterile areas	1 mL of fluid or a 1-g piece of tissue	Sterile "culturette"-type swab or similar transport system containing holding medium. Sterile bottle or jar should be used for tissue specimens.	Accurate identification of specimen and source is critical. Enough tissue should be collected for both microbiologic and histopathologic evaluations.

(*continued*)

TABLE 6-1

INSTRUCTIONS FOR COLLECTION AND TRANSPORT OF SPECIMENS FOR CULTURE (*CONTINUED*)

TYPE OF CULTURE (SYNONYMS)	SPECIMEN	MINIMAL VOLUME	CONTAINER	OTHER CONSIDERATIONS
Wounds	Purulent material or abscess contents obtained from wound or abscess without contamination by normal microflora	2 swabs or 0.5 mL of aspirated pus	Culturette swab or similar transport system or sterile tube with tight-fitting screw cap. For simultaneous anaerobic cultures, send specimen in anaerobic transport device or closed syringe.	*Collection:* When possible, abscess contents or other fluids should be collected in a syringe (rather than with a swab) to provide an adequate sample volume and an anaerobic environment.
Special recommendations				
Fungi	Specimen types listed above may be used. When urine or sputum is cultured for fungi, a first morning specimen usually is preferred.	1 mL or as specified above for individual listing of specimens. Large volumes may be useful for urinary fungi.	Sterile, leakproof container with tight-fitting cap	*Collection:* Specimen should be transported to microbiology laboratory within 1 h of collection. Contamination with normal flora from skin, rectum, vaginal tract, or other body surfaces should be avoided.
Mycobacterium (acid-fast bacilli)	Sputum, tissue, urine, body fluids	10 mL of fluid or small piece of tissue. Swabs should not be used.	Sterile container with tight-fitting cap	Detection of *Mycobacterium* spp. is improved by use of concentration techniques. Smears and cultures of pleural, peritoneal, and pericardial fluids often have low yields. Multiple cultures from the same patient are encouraged. Culturing in liquid media shortens time to detection.
Legionella	Pleural fluid, lung biopsy, bronchoalveolar lavage fluid, bronchial/transbronchial biopsy. Rapid transport to laboratory is critical.	1 mL of fluid; any size tissue sample, although a 0.5-g sample should be obtained when possible	—	—
Anaerobic organisms	Aspirated specimens from abscesses or body fluids	1 mL of aspirated fluid, 1 g of tissue, or 2 swabs	An appropriate anaerobic transport device is required.[e]	Specimens cultured for obligate anaerobes should be cultured for facultative bacteria as well. Fluid or tissue is preferred to swabs.

(*continued*)

TABLE 6-1

INSTRUCTIONS FOR COLLECTION AND TRANSPORT OF SPECIMENS FOR CULTURE (*CONTINUED*)

TYPE OF CULTURE (SYNONYMS)	SPECIMEN	MINIMAL VOLUME	CONTAINER	OTHER CONSIDERATIONS
Viruses[f]	Respiratory secretions, wash aspirates from respiratory tract, nasal swabs, blood samples (including buffy coats), vaginal and rectal swabs, swab specimens from suspicious skin lesions, stool samples (in some cases)	1 mL of fluid, 1 swab, or 1 g of stool in each appropriate transport medium	Fluid or stool samples in sterile containers or swab samples in viral culturette devices (kept on ice but not frozen) are generally suitable. Plasma samples and buffy coats in sterile collection tubes should be kept at 4–8°C. If specimens are to be shipped or kept for a long time, freezing at –80°C is usually adequate.	Most samples for culture are transported in holding medium containing antibiotics to prevent bacterial overgrowth and viral inactivation. Many specimens should be kept cool but not frozen, provided they are transported promptly to the laboratory. Procedures and transport media vary with the agent to be cultured and the duration of transport.

[a]For samples from adults, two bottles (smaller for pediatric samples) should be used: one with dextrose phosphate, tryptic soy, or another appropriate broth and the other with thioglycollate or another broth containing reducing agents appropriate for isolation of obligate anaerobes. For children, from whom only limited volumes of blood can be obtained, only an aerobic culture should be done unless there is specific concern about anaerobic sepsis (e.g., with abdominal infections). For special situations (e.g., suspected fungal infection, culture-negative endocarditis, or mycobacteremia), different blood collection systems may be used (Isolator systems; see table).

[b]Collection: An appropriate disinfecting technique should be used on both the bottle septum and the patient. Do not allow air bubbles to get into anaerobic broth bottles. Special considerations: There is no more important clinical microbiology test than the detection of bloodborne pathogens. The rapid identification of bacterial and fungal agents is a major determinant of patients' survival. Bacteria may be present in blood either continuously (as in endocarditis, overwhelming sepsis, and the early stages of salmonellosis and brucellosis) or intermittently (as in most other bacterial infections, in which bacteria are shed into the blood on a sporadic basis). Most blood culture systems employ two separate bottles containing broth medium: one that is vented in the laboratory for the growth of facultative and aerobic organisms and one that is maintained under anaerobic conditions. In cases of suspected continuous bacteremia/fungemia, two or three samples should be drawn before the start of therapy, with additional sets obtained if fastidious organisms are thought to be involved. For intermittent bacteremia, two or three samples should be obtained at least 1 h apart during the first 24 h.

[c]Normal microflora includes α-hemolytic streptococci, saprophytic *Neisseria* spp., diphtheroids, and *Staphylococcus* spp. Aerobic culture of the throat ("routine") includes screening for and identification of β-hemolytic *Streptococcus* spp. and other potentially pathogenic organisms. Although considered components of the normal microflora, organisms such as *Staphylococcus aureus*, *Haemophilus influenzae*, and *Streptococcus pneumoniae* will be identified by most laboratories, if requested. When *Neisseria gonorrhoeae* or *Corynebacterium diphtheriae* is suspected, a special culture request is recommended.

[d](1) Clean-voided specimens, midvoid specimens, and Foley or indwelling catheter specimens that yield 50,000 organisms/mL and from which no more than three species are isolated should have organisms identified. Neither indwelling catheter tips nor urine from the bag of a catheterized patient should be cultured. (2) Straight-catheterized, bladder-tap, and similar urine specimens should undergo a complete workup (identification and susceptibility testing) for all potentially pathogenic organisms regardless of colony count. (3) Certain clinical problems (e.g., acute dysuria in women) may warrant identification and susceptibility testing of isolates present at concentrations of <50,000 organisms/mL.

[e]Aspirated specimens in capped syringes or other transport devices designed to limit oxygen exposure are suitable for the cultivation of obligate anaerobes. A variety of commercially available transport devices may be used. Contamination of specimens with normal microflora from the skin, rectum, vaginal vault, or another body site should be avoided. Collection containers for aerobic culture (such as dry swabs) and inappropriate specimens (such as refrigerated samples; expectorated sputum; stool; gastric aspirates; and vaginal, throat, nose, and rectal swabs) should be rejected as unsuitable.

[f]Laboratories generally use diverse methods to detect viral agents, and the specific requirements for each specimen should be checked before a sample is sent.

proliferation of viral particles. Virus may be detected by direct observation of the cultured cells for cytopathic effects or by immunofluorescent detection of viral antigens after incubation. Conventional viral culture is useful for detection of rapidly propagated agents, such as herpes simplex virus. Viruses that grow more slowly (e.g., cytomegalovirus and varicella-zoster virus) can be detected quickly by shell-vial culture, in which the specimen is centrifuged on a monolayer of cells that is then incubated for 1–2 days and finally is stained for viral antigens with fluorochrome-conjugated antibodies.

AUTOMATION OF MICROBIAL DETECTION IN BLOOD

The detection of microbial pathogens in blood is difficult because the number of organisms present in the sample is often low and the organisms' integrity

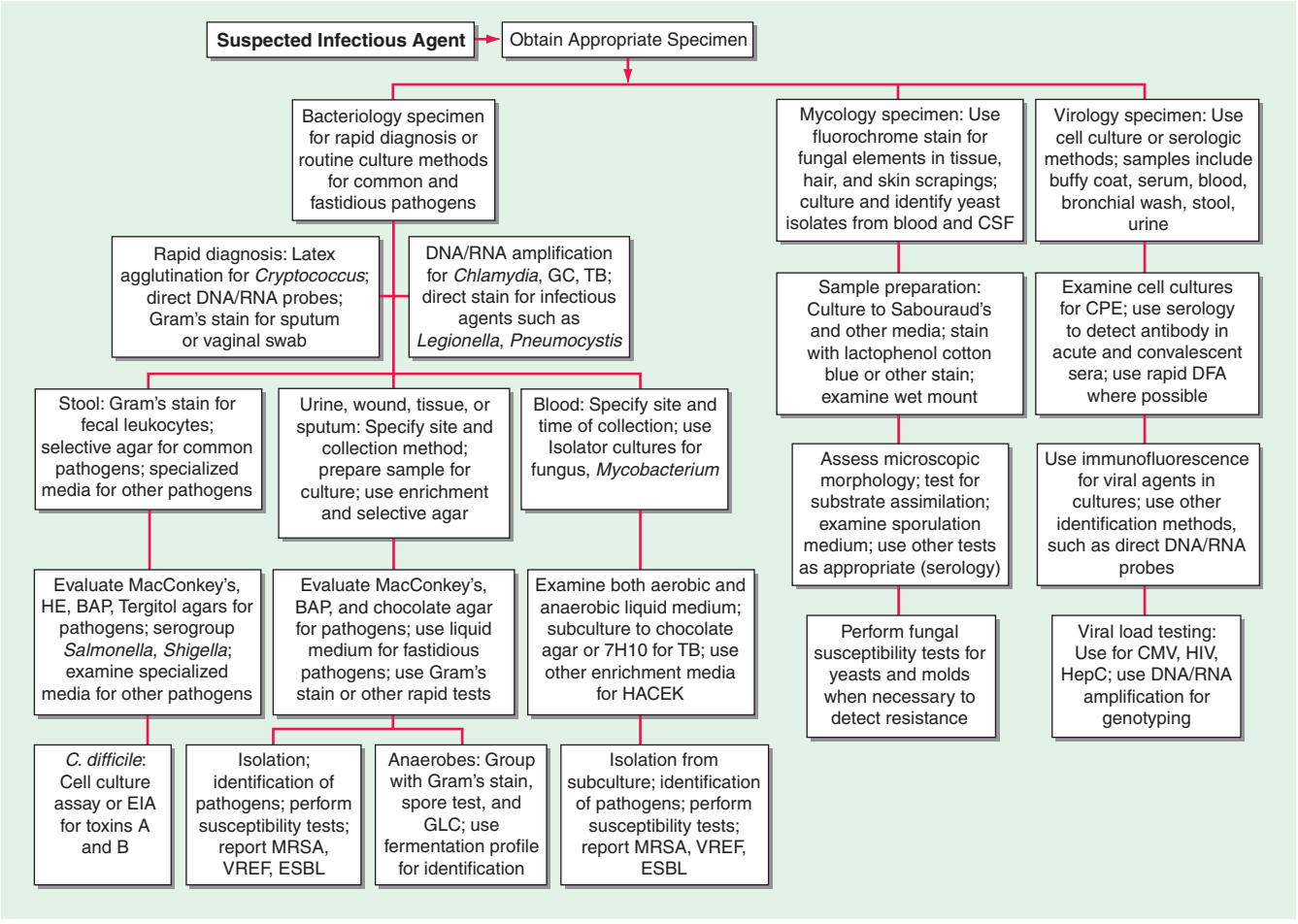


FIGURE 6-2
Common specimen-processing algorithms used in clinical microbiology laboratories. BAP, blood agar plate; CMV, cytomegalovirus; CPE, cytopathic effects; CSF, cerebrospinal fluid; DFA, direct fluorescent antibody; EIA, enzyme immunoassay; ESBL, extended-spectrum β-lactamase; GBS, group B *Streptococcus*; GC, *Neisseria gonorrhoeae*; GLC, gas-liquid chromatography; HACEK, *Haemophilus aphrophilus/parainfluenzae/paraphrophilus*, *Aggregatibacter actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*; HE, Hektoen enteric medium; HepC, hepatitis C virus; HIV, human immunodeficiency virus; MRSA, methicillin-resistant *Staphylococcus aureus*; TB, *Mycobacterium tuberculosis*; VREF, vancomycin-resistant *Enterococcus faecium*.

and ability to replicate may be damaged by humoral defense mechanisms or antimicrobial agents. Over the years, systems that rely on the detection of gas (usually CO_2) produced by bacteria and yeasts in blood culture medium have allowed the automation of the detection procedure. The most common systems involve either (1) the measurement of gas pressure in the headspace to indicate bacterial gas production or consumption or (2) the use of reflectance optics, with a light-emitting diode and photodiode employed to detect a color change in a CO_2-sensitive indicator built into the bottom of the culture bottle. These systems measure CO_2 concentration as indicative of microbial growth. Such methods are no more sensitive than the human eye in detecting a positive culture; however, because the bottles in an automated system are monitored more frequently, a positive culture often is detected more rapidly than by manual techniques, and important information, including the result of Gram's stain and preliminary susceptibility assays, can be obtained sooner. One advantage of automated blood culture systems is that the bottles are scanned continuously in a noninvasive monitoring procedure, and thus the likelihood of laboratory contamination is decreased.

Several factors affect the yield of blood culture from bacteremic patients. Increasing the volume of blood tested increases the chance of a positive culture. An increase from 10 to 20 mL of blood increases the proportion of positive cultures by ~30%; however, this effect is less pronounced in patients with bacterial endocarditis. Obtaining multiple cultures (up to three per 24-h period) also increases the chance of detecting a bacterial pathogen. Prolonged culture and blind subculture for detection of most fastidious bacteria (e.g., *Haemophilus*, *Actinobacillus*, *Cardiobacterium*, *Eikenella*, and *Kingella* species) are not needed with automated blood culture systems.

Automated systems also have been applied to the detection of microbial growth from specimens other than blood, such as peritoneal and other normally sterile fluids. *Mycobacterium* species can be detected in certain automated systems if appropriate liquid media are used for culture. Although automated blood culture systems are more sensitive than lysis-centrifugation methods (e.g., Isolator) for yeasts and most bacteria, lysis-centrifugation culture is recommended for filamentous fungi, *Histoplasma capsulatum*, and some fastidious bacteria (*Legionella* and *Bartonella*).

DETECTION OF PATHOGENIC AGENTS BY SEROLOGIC METHODS

Measurement of serum antibody provides an indirect marker for past or current infection with a specific viral agent or other pathogens, including *Brucella*, *Legionella*, *Rickettsia*, and *Helicobacter pylori*. The biologic signal is usually either IgM or IgG antibody directed at surface-expressed antigen. The detection systems include those used for bacterial antigens (agglutination reactions, immunofluorescence, and EIA) and unique systems such as hemolysis inhibition and complement fixation. Serologic methods generally fall into two categories: those that determine protective antibody levels and those that measure changing antibody titers during infection. Determination of an antibody response as a measure of current immunity is important in the case of viral agents for which there are vaccines, such as rubella virus and varicella-zoster virus; assays for this purpose normally use one or two dilutions of serum for a qualitative determination of protective antibody levels. Quantitative serologic assays to detect increases in antibody titers most often employ paired serum samples obtained at the onset of illness and 10–14 days later (i.e., acute- and convalescent-phase samples). Since the incubation period before symptoms are noted may be long enough for an antibody response to occur, the demonstration of acute-phase antibody alone is often insufficient to establish the diagnosis of active infection as opposed to past exposure. In such circumstances, IgM may be useful as a measure of an early, acute-phase antibody response. A fourfold increase in total antibody titer or in EIA activity between the acute- and convalescent-phase samples is also regarded as evidence for active infection.

For certain viral agents, such as Epstein-Barr virus, the antibodies produced may be directed at different antigens during different phases of the infection. For this reason, most laboratories test for antibody directed at both viral capsid antigens and antigens associated with recently infected host cells to determine the stage of infection.

IDENTIFICATION METHODS

Once bacteria are isolated, characteristics that are readily detectable after growth on agar media (colony size, color, hemolytic reactions, odor, microscopic appearance) may suggest a species, but definitive identification requires additional tests. Identification methods include classic biochemical phenotyping, which is still the most common approach, and more sophisticated methods such as gas chromatography and nucleic acid tests.

CLASSIC PHENOTYPING

Classic phenotypic identification of bacteria entails tests for protein or carbohydrate antigens, the production of specific enzymes, the ability to metabolize specific substrates and carbon sources (such as carbohydrates), or the production of certain metabolites. Rapid versions of some of these tests are available, and many common organisms can be identified on the first day of growth. Other organisms, particularly gram-negative bacteria, require more extensive testing, either manual or automated.

Automated systems allow rapid phenotypic identification of bacterial pathogens. Most of these systems are based on biotyping techniques in which isolates are grown on multiple substrates and the reaction pattern is compared with known patterns for various bacterial species. This procedure is relatively fast, and commercially available systems include miniaturized fermentation, coding to simplify recording of results, and probability calculations for the most likely pathogens. If the biotyping approach is automated and the reading process is coupled to computer-based data analysis, rapidly growing organisms (such as Enterobacteriaceae) can be identified within hours of detection on agar plates.

Several systems use preformed enzymes for even speedier identification (within 2–3 h). Those systems do not rely on bacterial growth per se to determine whether a substrate has been used. They employ a heavy inoculum in which specific bacterial enzymes are present in amounts sufficient to convert substrate to product rapidly. In addition, some systems use fluorogenic substrate/end-product detection methods to increase sensitivity (through signal amplification).

GAS-LIQUID CHROMATOGRAPHY

Gas-liquid chromatography often is used to detect metabolic end products of bacterial fermentations. One common application is identification of short-chain fatty acids produced by obligate anaerobes during glucose fermentation. Because the types and relative concentrations of volatile acids differ among the various genera and species that make up this group of organisms, such information serves as a metabolic "fingerprint" for a particular isolate.

Gas-liquid chromatography can be coupled to a sophisticated signal-analysis software system for identification and quantitation of long-chain fatty acids (LCFAs) in the outer membranes and cell walls of bacteria and fungi. For any particular species, the types and relative concentrations of LCFAs are distinctive

enough to allow differentiation even from closely related species. An organism may be identified definitively within a few hours after detection of growth on appropriate media. LCFA analysis is one of the most advanced procedures currently available for phenotypic characterization.

NUCLEIC ACID TESTS

Techniques for the detection and quantitation of specific DNA and RNA base sequences in clinical specimens have become powerful tools for the diagnosis of bacterial, viral, parasitic, and fungal infections. Nucleic acid tests are used for four purposes. First, they are used to detect, and sometimes to quantify, specific pathogens in clinical specimens. Second, such tests are used for identification of organisms (usually bacteria) that are difficult to identify by conventional methods. Third, nucleic acid tests are used to determine whether two or more isolates of the same pathogen are closely related (belonging to the same "clone" or "strain"). Fourth, these tests are used to predict the sensitivity of organisms (typically viruses) to chemotherapeutic agents. Current technology encompasses a wide array of methods for amplification and signal detection, some of which have been approved by the U.S. Food and Drug Administration (FDA) for clinical diagnosis.

Use of nucleic acid tests generally involves lysis of intact cells or viruses and denaturation of the DNA or RNA to render it single-stranded. Probe(s) or primer(s) complementary to the pathogen-specific target sequence may be hybridized to the target sequence in a solution or on a solid support, depending on the system employed. In situ hybridization of a probe to a target is also possible and allows the use of probes with agents present in tissue specimens. Once the probe(s) or primer(s) have been hybridized to the target (biologic signal), a variety of strategies may be employed to detect, amplify, and/or quantify the target-probe complex **(Fig. 6-3)**.

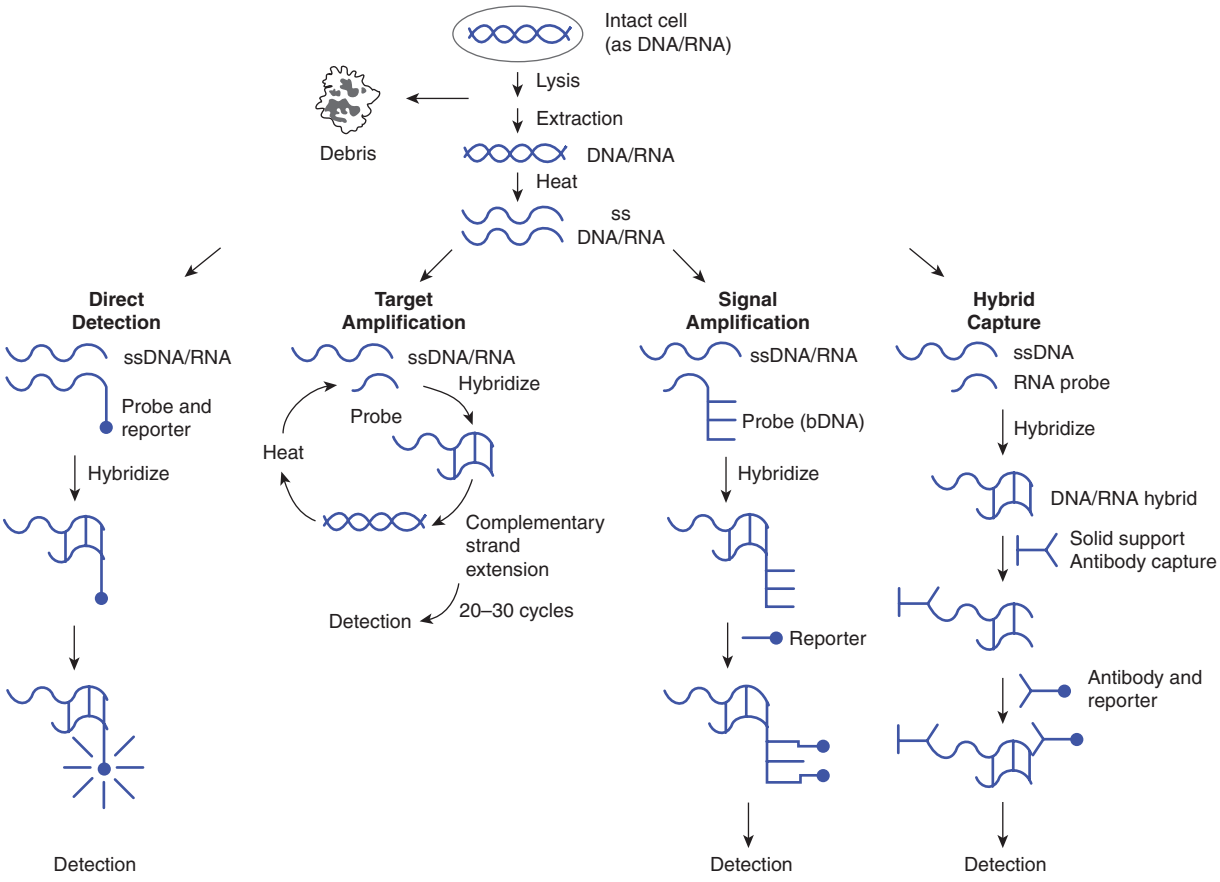


FIGURE 6-3

Strategies for amplification and/or detection of a target-probe complex. DNA or RNA extracted from microorganisms is heated to create single-stranded (ss) DNA/RNA containing appropriate target sequences. These target sequences may be hybridized directly (direct detection) with probes attached to reporter molecules; they may be amplified by repetitive cycles of complementary strand extension (polymerase chain reaction) before attachment of a reporter probe; or the original target-probe signal may be amplified via hybridization with an additional probe containing multiple copies of a secondary reporter target sequence (branched-chain DNA, or bDNA). DNA/RNA hybrids also can be "captured" on a solid support (hybrid capture), with antibody directed at the DNA/RNA hybrids used to concentrate them and a second antibody coupled to a reporter molecule attached to the captured hybrid.

Probes for direct detection of pathogens in clinical specimens

Nucleic acid probes are used for direct detection of pathogens in clinical specimens without amplification of the target strand of DNA or RNA. Such tests detect a relatively short sequence of bases specific for a particular pathogen on single-stranded DNA or RNA by hybridization of a complementary sequence of bases (probe) coupled to a "reporter" system that serves as the signal for detection. Nucleic acid probes are available commercially for direct detection of various bacterial and parasitic pathogens, including *Chlamydia trachomatis*, *N. gonorrhoeae*, and group A *Streptococcus*. A combined assay to detect and differentiate agents of vaginitis/vaginosis (*Gardnerella vaginalis*, *Trichomonas vaginalis*, and *Candida* species) also has been approved. An assortment of probes are available for confirming the identity of cultured pathogens, including some dimorphic molds, *Mycobacterium* species, and other bacteria (e.g., *Campylobacter* species, *Streptococcus* species, and *Staphylococcus aureus*). Probes for the direct detection of bacterial pathogens often are aimed at highly conserved 16S ribosomal RNA sequences, of which there are many more copies than there are of any single genomic DNA sequence in a bacterial cell. The sensitivity and specificity of probe assays for direct detection are comparable to those of more traditional assays, including EIA and culture.

In an alternative probe assay called *hybrid capture*, an RNA probe anneals to a DNA target, and the resulting DNA/RNA hybrid is captured on a solid support by antibody specific for DNA/RNA hybrids (concentration/amplification) and detected by chemiluminescent-labeled antibody specific for DNA/RNA hybrids. Hybrid capture assays are available for *C. trachomatis*, *N. gonorrhoeae*, cytomegalovirus, and human papillomavirus.

Many laboratories have developed their own probes for pathogens; however, unless a method-validation protocol for diagnostic testing has been performed, federal law in the United States restricts the use of such probes to research.

Nucleic acid amplification test strategies

In theory, a single target nucleic acid sequence can be amplified to detectable levels. There are several strategies for nucleic acid amplification tests (NAATs), including PCR, LCR, strand displacement amplification, and self-sustaining sequence replication. In each case, exponential amplification of a pathogen-specific DNA or RNA sequence depends on primers that anneal to the target sequence. The amplified nucleic acid can be detected after the reaction is complete or (in *real-time* detection) as amplification proceeds. The sensitivity of NAATs is far greater than that of traditional assay methods such as culture. However, the care with which the assays are performed is important, because cross-contamination of clinical material with DNA or RNA from other sources (even at low levels) can cause false-positive results.

PCR, the first and still the most common NAAT, requires repeated heating of the DNA to separate the two complementary strands of the double helix, hybridization of a primer sequence to the appropriate target sequence, target amplification using PCR for complementary strand extension, and signal detection via a labeled probe. Methods for the monitoring of PCR after each amplification cycle—via either incorporation of fluorescent dyes into the DNA during primer extension or use of fluorescent probes capable of fluorescence resonance energy transfer—have decreased the period required to detect a specific target. An alternative NAAT employs transcription-mediated amplification, in which an RNA target sequence is converted to DNA, which then is exponentially transcribed into an RNA target. The advantage of this method is that only a single heating/annealing step is required for amplification. At present, amplification assays for *Mycobacterium tuberculosis*, *N. gonorrhoeae*, *C. trachomatis*, *Mycoplasma hominis*, group B *Streptococcus*, and methicillin-resistant *S. aureus* are on the market. Again, many laboratories have used commercially available *taq* polymerase, probe sequences, and analyte-specific reagents to develop "in-house" assays for diagnostic use. Issues related to quality control, interpretation of results, sample processing, and regulatory requirements have slowed the commercial development of many diagnostic assay kits.

Identification of otherwise difficult-to-identify bacteria involves an initial amplification of a highly conserved region of 16S rDNA by PCR. Automated sequencing of several hundred bases is then performed, and the sequence information is compared with large databases containing sequence information for thousands of different organisms. Although 16S sequencing is not as rapid as other methods and is still relatively expensive for routine use in a clinical microbiology laboratory, it is becoming the definitive method for identification of unusual or difficult-to-cultivate organisms.

Quantitative nucleic acid test strategies

With the advent of newer therapeutic regimens for HIV-associated disease, cytomegalovirus infection, and hepatitis B and C virus infections, the response to therapy has been monitored by determining both genotype and "viral load" at various times after treatment initiation. Quantitative NAATs are available for HIV (PCR), cytomegalovirus (PCR), hepatitis B (PCR), and hepatitis C (PCR and TMA). Many laboratories have validated and perform quantitative assays for these and other pathogens (e.g., Epstein-Barr virus), using analyte-specific reagents for NAATs.

Branched-chain DNA (bDNA) testing is an alternative to NAATs for quantitative nucleic acid testing. In such testing, bDNA attaches to a site different from the target-binding sequence of the original probe. Chemiluminescent-labeled oligonucleotides can then bind to multiple repeating sequences on the bDNA. The amplified bDNA signal is detected by chemiluminescence. bDNA assays for viral load of HIV, hepatitis B virus, and hepatitis C virus have been approved by the FDA. The advantage of bDNA assays over PCR is that only a single

heating/annealing step is required to hybridize the target-binding probe to the target sequence for amplification.

Application of nucleic acid tests

In addition to the applications already discussed, nucleic acid tests are used to detect and identify difficult-to-grow or noncultivable bacterial pathogens such as *Mycobacterium*, *Legionella*, *Ehrlichia*, *Rickettsia*, *Babesia*, *Borrelia*, and *Tropheryma whippelii*. In addition, methods for rapid detection of agents of public health concern, such as *Franciscella tularensis*, *Bacillus anthracis*, smallpox virus, and *Yersinia pestis*, have been developed.

Nucleic acid tests also are used to determine how close the relationship is among different isolates of the same species of pathogen. The demonstration that bacteria of a single clone have infected multiple patients in the context of a possible means of transmission (e.g., a health care provider) offers confirmatory evidence for an outbreak. Pulsed-field gel electrophoresis remains the gold standard for bacterial strain analysis. This method involves the use of restriction enzymes that recognize rare sequences of nucleotides to digest bacterial DNA, resulting in large DNA fragments. These fragments are separated by gel electrophoresis with variable polarity of the electrophoretic current and then are visualized. Similar band patterns (i.e., differences in ≤3 bands) suggest that different bacterial isolates are closely related, or clonal. Simpler methods of strain typing include sequencing of single or multiple genes and PCR-based amplification of repetitive DNA sequences in the bacterial chromosome.

Future applications of nucleic acid testing probably will include the replacement of culture for identification of many pathogens with solid-state DNA/RNA chip technology, in which thousands of unique nucleic acid sequences can be detected on a single silicon chip.

SUSCEPTIBILITY TESTING OF BACTERIA

A principal responsibility of the clinical microbiology laboratory is to determine which antimicrobial agents inhibit a specific bacterial isolate. Such testing is used for patient care and for monitoring of infection control problems, such as methicillin-resistant *S. aureus* or vancomycin-resistant *Enterococcus faecium*. Two approaches are useful. The first is a qualitative assessment of susceptibility, with responses categorized as susceptible, resistant, or intermediate. This approach can involve either the placement of paper disks containing antibiotics on an agar surface inoculated with the bacterial strain to be tested (Kirby-Bauer or disk/agar diffusion method), with measurement of the zones of growth inhibition after incubation, or the use of broth cultures containing a set concentration of antibiotic (breakpoint method). These methods have been calibrated carefully against quantitative methods and clinical experience with each antibiotic, and zones of inhibition and breakpoints have been calculated on a species-by-species basis.

The second approach is to inoculate the test strain of bacteria into a series of broth cultures (or agar plates) with increasing concentrations of antibiotic. The lowest concentration of antibiotic that inhibits visual microbial growth in this test system is known as the *minimal inhibitory concentration* (MIC). If tubes in which no growth is seen are subcultured, the minimal concentration of antibiotic required to kill 99.9% of the starting inoculum also can be determined (*minimal bactericidal concentration,* or MBC). The MIC value can be given a categorical interpretation of susceptible, resistant, or intermediate and so is more widely used than the MBC. Quantitative susceptibility testing by the microbroth dilution technique, a miniaturized version of the broth dilution technique using microwell plates, lends itself to automation and is used commonly in larger clinical laboratories.

A novel version of the disk/agar diffusion method employs a quantitative diffusion gradient, or epsilometer (E-test), and uses an absorbent strip with a known gradient of antibiotic concentrations along its length. When the strip is placed on the surface of an agar plate seeded with a bacterial strain to be tested, antibiotic diffuses into the medium, and bacterial growth is inhibited. The MIC is estimated as the lowest concentration that inhibits visible growth.

For some organisms, such as obligate anaerobes, routine susceptibility testing generally is not performed because of the difficulty of growing the organisms and the predictable sensitivity of most isolates to specific antibiotics.

SUSCEPTIBILITY TESTING OF FUNGAL AGENTS

With the advent of many new agents for treating yeasts and systemic fungal agents, the need for testing of individual isolates for susceptibility to specific antifungal agents has increased. In the past, few laboratories participated in such testing because of a lack of standard methods like those available for testing bacterial agents. However, several systems have been approved for antifungal susceptibility testing. These methods, which determine the minimal fungicidal concentration (MFC), are similar to the broth microdilution methods used to determine the MIC for bacteria. The E-test method is approved for testing the susceptibility of yeasts to fluconazole, itraconazole, and flucytosine, and disk diffusion can be used to test the susceptibility of *Candida* species to fluconazole and voriconazole. Methods for determining the MFC against fungal agents such as *Aspergillus* species are technically difficult, and most clinical laboratories refer requests for such testing to reference laboratories.

ANTIVIRAL TESTING

See Chap. 82.

CHAPTER 7

MICROBIAL BIOTERRORISM

H. Clifford Lane ■ Anthony S. Fauci

Descriptions of the use of microbial pathogens as potential weapons of war or terrorism date from ancient times. Among the most frequently cited of such episodes are the poisoning of water supplies in the sixth century B.C. with the fungus *Claviceps purpurea* (rye ergot) by the Assyrians, the hurling of the dead bodies of plague victims over the walls of the city of Kaffa by the Tartar army in 1346, and the efforts by the British to spread smallpox to the Native American population loyal to the French via contaminated blankets in 1767. Although the use of chemical weapons in wartime took place in the not-too-distant past, the tragic events of September 11, 2001, followed closely by the mailing of letters containing anthrax spores to media and congressional offices through the U.S. Postal Service, dramatically changed the mindset of the American public regarding both our vulnerability to microbial bioterrorist attacks and the seriousness and intent of the federal government to protect its citizens against future attacks. Modern science has revealed methods of deliberately spreading or enhancing disease in ways not appreciated by our ancestors. The combination of basic research, good medical practice, and constant vigilance will be needed to defend against such attacks.

Although the potential impact of a bioterrorist attack could be enormous, leading to thousands of deaths and high morbidity rates, acts of bioterrorism would be expected to produce their greatest impact through the fear and terror they generate. In contrast to biowarfare, where the primary goal is destruction of the enemy through mass casualties, an important goal of bioterrorism is to destroy the morale of a society through fear and uncertainty. While the actual biologic impact of a single act may be small, the degree of disruption created by the realization that such an attack is possible may be enormous. This was readily apparent with the impact on the U.S. Postal Service and the functional interruption of the activities of the legislative branch of the United States government following the anthrax attacks noted above. Thus, the key to the defense against these attacks is a highly functioning system of public health surveillance and education so that attacks can be quickly recognized and effectively contained. This is complemented by the availability of appropriate countermeasures in the form of diagnostics, therapeutics, and vaccines, both in response to and in anticipation of bioterrorist attacks.

The Working Group for Civilian Biodefense has put together a list of key features that characterize the elements of biologic agents that make them particularly effective as weapons **(Table 7-1)**. Included among these are the ease of spread and transmission of the agent as well as the presence of an adequate database to allow newcomers to the field to quickly apply the good science of others to bad intentions of their own. Agents of bioterrorism may be used in their naturally occurring forms or they can be deliberately modified to provide maximal impact. Among the approaches to maximizing the deleterious effects of biologic agents are the genetic modification of microbes for the purposes of antimicrobial resistance or evasion by the immune system, creation of fine-particle aerosols, chemical treatment to stabilize and prolong infectivity, and alteration of host range through changes in surface proteins. Certain of these

TABLE 7-1

KEY FEATURES OF BIOLOGIC AGENTS USED AS BIOWEAPONS

1. High morbidity and mortality rates
2. Potential for person-to-person spread
3. Low infective dose and highly infectious by aerosol
4. Lack of rapid diagnostic capability
5. Lack of universally available effective vaccine
6. Potential to cause anxiety
7. Availability of pathogen and feasibility of production
8. Environmental stability
9. Database of prior research and development
10. Potential to be "weaponized"

Source: From L Borio et al: JAMA 287:2391, 2002; with permission.

approaches fall under the category of *weaponization*, which is a term generally used to describe the processing of microbes or toxins in a manner that would ensure a devastating effect of a release. For example, weaponization of anthrax by the Soviets comprised the production of vast amounts of spores in a form that maintained aerosolization for prolonged periods of time; the spores were of appropriate size to reach the lower respiratory tract easily and could be delivered in a massive release, such as via widely dispersed bomblets.

The U.S. Centers for Disease Control and Prevention (CDC) classifies potential biologic threats into three categories: A, B, and C **(Table 7-2)**. Category A agents are the highest-priority pathogens. They pose the greatest risk to national security because they (1) can be easily disseminated or transmitted from person to person, (2) result in high mortality rates and have the potential for major public health impact, (3) might cause public panic and social disruption, and (4) require special action for public health preparedness. Category B agents are the second highest priority pathogens and include those that are moderately easy to disseminate, result in moderate morbidity rates and low mortality rates, and require specifically enhanced diagnostic capacity. Category C agents are the third highest priority. These include certain emerging pathogens to which the general population lacks immunity that could be engineered for mass dissemination in the future because of availability, ease of production, to ease of dissemination, and that have a major public health impact and the potential for high morbidity and mortality rates. It should be pointed out, however, that these A, B, and C designations are empirical, and, depending on evolving circumstances such as intelligence-based threat assessments, the priority rating of any given microbe or toxin could change. The CDC classification system also largely reflects the severity of illness produced by a given agent, rather than its accessibility to potential terrorists.

TABLE 7-2

CDC CATEGORY A, B, AND C AGENTS

Category A
Anthrax (*Bacillus anthracis*)
Botulism (*Clostridium botulinum* toxin)
Plague (*Yersinia pestis*)
Smallpox (*Variola major*)
Tularemia (*Francisella tularensis*)
Viral hemorrhagic fevers
Arenaviruses: Lassa, New World (Machupo, Junin, Guanarito, and Sabia)
Bunyaviridae: Crimean-Congo, Rift Valley
Filoviridae: Ebola, Marburg
Category B
Brucellosis (*Brucella* spp.)
Epsilon toxin of *Clostridium perfringens*
Food safety threats (e.g., *Salmonella* spp., *Escherichia coli* O157:H7, *Shigella*)
Glanders (*Burkholderia mallei*)
Melioidosis (*B. pseudomallei*)
Psittacosis (*Chlamydophila psittaci*)
Q fever (*Coxiella burnetii*)
Ricin toxin from *Ricinus communis* (castor beans)
Staphylococcal enterotoxin B
Typhus fever (*Rickettsia prowazekii*)
Viral encephalitis [alphaviruses (e.g., Venezuelan, eastern, and western equine encephalitis)]
Water safety threats (e.g., *Vibrio cholerae, Cryptosporidium parvum*)
Category C
Emerging infectious disease threats such as Nipah, hantavirus, SARS coronavirus, and pandemic influenza

Abbreviation: SARS, severe acute respiratory syndrome.
Source: Centers for Disease Control and Prevention and the National Institute of Allergy and Infectious Diseases.

CATEGORY A AGENTS

ANTHRAX

Bacillus anthracis *as a bioweapon*

Anthrax may be the prototypic disease of bioterrorism. Although rarely, if ever, spread from person to person, the illness embodies the other major features of a disease introduced through terrorism, as outlined in Table 7-1. U.S. and British government scientists studied anthrax as a potential biologic weapon beginning approximately at the time of World War II (WWII). Offensive bioweapons activity including bioweapons research on microbes and toxins in the United States ceased in 1969 as a result of two executive orders by President Richard M. Nixon. Although the 1972 Biological and Toxin Weapons Convention Treaty outlawed research of this type worldwide, the Soviet Union produced and stored tons of anthrax spores for potential use as a bioweapon until at least the late 1980s. At present, there is suspicion that research on anthrax as an agent of bioterrorism is ongoing by several nations and extremist groups. One example of this is the release of anthrax spores by the Aum Shinrikyo cult in Tokyo in 1993. Fortunately, there were no casualties associated with this episode because of the inadvertent use of a nonpathogenic strain of anthrax by the terrorists.

The potential impact of anthrax spores as a bioweapon was clearly demonstrated in 1979 following the accidental release of spores into the atmosphere from a Soviet Union bioweapons facility in Sverdlosk, Russia. While actual figures are not known, at least 77 cases of anthrax were diagnosed with certainty, of which 66 were fatal. These victims were exposed in an area within 4 km downwind of the facility, and deaths due to anthrax were also noted in livestock up to 50 km further downwind. Based on recorded wind patterns, the interval between the time of exposure and development of clinical illness ranged from 2

to 43 days. The majority of cases were within the first 2 weeks. Death typically occurred within 1–4 days following the onset of symptoms. It is likely that the widespread use of postexposure penicillin prophylaxis limited the total number of cases. The extended period of time between exposure and disease in some individuals supports the data from nonhuman primate studies, suggesting that the anthrax spores can lie dormant in the respiratory tract for at least 4–6 weeks without evoking an immune response. This extended period of microbiologic latency following exposure poses a significant challenge for management of victims in the postexposure period.

In September 2001, the American public was exposed to anthrax spores as a bioweapon delivered through the U.S. Postal Service by an employee of the United States Army Research Institute for Infectious Diseases (USAMRIID) who had access to such materials and who committed suicide prior to being indicted for this crime. The CDC identified 22 confirmed or suspected cases of anthrax as a consequence of this attack. These included 11 patients with inhalational anthrax, of whom 5 died, and 11 patients with cutaneous anthrax (7 confirmed), all of whom survived **(Fig. 7-1)**. Cases occurred in individuals who opened contaminated letters as well as in postal workers involved in the processing of mail. A minimum of five letters mailed from Trenton, NJ, served as the vehicles for these attacks. One of these letters was reported to contain 2 g of material, equivalent to 100 billion to 1 trillion weapon-grade spores. Since studies performed in the 1950s using monkeys exposed to aerosolized anthrax suggested that ~10,000 spores were required to produce lethal disease in 50% of animals exposed to this dose (the LD_{50}), the contents of one letter had the theoretical potential, under optimal conditions, of causing illness or death in up to 50 million individuals when one considers an LD_{50} of 10,000 spores. The strain used in this attack was the Ames strain. Although it was noted to have an inducible β-lactamase and to constitutively express a cephalosporinase, it was susceptible to all antibiotics standard for *B. anthracis*.

Microbiology and clinical features

Anthrax is caused by *B. anthracis*, a gram-positive, nonmotile, spore-forming rod that is found in soil and predominantly causes disease in herbivores such as cattle, goats, and sheep. Anthrax spores can remain viable for decades. The remarkable stability of these spores makes them an ideal bioweapon, and their destruction in decontamination activities can be a challenge. Naturally occurring human infection is generally the result of contact with anthrax-infected animals or animal products such as goat hair in textile mills or animal skins used in making drums. While an LD_{50} of 10,000 spores is a generally accepted number, it has also been suggested that as few as one to three spores may be adequate to cause disease in some settings. Advanced technology is likely to be necessary to generate spores of the optimal size (1–5 μm) to travel to the alveolar spaces as a bioweapon.

The three major clinical forms of anthrax are gastrointestinal, cutaneous, and inhalational. *Gastrointestinal anthrax* typically results from the ingestion of contaminated meat; the condition is rarely seen and is unlikely

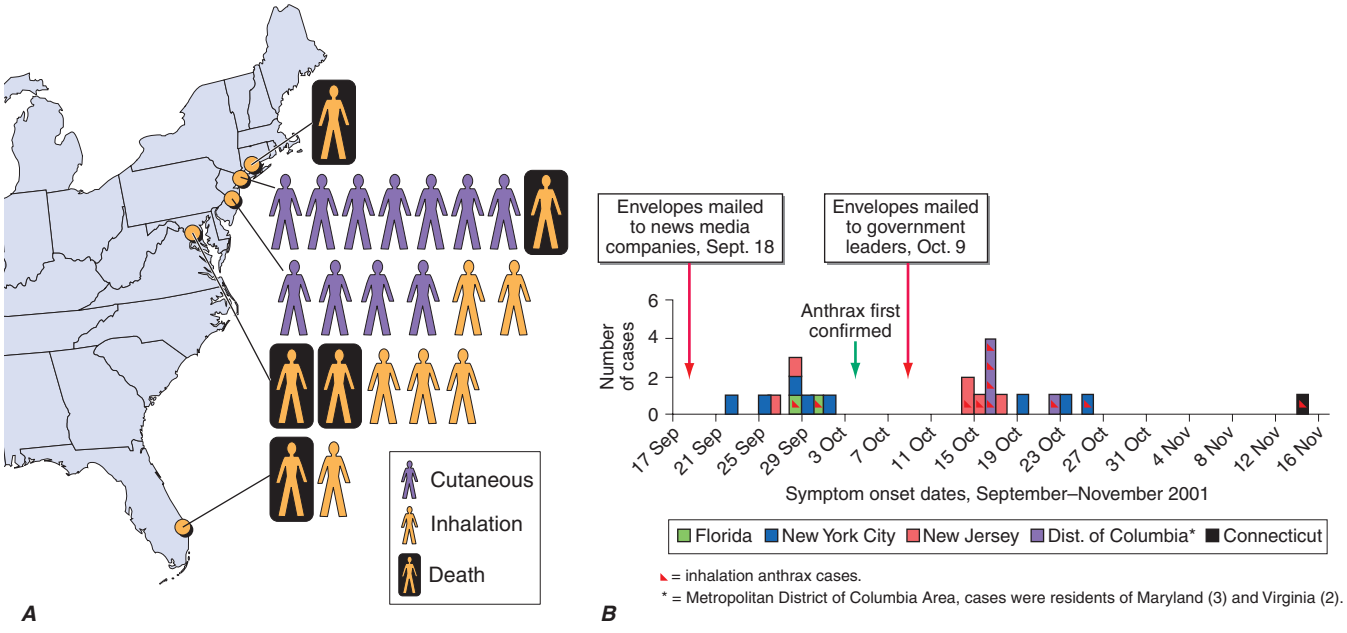


FIGURE 7-1
Confirmed anthrax cases associated with bioterrorism: United States, 2001. *A.* Geographic location, clinical manifestations, and outcome of the 11 cases of confirmed inhalational and 11 cases of confirmed cutaneous anthrax. ***B.*** Epidemic curve for 22 cases of anthrax. (*From DB Jernigan et al: Emerg Infect Dis 8:1019, 2002; with permission.*)

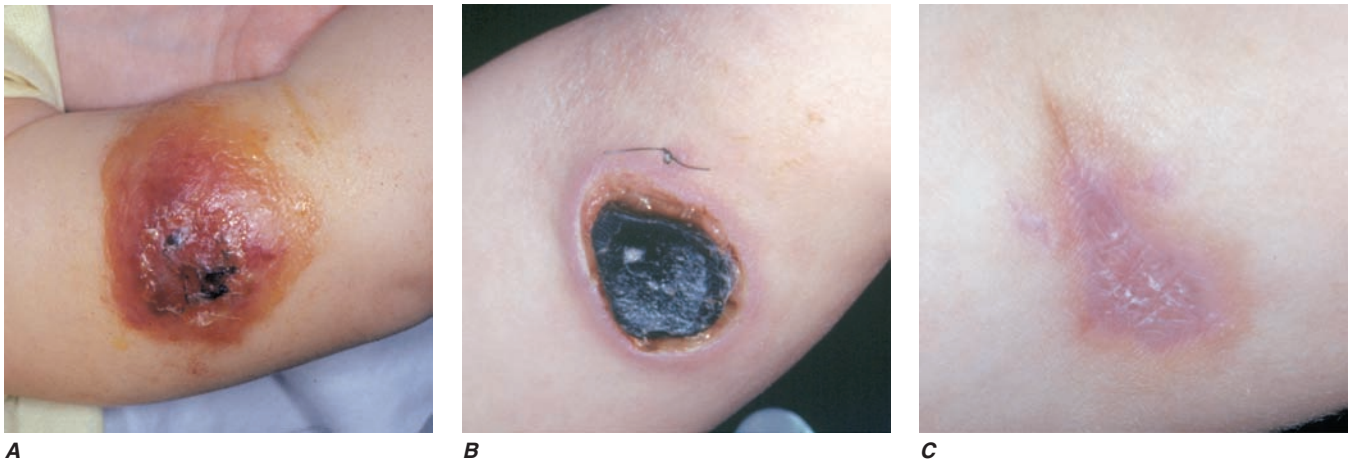
to be the result of a bioterrorism event. The lesion of *cutaneous anthrax* typically begins as a papule following the introduction of spores through an opening in the skin. This papule then evolves to a painless vesicle followed by the development of a coal-black, necrotic eschar **(Fig. 7-2)**. It is the Greek word for coal (*anthrax*) that gives the organism and the disease its name. Cutaneous anthrax was ~20% fatal prior to the availability of antibiotics. *Inhalational anthrax* is the form most likely to be responsible for death in the setting of a bioterrorist attack. It occurs following the inhalation of spores that become deposited in the alveolar spaces. These spores are phagocytosed by macrophages and transported to the mediastinal and peribronchial lymph nodes where they germinate, leading to active bacterial growth and elaboration of the bacterial products edema toxin and lethal toxin. Subsequent hematogenous spread of bacteria is accompanied by cardiovascular collapse and death. The earliest symptoms are typically a viral-like prodrome with fever, malaise, and abdominal and/or chest symptoms that progress over the course of a few days to a moribund state. A characteristic finding is mediastinal widening and pleural effusions on chest x-ray **(Fig. 7-3)**. While initially thought to be 100% fatal, the experiences at Sverdlosk in 1979 and in the United States in 2001 (see below) indicate that with prompt initiation of antibiotic therapy, survival is possible. The characteristics of the 11 cases of inhalational anthrax diagnosed in the United States in 2001 following exposure to contaminated letters postmarked September 18 or October 9, 2001, followed the classic pattern established for this illness, with patients presenting with a rapidly progressive course characterized by fever, fatigue or malaise, nausea or vomiting, cough, and shortness of breath. At presentation, the total white blood cell counts were ~10,000 cells/μL; transaminases tended to be elevated, and all 11 had abnormal findings on chest x-ray and CT. Radiologic findings included infiltrates, mediastinal widening, and hemorrhagic pleural effusions. For cases in which the dates of exposure were known, symptoms appeared within 4–6 days. Death occurred within 7 days of diagnosis in the five fatal cases (overall mortality rate 55%). Rapid diagnosis and prompt initiation of antibiotic therapy were key to survival.

TREATMENT **Anthrax**

Anthrax can be successfully treated if the disease is promptly recognized and appropriate therapy is initiated early. While penicillin, ciprofloxacin, and doxycycline are the currently licensed antibiotics for this indication, clindamycin and rifampin also have in vitro activity against the organism and have been used as part of treatment regimens. Until sensitivity results are known, suspected cases are best managed with a combination of broadly active agents **(Table 7-3)**. Patients with inhalational anthrax are not contagious and do not require special isolation procedures.

Vaccination and prevention

The first successful vaccine for anthrax was developed for animals by Louis Pasteur in 1881. At present, the single vaccine licensed for human use is a product produced from the cell-free culture supernatant of an attenuated, nonencapsulated strain of *B. anthracis* (Stern strain), referred to as *anthrax vaccine adsorbed* (AVA). Clinical trials for safety in humans and efficacy in animals are currently under way to evaluate the role of recombinant protective antigen (one of the major components, along with lethal factor and edema factor, of *B. anthracis* toxins) as an alternative to AVA. In a post-exposure setting in non-human primates, a 2-week course of AVA + ciprofloxacin was found to be superior



A ***B*** ***C***

FIGURE 7-2

Clinical manifestations of a pediatric case of cutaneous anthrax associated with the bioterrorism attack of 2001. The lesion progresses from vesicular on day 5 ***(A)*** to necrotic with the classic black eschar on day 12 ***(B)*** to a healed scar 2 months later ***(C)***. (*Photographs provided by Dr. Mary Wu Chang and (A) reprinted with permission of the New England Journal of Medicine.*)

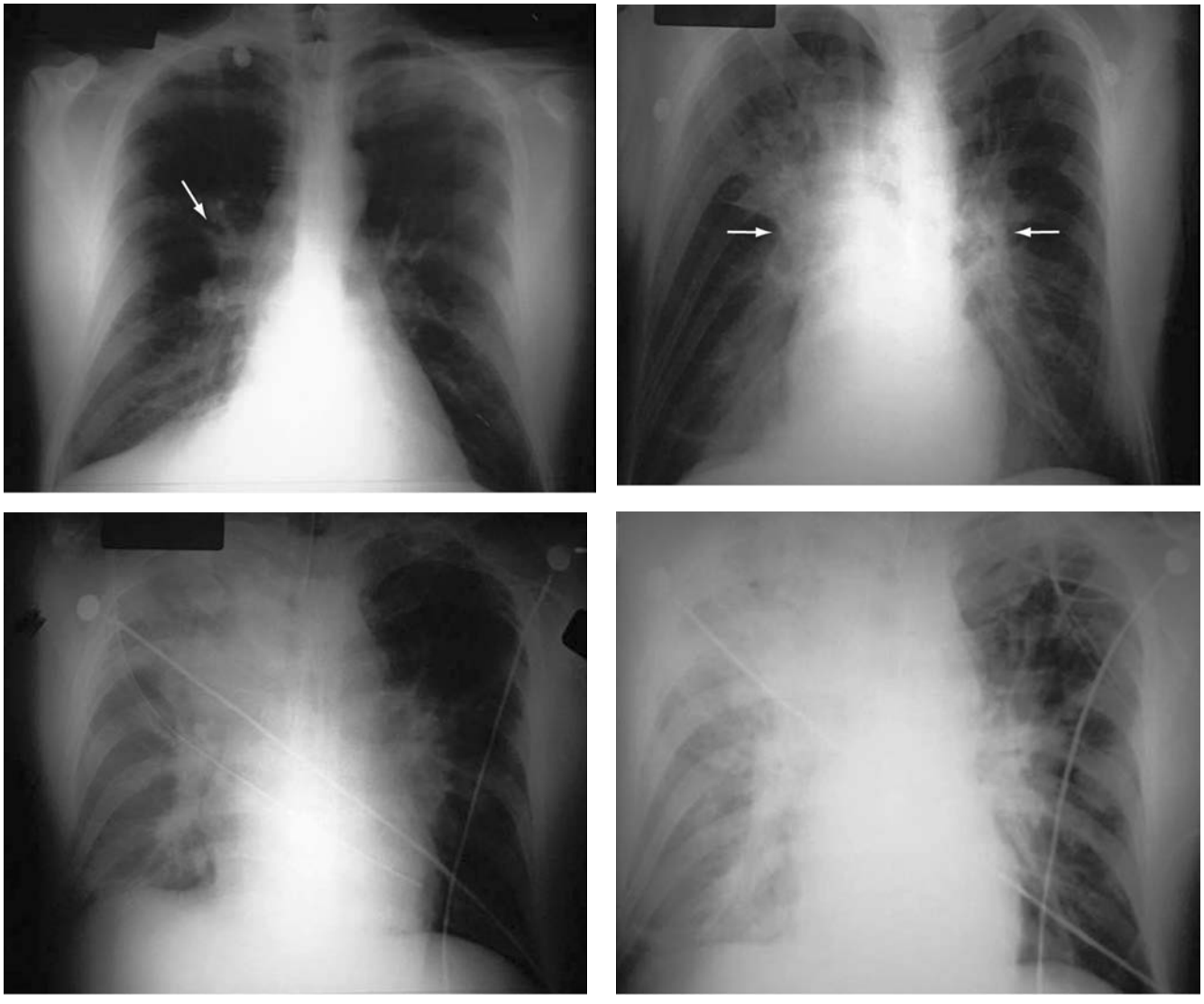


FIGURE 7-3
Progression of chest x-ray findings in a patient with inhalational anthrax. Findings evolved from subtle hilar prominence and right perihilar infiltrate to a progressively widened mediastinum, marked perihilar infiltrates, peribronchial cuffing, and air bronchograms. (*From L Borio et al: JAMA 286:2554, 2001; with permission*.)

to ciprofloxacin alone in preventing the development of clinical disease and death. While the current recommendation for postexposure prophylaxis is 60 days of antibiotics, it would seem prudent to include immunization with anthrax vaccine if available. Given the potential for *B. anthracis* to be engineered to express penicillin resistance, the empirical regimen of choice in this setting is either ciprofloxacin or doxycycline.

PLAGUE

See also Chap. 64.

Yersinia pestis *as a bioweapon*

Although it lacks the environmental stability of anthrax, the highly contagious nature and high mortality rate of plague make it a close to ideal agent of bioterrorism, particularly if delivered in a weaponized form. Occupying a unique place in history, plague has been alleged to have been used as a biologic weapon for centuries. The catapulting of plague-infected corpses into besieged fortresses is a practice that was first noted in 1346 during the assault of the city of Kaffa by the Tartars. Although unlikely to have resulted in disease transmission, some believe that this event may have played a role in the start of the Black Death pandemic of the fourteenth and fifteenth centuries in Europe. Given that plague was already moving across Asia toward Europe at this time, it is unclear whether such an allegation is accurate. During WWII, the infamous Unit 731 of the Japanese army was reported to have repeatedly dropped plague-infested fleas over parts of China, including Manchuria. These drops were associated with subsequent outbreaks

TABLE 7-3

CLINICAL SYNDROMES, PREVENTION, AND TREATMENT STRATEGIES FOR DISEASES CAUSED BY CATEGORY A AGENTS

AGENT	CLINICAL SYNDROME	INCUBATION PERIOD	DIAGNOSIS	TREATMENT	PROPHYLAXIS
Bacillus anthracis (anthrax)	Cutaneous lesion: Papule to eschar Inhalational disease: Fever, malaise, chest and abdominal discomfort Pleural effusion, widened mediastinum on chest x-ray	1–12 days 1–60 days	Culture, Gram stain, PCR, Wright stain of peripheral smear	*Postexposure:* Ciprofloxacin, 500 mg PO bid × 60 d *or* Doxycycline, 100 mg PO bid × 60 d *or* Amoxicillin, 500 mg PO q8h; likely to be effective if strain penicillin sensitive *Active disease:* Ciprofloxacin, 400 mg IV q12h *or* doxycycline, 100 mg IV q12h *plus* Clindamycin, 900 mg IV q8h and/or rifampin, 300 mg IV q12h; switch to PO when stable × 60 d total *Antitoxin strategies:* Neutralizing monoclonal and polyclonal antibodies are under study	Anthrax vaccine adsorbed Recombinant protective antigen vaccines are under study
Yersinia pestis (pneumonic plague)	Fever, cough, dyspnea, hemoptysis Infiltrates and consolidation on chest x-ray	1–6 days	Culture, Gram stain, direct fluorescent antibody, PCR	Gentamicin, 2.0 mg/kg IV loading, then 1.7 mg/kg q8h IV *or* Streptomycin, 1.0 g q12h IM or IV Alternatives include doxycycline, 100 mg bid PO or IV; chloramphenicol, 500 mg qid PO or IV	Doxycycline, 100 mg PO bid (ciprofloxacin may also be active) Formalin-fixed vaccine (FDA licensed; not available)
Variola major (smallpox)	Fever, malaise, headache, backache, emesis Maculopapular to vesicular to pustular skin lesions	7–17 days	Culture, PCR, electron microscopy	Supportive measures; consideration of cidofovir, antivaccinia immunoglobulin	Vaccinia immunization
Francisella tularensis (tularemia)	Fever, chills, malaise, myalgia, chest discomfort, dyspnea, headache, skin rash, pharyngitis, conjunctivitis Hilar adenopathy on chest x-ray	1–14 days	Gram stain, culture, immunohistochemistry, PCR	Streptomycin, 1 g IM bid *or* Gentamicin, 5 mg/kg per day div q8h IV for 14 days *or* Doxycycline, 100 mg IV bid *or* Chloramphenicol, 15 mg/kg up to 1 g IV qid *or* Ciprofloxacin, 400 mg IV bid	Doxycycline, 100 mg PO bid × 14 days *or* Ciprofloxacin, 500 mg PO bid × 14 days

(*continued*)

TABLE 7-3

CLINICAL SYNDROMES, PREVENTION, AND TREATMENT STRATEGIES FOR DISEASES CAUSED BY CATEGORY A AGENTS (*CONTINUED*)

AGENT	CLINICAL SYNDROME	INCUBATION PERIOD	DIAGNOSIS	TREATMENT	PROPHYLAXIS
Viral hemorrhagic fevers	Fever, myalgia, rash, encephalitis, prostration	2–21 days	RT-PCR, serologic testing for antigen or antibody Viral isolation by CDC or U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID)	Supportive measures: Ribavirin 30 mg/kg up to 2 g × 1, followed by 16 mg/kg IV up to 1 g q6h for 4 days, followed by 8 mg/kg IV up to 0.5 g q8h × 6 days	No known chemoprophylaxis Consideration for ribavirin in high-risk situations
Botulinum toxin (*Clostridium botulinum*)	Dry mouth, blurred vision, ptosis, weakness, dysarthria, dysphagia, dizziness, respiratory failure, progressive paralysis, dilated pupils	12–72 h	Mouse bioassay, toxin immunoassay	Supportive measures including ventilation, HBAT equine antitoxin from the CDC Emergency Operations Center, 770-488-7100	Administration of antitoxin

Abbreviations: CDC, U.S. Centers for Disease Control and Prevention; FDA, U.S. Food and Drug Administration; HBAT, heptavalent botulinum antitoxin; PCR, polymerase chain reaction; RT-PCR, reverse transcriptase PCR.

of plague in the targeted areas. Following WWII, the United States and the Soviet Union conducted programs of research on how to create aerosolized *Y. pestis* that could be used as a bioweapon to cause primary pneumonic plague. As mentioned above, plague was thought to be an excellent bioweapon due to the fact that in addition to causing infection in those inhaling the aerosol, significant numbers of secondary cases of primary pneumonic plague would likely occur due to the contagious nature of the disease and person-to-person transmission via respiratory aerosol. Secondary reports of research conducted during that time suggest that organisms remain viable for up to 1 h and can be dispersed for distances up to 10 km. While the offensive bioweapons program in the United States was terminated prior to production of sufficient quantities of plague organisms for use as a weapon, it is believed that Soviet scientists did manufacture quantities sufficient for such a purpose. It has also been reported that more than 10 Soviet Institutes and >1000 scientists were working with plague as a biologic weapon. Of concern is the fact that in 1995 a microbiologist in Ohio was arrested for having obtained *Y. pestis* in the mail from the American Type Culture Collection, using a credit card and a false letterhead. In the wake of this incident, the U.S. Congress passed a law in 1997 requiring that anyone intending to send or receive any of 42 different agents that could potentially be used as bioweapons first register with the CDC.

Microbiology and clinical features

Plague is caused by *Y. pestis*, a nonmotile, gram-negative bacillus that exhibits bipolar, or "safety pin," staining with Wright, Giemsa, or Wayson stains. It has had a major impact on the course of history, thus adding to the element of fear evoked by its mention. The earliest reported plague epidemic was in 224 B.C. in China. The most infamous pandemic began in Europe in the fourteenth century, during which time one-third to one-half of the entire population of Europe was killed. During a plague outbreak in India in 1994, even though the number of confirmed cases was relatively small, it is estimated that 500,000 individuals fled their homes in fear of this disease.

The clinical syndromes of plague generally reflect the mode of infection. *Bubonic plague* is the consequence of an insect bite; primary *pneumonic plague* arises through the inhalation of bacteria. Most of the plague seen in the world today is bubonic plague and is the result of a bite by a plague-infected flea. In part as a consequence of past pandemics, plague infection of rodents exists widely in nature, including in the southwestern United States, and each year thousands of cases of plague occur worldwide through contact with infected animals or fleas. Following inoculation of regurgitated bacteria into the skin by a flea bite, organisms travel through the lymphatics to regional lymph nodes, where they are phagocytized but not destroyed. Inside the cell, they multiply rapidly leading

to inflammation, painful lymphadenopathy with necrosis, fever, bacteremia, septicemia, and death. The characteristic enlarged, inflamed lymph nodes, or *buboes*, give this form of plague its name. In some instances, patients may develop bacteremia without lymphadenopathy following infection, a condition referred to as *primary septicemic plague*. Extensive ecchymoses may develop due to disseminated intravascular coagulation, and gangrene of the digits and/or nose may develop in patients with advanced septicemic plague. It is thought that this appearance of some patients gave rise to the term *Black Death* in reference to the plague epidemic of the fourteenth and fifteenth centuries. Some patients may develop pneumonia (secondary pneumonic plague) as a complication of bubonic or septicemic plague. These patients may then transmit the agent to others via the respiratory route, causing cases of primary pneumonic plague. Primary pneumonic plague is the manifestation most likely to occur as the result of a bioterrorist attack, with an aerosol of bacteria spread over a wide area or a particular environment that is densely populated. In this setting, patients would be expected to develop fever, cough with hemoptysis, dyspnea, and gastrointestinal symptoms 1–6 days following exposure. Clinical features of pneumonia would be accompanied by pulmonary infiltrates and consolidation on chest x-ray. In the absence of antibiotics, the mortality rate of this disease is on the order of 85%, and death usually occurs within 2–6 days.

TREATMENT **Plague**

Streptomycin, tetracycline, and doxycycline are licensed by the U.S. Food and Drug Administration (FDA) for the treatment of plague. Multiple additional antibiotics licensed for other infections are commonly used and are likely effective. Among these are aminoglycosides such as gentamicin, cephalosporins, trimethoprim-sulfamethoxazole, chloramphenicol, and ciprofloxacin (Table 7-3). A multidrug-resistant strain of *Y. pestis* was identified in 1995 from a patient with bubonic plague in Madagascar. While this organism was resistant to streptomycin, ampicillin, chloramphenicol, sulfonamides, and tetracycline, it retained its susceptibility to other aminoglycosides and cephalosporins. Given the subsequent identification of a similar organism in 1997 coupled with the fact that this resistance is plasmid-mediated, it seems likely that genetically modifying *Y. pestis* to a multidrug-resistant form is possible. Unlike patients with inhalational anthrax (see above), patients with pulmonary plague should be cared for under conditions of strict respiratory isolation comparable to that used for multidrug-resistant tuberculosis.

Vaccination and prevention

A formalin-fixed, whole-organism vaccine was licensed by the FDA for the prevention of plague. That vaccine is no longer being manufactured, but its potential value as a current countermeasure against bioterrorism would likely have been modest at best as it was ineffective against animal models of primary pneumonic plague. Efforts are under way to develop a second generation of vaccines that will protect against aerosol challenge. Among the candidates being tested are recombinant forms of the F1 and V antigens of *Y. pestis*. It is likely that doxycycline or ciprofloxacin would provide coverage in a chemoprophylaxis setting. Unlike the case with anthrax, in which one has to be concerned about the persistence of ungerminated spores in the respiratory tract, the duration of prophylaxis against plague need only extend to 7 days following exposure.

SMALLPOX

See also Chap. 88.

Variola virus as a bioweapon

Given that most of the world's population was once vaccinated against smallpox, variola virus would not have been considered a good candidate as a bioweapon 30 years ago. However, with the cessation of immunization programs in the United States in 1972 and throughout the world in 1980 due to the successful global eradication of smallpox, close to 50% of the U.S. population is fully susceptible to smallpox today. Given its infectious nature and the 10–30% mortality rate in unimmunized individuals, the deliberate spread of this virus could have a devastating effect on our society and unleash a previously conquered deadly disease. It is estimated that an initial infection of 50–100 persons in a first generation of cases could expand by a factor of 10–20 with each succeeding generation in the absence of any effective containment measures. While the likely implementation of an effective public health response makes this scenario unlikely, it does illustrate the potential damage and disruption that can result from a smallpox outbreak.

In 1980, the World Health Organization (WHO) recommended that all immunization programs be terminated; that representative samples of variola virus be transferred to two locations, one at the CDC in Atlanta, GA, in the United States and the other at the Institute of Virus Preparations in the Soviet Union; and that all other stocks of smallpox be destroyed. Several years later, it was recommended that these two authorized collections be destroyed. However, these latter recommendations were placed on hold in the wake of increased concerns on the use of variola virus as a biologic weapon and thus the need to maintain an active program of defensive research. Many of these concerns were based upon allegations made by former Soviet officials that extensive programs had been in place in that country for the production and weaponization of large quantities of smallpox virus. The dismantling of these programs with the fall of the Soviet Union and the subsequent weakening of security measures led to fears that stocks of *V. major* may have made their way to other countries or terrorist

organizations. In addition, accounts that efforts had been taken to produce recombinant strains of *Variola* that would be more virulent and more contagious than the wild-type virus have led to an increase in the need to be vigilant for the reemergence of this often fatal infectious disease.

Microbiology and clinical features

Smallpox is caused by one of two variants of variola virus, *V. major* and *V. minor*. Variola is a double-strand DNA virus and member of the *Orthopoxvirus* genus of the Poxviridae family. Infections with *V. minor* are generally less severe than those with *V. major*, with milder constitutional symptoms and lower mortality rates; thus, *V. major* is the only variant considered to be a viable bioweapon. Infection with *V. major* typically occurs following contact with an infected person. Patients are infectious from the time that a maculopapular rash appears on the skin and oropharynx through the resolution and scabbing of the pustular lesions. Infection occurs principally during close contact, through the inhalation of saliva droplets containing virus from the oropharyngeal exanthem. Aerosolized material from contaminated clothing or linen can also spread infection. Several days after exposure, a primary viremia is believed to occur that results in dissemination of virus to lymphoid tissues. A secondary viremia occurs ~4 days later that leads to localization of infection in the dermis. Approximately 12–14 days following the initial exposure, the patient develops high fever, malaise, vomiting, headache, backache, and a maculopapular rash that begins on the face and extremities and spreads to the trunk (centripetal) with lesions in the same developmental stage in any given location. This is in contrast to the rash of varicella (chickenpox) that begins on the trunk and face and spreads to the extremities (centrifugal) with lesions at all stages of development. The lesions are initially maculopapular and evolve to vesicles that eventually become pustules and then scabs. The oral mucosa also develops maculopapular lesions that evolve to ulcers. The lesions appear over a period of 1–2 days and evolve at the same rate. Although virus can be isolated from the scabs on the skin, the conventional thinking is that once the scabs have formed the patient is no longer contagious. Smallpox is associated with 10–30% mortality rates, with patients typically dying of severe systemic illness during the second week of symptoms. Historically, ~5–10% of naturally occurring smallpox cases take either of two highly virulent atypical forms, classified as *hemorrhagic* and *malignant*. These are difficult to diagnose because of their atypical presentations. The hemorrhagic form is uniformly fatal and begins with the relatively abrupt onset of a severely prostrating illness characterized by high fevers and severe headache and back and abdominal pain. This form of the illness resembles a severe systemic inflammatory syndrome, in which patients have a high viremia but die without developing the characteristic rash. Cutaneous erythema develops accompanied by petechiae and hemorrhages into the skin and mucous membranes. Death usually occurs within 5–6 days. The malignant, or "flat," form of smallpox is frequently fatal and has an onset similar to the hemorrhagic form, but with confluent skin lesions developing more slowly and never progressing to the pustular stage.

TREATMENT **Smallpox**

Given the infectious nature of smallpox and the extreme vulnerability of contemporary society, patients who are suspected cases should be handled with strict isolation procedures. While laboratory confirmation of a suspected case by culture, PCR and electron microscopy is essential, it is equally important that appropriate precautions be employed when obtaining samples for culture and laboratory testing. All health care and laboratory workers caring for patients should have been recently immunized with vaccinia, and all samples should be transported in doubly sealed containers. Patients should be cared for in negative-pressure rooms with strict isolation precautions.

There is no licensed specific therapy for smallpox, and historic treatments have focused solely on supportive care. While several antiviral agents, including cidofovir, that are licensed for other diseases have in vitro activity against *V. major*, they have never been tested in the setting of human disease. For this reason, it is difficult to predict whether or not they would be effective in cases of smallpox and, if effective, whether or not they would be of value in patients with advanced disease. Research programs studying the efficacy of new antiviral compounds (ST-246 and others) against *V. major* are currently under way.

Vaccination and prevention

In 1796, Edward Jenner demonstrated that deliberate infection with cowpox virus could prevent illness on subsequent exposure to smallpox. Today, smallpox is a preventable disease following immunization with vaccinia. The current dilemma facing our society regarding assessment of the risk and benefit of smallpox vaccination is that the degree of risk that someone will deliberately and effectively release smallpox into our society is unknown. As a prudent first step in preparedness for a smallpox attack, virtually all members of the U.S. armed services have received primary or booster immunizations with vaccinia. In addition, tens of thousands of civilian health care workers who comprise smallpox-response teams at the state and local public health level have been vaccinated.

Initial fears regarding the immunization of a segment of the American population with vaccinia when there are more individuals receiving immunosuppressive drugs and

other immunocompromised patients than ever before were dispelled by the data generated from the military and civilian immunization campaigns of 2002–2004. Adverse event rates for the first 450,000 immunizations were similar to and, in certain categories of adverse events, even lower than those from prior historic data, in which most severe sequelae of vaccination occurred in young infants (Table 7-4). In addition, 11 patients with early-stage HIV infection were inadvertently immunized without problem. One significant concern during that immunization campaign, however, was the description of a syndrome of myopericarditis, which had not been appreciated during prior immunization campaigns with vaccinia. In an effort to provide a safer vaccine to protect against smallpox, ACAM 2000, a cloned virus propagated in tissue culture, was developed and became the first second-generation smallpox vaccine to be licensed. This vaccine is now used by the U.S. military and is part of the U.S. government stockpile. Research continues on attenuated forms of vaccinia such as modified vaccinia Ankara (MVA). Vaccinia immune globulin is available to treat those who experience a severe reaction to immunization with vaccinia.

TABLE 7-4

COMPLICATIONS FROM 438,134 ADMINISTRATIONS OF VACCINIA DURING THE UNITED STATES DEPARTMENT OF DEFENSE (DOD) SMALLPOX IMMUNIZATION CAMPAIGN INITIATED IN DECEMBER 2002

COMPLICATION	NUMBER OF CASES	DOD RATE PER MILLION VACCINEES (95% CONFIDENCE INTERVAL)	HISTORIC RATE PER MILLION VACCINEES
Mild or temporary:			
Generalized vaccinia, mild	35	67 (52, 85)	45–212[a]
Inadvertent inoculation, self	62	119 (98, 142)	606[a]
Vaccinia transfer to contact	28	53 (40, 69)	8–27[a]
Moderate or serious:			
Encephalitis	1	2.2 (0.6, 7.2)	2.6–8.7[a]
Acute myopericarditis	69	131 (110, 155)	100[b]
Eczema vaccinatum	0	0 (0, 3.7)	2–35[a]
Progressive vaccinia	0	0 (0, 3.7)	1–7[a]
Death	1[c]	1.9 (0.2, 5.6)	1–2[a]

[a]Based on adolescent and adult smallpox vaccinations from 1968 studies, both primary and revaccinations.
[b]Based on case series in Finnish military recruits given the Finnish strain of smallpox vaccine.
[c]Potentially attributable to vaccination; after lupus-like illness.
Source: From JD Grabenstein and W Winkenwerder: *http://www.smallpox.mil/event/SPSafetySum.asp.*

TULAREMIA

See also Chap. 63.

Francisella tularensis *as a bioweapon*

Tularemia has been studied as an agent of bioterrorism since the mid-twentieth century. It has been speculated by some that the outbreak of tularemia among German and Soviet soldiers during fighting on the Eastern Front during WWII was the consequence of a deliberate release. Unit 731 of the Japanese Army studied the use of tularemia as a bioweapon during WWII. Large preparations were made for mass production of *F. tularensis* by the United States, but no stockpiling of any agent took place. Stocks of *F. tularensis* were reportedly generated by the Soviet Union in the mid-1950s. It has also been suggested that the Soviet program extended into the era of molecular biology and that some strains were engineered to be resistant to common antibiotics. *F. tularensis* is an extremely infectious organism, and human infections have occurred from merely examining an uncovered petri dish streaked with colonies. Given these facts, it is reasonable to conclude that this organism might be utilized as a bioweapon through either an aerosol or contamination of food or drinking water.

Microbiology and clinical features

While similar in many ways to anthrax and plague, tularemia, also referred to as rabbit fever or deer fly fever, is neither as lethal nor as fulminant as either of these other two category A bacterial infections. It is, however, extremely infectious, and as few as 10 organisms can lead to establishment of infection. Despite this fact, it is not spread from person to person. Tularemia is caused by *F. tularensis*, a small, nonmotile, gram-negative coccobacillus. Although it is not a spore-forming organism, it is a hardy bacterium that can survive for weeks in the environment. Infection typically comes from insect bites or contact with organisms in the environment. Infections have occurred in laboratory workers studying the agent. Large waterborne outbreaks have been recorded. It is most likely that the outbreak among German and Russian soldiers and Russian civilians noted above during WWII represented a large waterborne tularemia outbreak in a *Tularensis*-enzootic area devastated by warfare.

Humans can become infected through a variety of environmental sources. Infection is most common

in rural areas where a variety of small mammals may serve as reservoirs. Human infections in the summer are often the result of insect bites from ticks, flies, or mosquitoes that have bitten infected animals. In colder months, infections are most likely the result of direct contact with infected mammals and are most common in hunters. In these settings, infection typically presents as a systemic illness with an area of inflammation and necrosis at the site of tissue entry. Drinking of contaminated water may lead to an oropharyngeal form of tularemia characterized by pharyngitis with cervical and/or retropharyngeal lymphadenopathy (Chap. 63). The most likely mode of dissemination of tularemia as a biologic weapon would be as an aerosol, as has occurred in a number of natural outbreaks in rural areas, including Martha's Vineyard in the United States. Approximately 1–14 days following exposure by this route, one would expect to see inflammation of the airways with pharyngitis, pleuritis, and bronchopneumonia. Typical symptoms would include the abrupt onset of fever, fatigue, chills, headache, and malaise (Table 7-3). Some patients might experience conjunctivitis with ulceration, pharyngitis, and/or cutaneous exanthems. A pulse-temperature dissociation might be present. Approximately 50% of patients would show a pulmonary infiltrate on chest x-ray. Hilar adenopathy might also be present, and a small percentage of patients could have adenopathy without infiltrates. The highly variable presentation makes acute recognition of aerosol-disseminated tularemia very difficult. The diagnosis would likely be made by immunohistochemistry or culture of infected tissues or blood. Untreated, mortality rates range from 5 to 15% for cutaneous routes of infection and from 30 to 60% for infection by inhalation. Since the advent of antibiotic therapy, these rates have dropped to <2%.

TREATMENT **Tularemia**

Both streptomycin and doxycycline are licensed for treatment of tularemia. Other agents likely to be effective include gentamicin, chloramphenicol, and ciprofloxacin (Table 7-3). Given the potential for genetic modification of this organism to yield antibiotic-resistant strains, broad-spectrum coverage should be the rule until sensitivities have been determined. As mentioned above, special isolation procedures are not required.

Vaccination and prevention

There are no vaccines currently licensed for the prevention of tularemia. While a live, attenuated strain of the organism has been used in the past with some reported success, there are inadequate data to support its widespread use at this time. Development of a vaccine for this agent is an important part of the current biodefense research agenda. In the absence of an effective vaccine, postexposure chemoprophylaxis with either doxycycline or ciprofloxacin appears to be a reasonable approach (Table 7-3).

VIRAL HEMORRHAGIC FEVERS

See also Chaps. 102 and 103.

Hemorrhagic fever viruses as bioweapons

Several of the hemorrhagic fever viruses have been reported to have been weaponized by the Soviet Union and the United States. Nonhuman primate studies indicate that infection can be established with very few virions and that infectious aerosol preparations can be produced. Under the guise of wanting to aid victims of an Ebola outbreak, members of the Aum Shinrikyo cult in Japan were reported to have traveled to central Africa in 1992 in an attempt to obtain Ebola virus for use in a bioterrorist attack. Thus, while there has been no evidence that these agents have ever been used in a biologic attack, there is clear interest in their potential for this purpose.

Microbiology and clinical features

The viral hemorrhagic fevers are a group of illnesses caused by any one of a number of similar viruses (Table 7-2). These viruses are all enveloped, single-strand RNA viruses that are thought to depend upon a host reservoir for long-term survival. While rodents or insects have been indentified as the hosts for some of these viruses, for others the hosts are unknown. These viruses tend to be geographically restricted according to the migration patterns of their hosts. Great apes are not a natural reservoir for Ebola virus, but large numbers of these animals in sub-Saharan Africa have died from Ebola infection over the past decade. Humans can become infected with hemorrhagic fever viruses if they come into contact with an infected host or other infected animals. Person-to-person transmission, largely through direct contact with virus-containing body fluids, has been documented for Ebola, Marburg, and Lassa viruses and rarely for the New World arenaviruses. While there is no clear evidence of respiratory spread among humans, these viruses have been shown in animal models to be highly infectious by the aerosol route. This, coupled with mortality rates as high as 90%, makes them excellent candidate agents of bioterrorism.

The clinical features of the viral hemorrhagic fevers vary depending upon the particular agent (Table 7-3). Initial signs and symptoms typically include fever, myalgia, prostration, and disseminated intravascular coagulation with thrombocytopenia and capillary hemorrhage. These findings are consistent with a cytokine-mediated systemic inflammatory syndrome. A variety of different maculopapular or erythematous rashes may be seen. Leukopenia, temperature-pulse dissociation, renal failure, and seizures may also be part of the clinical presentation.

Outbreaks of most of these diseases are sporadic and unpredictable. As a consequence, most studies of pathogenesis have been performed using laboratory animals. The diagnosis should be suspected in anyone with temperature >38.3°C for <3 weeks who also exhibits at least two of the following: hemorrhagic or purpuric rash, epistaxis, hematemesis, hemoptysis, or hematochezia in the absence of any other identifiable cause. In this setting, samples of blood should be sent after consultation to the CDC or the USAMRIID for serologic testing for antigen and antibody as well as reverse transcriptase polymerase chain reaction (RT-PCR) testing for hemorrhagic fever viruses. All samples should be handled with double-bagging. Given how little is known regarding the human-to-human transmission of these viruses, appropriate isolation measures would include full barrier precautions with negative-pressure rooms and use of powered air-purifying respirators (PAPRs). Unprotected skin contact with cadavers has been implicated in the transmission of certain hemorrhagic fever viruses such as Ebola, so it is recommended that autopsies of suspected cases be performed using the strictest measures for protection and that burial or cremation be performed promptly without embalming.

TREATMENT **Viral Hemorrhagic Fevers**

There are no approved and effective antiviral therapies for this class of viruses (Table 7-3). While there are anecdotal reports of the efficacy of ribavirin, interferon-α, or hyperimmune immunoglobulin, definitive data are lacking. The best data for ribavirin are in arenavirus (Lassa and New World) infections. In some in vitro systems, specific immunoglobulin has been reported to enhance infectivity, and thus these potential treatments must be approached with caution.

Vaccination and prevention

There are no licensed and effective vaccines for these agents. Studies are currently under way examining the potential role of DNA, recombinant viruses, and attenuated viruses as vaccines for several of these infections. Among the most promising at present are vaccines for Argentine, Ebola, Rift Valley, and Kayasanur Forest viruses.

BOTULISM TOXIN (*Clostridium botulinum*)

See also Chap. 45.

Botulinum toxin as a bioweapon

In a bioterrorist attack, botulinum toxin would likely be dispersed as an aerosol or as contamination of a food supply. While contamination of a water supply is possible, it is likely that any toxin would be rapidly inactivated by the chlorine used to purify drinking water. Similarly, toxin can be inactivated by heating any food to >85°C for >5 min. Without external facilitation, the environmental decay rate is estimated at 1% per minute, and thus the time interval between weapon release and ingestion or inhalation needs to be rather short. The Japanese biologic warfare group, Unit 731, is reported to have conducted experiments on botulism poisoning in prisoners in the 1930s. The United States and the Soviet Union both acknowledged producing botulinum toxin, and there is some evidence that the Soviet Union attempted to create recombinant bacteria containing the gene for botulinum toxin. In records submitted to the United Nations, Iraq admitted to having produced 19,000 L of concentrated toxin—enough toxin to kill the entire population of the world three times over. By many accounts, botulinum toxin was the primary focus of the pre-1991 Iraqi bioweapons program. In addition to these examples of state-supported research into the use of botulinum toxin as a bioweapon, the Aum Shinrikyo cult unsuccessfully attempted on at least three occasions to disperse botulinum toxin into the civilian population of Tokyo.

Microbiology and clinical features

Unique among the category A agents for not being a live microorganism, botulinum toxin is one of the most potent toxins ever described and is thought by some to be the most poisonous substance in existence. It is estimated that 1 g of botulinum toxin would be sufficient to kill 1 million individuals if adequately dispersed. Botulinum toxin is produced by the gram-positive, spore-forming anaerobe *C. botulinum* (Chap. 45). Its natural habitat is soil. There are seven antigenically distinct forms of botulinum toxin, designated A–G. The majority of naturally occurring human cases are of types A, B, and E. Antitoxin directed toward one of these will have little to no activity against the others. The toxin is a 150-kDa zinc-containing protease that prevents the intracellular fusion of acetylcholine vesicles with the motor neuron membrane, thus preventing the release of acetylcholine. In the absence of acetylcholine-dependent triggering of muscle fibers, a flaccid paralysis develops. Although botulism does not spread from person to person, the ease of production of the toxin coupled with its high morbidity and 60–100% mortality make it a close to ideal bioweapon.

Botulism can result from the growth of *C. botulinum* infection in a wound or the intestine, the ingestion of contaminated food, or the inhalation of aerosolized toxin. The latter two forms are the most likely modes of transmission for bioterrorism. Once toxin is absorbed into the bloodstream, it binds to the neuronal cell membrane, enters the cell, and cleaves one of the proteins required for the intracellular binding of the synaptic vesicle to the cell membrane, thus preventing release of the neurotransmitter to the membrane of the adjacent muscle cell. Patients initially develop multiple cranial nerve palsies that are followed by a descending flaccid paralysis. The extent of the neuromuscular compromise is dependent upon

the level of toxemia. The majority of patients experience diplopia, dysphagia, dysarthria, dry mouth, ptosis, dilated pupils, fatigue, and extremity weakness. There are minimal true central nervous system effects, and patients rarely show significant alterations in mental status. Severe cases can involve complete muscular collapse, loss of the gag reflex, and respiratory failure, requiring weeks or months of ventilator support. Recovery requires the regeneration of new motor neuron synapses with the muscle cell, a process that can take weeks to months. In the absence of secondary infections, which may be common during the protracted recovery phase of this illness, patients remain afebrile. The diagnosis is suspected on clinical grounds and confirmed by a mouse bioassay or toxin immunoassay.

TREATMENT **Botulism**

Treatment for botulism is mainly supportive and may require intubation, mechanical ventilation, and parenteral nutrition (Table 7-3). If diagnosed early enough, administration of equine antitoxin may reduce the extent of nerve injury and decrease the severity of disease. At present, a heptavalent botulinum antitoxin (HBAT) is available through the CDC as an investigational agent for treatment of naturally occurring noninfant botulism. HBAT contains horse serum—derived antibody fragments to all seven known botulinum toxins (A–G). It is composed of <2% intact immunoglobulin and ≥90% Fab and $F(ab')_2$ immunoglobulin fragments. A single dose of antitoxin is usually adequate to neutralize any circulating toxin. Repeat dosing may be needed in a setting of continued toxin exposure. Given that this product is derived from horse serum, one needs to be vigilant for hypersensitivity reactions, including serum sickness and anaphylaxis following its administration. Once the damage to the nerve axon has been done, however, there is little possible in the way of specific therapy. At this point, vigilance for secondary complications such as infections during the protracted recovery phase is of the utmost importance. Due to their ability to worsen neuromuscular blockade, aminoglycosides and clindamycin should be avoided in the treatment of these infections.

Vaccination and prevention

A botulinum toxoid preparation has been used as a vaccine for laboratory workers at high risk of exposure and in certain military situations; however, it is not currently available in quantities that could be used for the general population. At present, early recognition of the clinical syndrome and use of appropriate equine antitoxin is the mainstay of prevention of full-blown disease in exposed individuals. The development of human monoclonal antibodies as a replacement for equine antitoxin antibodies is an area of active research interest.

CATEGORY B AND C AGENTS

The category B agents include those that are easy or moderately easy to disseminate and result in moderate morbidity and low mortality rates. A listing of the current category B agents is provided in Table 7-2. As can be seen, it includes a wide array of microorganisms and products of microorganisms. Several of these agents have been used in bioterrorist attacks, although never with the impact of the Category A agents described above. Among the more notorious of these was the contamination of salad bars in Oregon in 1984 with *Salmonella typhimurium* by the religious cult Rajneeshee. In this outbreak, which many consider to be the first bioterrorist attack against U.S. citizens, >750 individuals were poisoned and 40 were hospitalized in an effort to influence a local election. The intentional nature of this outbreak went unrecognized for more than a decade.

Category C agents are the third highest priority agents in the biodefense agenda. These agents include emerging pathogens to which little or no immunity exists in the general population, such as the severe acute respiratory syndrome (SARS) coronavirus or pandemic-potential strains of influenza that could be obtained from nature and deliberately disseminated. These agents are characterized as being relatively easy to produce and disseminate, having high morbidity and mortality rates and having a significant public health impact. There is no running list of category C agents at the present time.

PREVENTION AND PREPAREDNESS

As noted above, a large and diverse array of agents has the potential to be used in a bioterrorist attack. In contrast to the military situation with biowarfare, where the primary objective is to inflict mass casualties on a healthy and prepared militia, the objectives of bioterrorism are to harm civilians as well as to create fear and disruption among the civilian population. While the military needs only to prepare their troops to deal with the limited number of agents that pose a legitimate threat of biowarfare, the public health system needs to prepare the entire civilian population to deal with the multitude of agents and settings that could be utilized in a bioterrorism attack. This includes anticipating issues specific to the very young and the very old, the pregnant patient, and the immunocompromised individual. The challenges in this regard are enormous and immediate. While military preparedness emphasizes vaccines toward a limited number of agents, civilian preparedness needs to rely upon rapid diagnosis and treatment of a wide array of conditions.

The medical profession must maintain a high index of suspicion that unusual clinical presentations or the clustering of cases of a rare disease may not be a chance occurrence but rather the first sign of a bioterrorist event. This is particularly true when such diseases occur

in traditionally healthy populations, when surprisingly large numbers of rare conditions occur, and when diseases commonly seen in rural settings appear in urban populations. Given the importance of rapid diagnosis and early treatment for many of these conditions, it is essential that the medical care team report any suspected cases of bioterrorism immediately to local and state health authorities and/or to the CDC (888-246-2675). Enhancements have been made to the public health surveillance network to facilitate the rapid sharing of information among public health agencies.

At present a series of efforts are in place to ensure the biomedical security of the civilian population of the United States. The Public Health Service is moving toward a more highly trained, fully deployable force. The Strategic National Stockpile (SNS) maintained by the CDC provides rapid access to quantities of pharmaceuticals, antidotes, vaccines, and other medical supplies that may be of value in the event of biologic or chemical terrorism. The SNS has two basic components. The first of these consists of "push packages" that can be deployed anywhere in the United States within 12 h. These push packages are a preassembled set of supplies, pharmaceuticals, and medical equipment ready for immediate delivery to the field. They provide treatment for a variety of conditions given the fact that an actual threat may not have been precisely identified at the time of stockpile deployment. The contents of the push packs are constantly updated to ensure that they reflect current needs as determined by national security threat assessments; they include antibiotics for treatment of anthrax, plague, and tularemia as well as a cache of vaccine to deal with a smallpox threat. The second component of the SNS comprises inventories managed by specific vendors and consists of the provision of additional pharmaceuticals, supplies, and/or products tailored to the specific attack.

The number of FDA-approved and -licensed drugs and vaccines for category A and B agents is currently limited and not reflective of the pharmacy of today. In an effort to speed the licensure of additional drugs and vaccines for these diseases, the FDA has a rule for the licensure of such countermeasures against agents of bioterrorism when adequate and well-controlled clinical efficacy studies cannot be ethically conducted in humans. This is commonly referred to as the "Animal Rule." Thus, for indications in which field trials of prophylaxis or therapy for a naturally occurring disease are not feasible, the FDA will rely on evidence solely from laboratory animal studies. For this rule to apply, it must be shown that (1) there are reasonably well-understood pathophysiologic mechanisms for the condition and its treatment; (2) the effect of the intervention is independently substantiated in at least two animal species, including species expected to react with a response predictive for humans; (3) the animal study endpoint is clearly related to the desired benefit in humans; and (4) the data in animals allow selection of an effective dose in humans.

Finally, the Biomedical Advanced Research and Development Authority (BARDA) was established within the U.S. Department of Health and Human Services to provide an integrated, systematic approach to the development and purchase of the necessary vaccines, drugs, therapies, and diagnostic tools for public health medical emergencies. BARDA manages Project BioShield, an initiative established to facilitate biodefense research within the federal government, create a stable source of funding for the purchase of countermeasures against agents of bioterrorism, and create a category of "emergency use authorization" to allow the FDA to approve the use of unlicensed countermeasures during times of extraordinary unmet needs, as might be present in the context of a bioterrorist attack.

While the prospect of a deliberate attack on civilians with disease-producing agents may seem to be an act of incomprehensible evil, history shows us that it is something that has been done in the past and will likely be done again in the future. It is the responsibility of health care providers to be aware of this possibility, to be able to recognize early signs of a potential bioterrorist attack and alert the public health system, and to respond quickly to provide care to the individual patient. Among the web sites with current information on microbial bioterrorism are *www.bt.cdc.gov*, *www.niaid.nih.gov*, and *www.cidrap.umn.edu*.

SECTION II

FEVER AND APPROACH TO THE FEBRILE PATIENT

CHAPTER 8

FEVER AND HYPERTHERMIA

Charles A. Dinarello ■ Reuven Porat

Body temperature is controlled by the hypothalamus. Neurons in both the preoptic anterior hypothalamus and the posterior hypothalamus receive two kinds of signals: one from peripheral nerves that transmit information from warmth/cold receptors in the skin and the other from the temperature of the blood bathing the region. These two types of signals are integrated by the thermoregulatory center of the hypothalamus to maintain normal temperature. In a neutral temperature environment, the metabolic rate of humans produces more heat than is necessary to maintain the core body temperature in the range of 36.5–37.5°C (97.7–99.5°F).

A normal body temperature is maintained ordinarily, despite environmental variations, because the hypothalamic thermoregulatory center balances the excess heat production derived from metabolic activity in muscle and the liver with heat dissipation from the skin and lungs. According to studies of healthy individuals 18–40 years of age, the mean oral temperature is 36.8° ± 0.4°C (98.2° ± 0.7°F), with low levels at 6 A.M. and higher levels at 4–6 P.M. The maximum normal oral temperature is 37.2°C (98.9°F) at 6 A.M. and 37.7°C (99.9°F) at 4 P.M.; these values define the 99th percentile for healthy individuals. In light of these studies, *an A.M. temperature of >37.2°C (>98.9°F) or a P.M. temperature of >37.7°C (>99.9°F) defines a fever.* The normal daily temperature variation is typically 0.5°C (0.9°F). However, in some individuals recovering from a febrile illness, this daily variation can be as great as 1.0°C. During a febrile illness, the diurnal variation usually is maintained, but at higher, febrile levels. The daily temperature variation appears to be fixed in early childhood; in contrast, elderly individuals can exhibit a reduced ability to develop fever, with only a modest fever even in severe infections.

Rectal temperatures are generally 0.4°C (0.7°F) higher than oral readings. The lower oral readings are probably attributable to mouth breathing, which is a factor in patients with respiratory infections and rapid breathing. Lower-esophageal temperatures closely reflect core temperature. Tympanic membrane (TM) thermometers measure radiant heat from the tympanic membrane and nearby ear canal and display that absolute value (unadjusted mode) or a value automatically calculated from the absolute reading on the basis of nomograms relating the radiant temperature measured to actual core temperatures obtained in clinical studies (adjusted mode). These measurements, although convenient, may be more variable than directly determined oral or rectal values. Studies in adults show that readings are lower with unadjusted-mode than with adjusted-mode TM thermometers and that unadjusted-mode TM values are 0.8°C (1.6°F) lower than rectal temperatures.

In women who menstruate, the A.M. temperature is generally lower in the 2 weeks before ovulation; it then rises by ~0.6°C (1°F) with ovulation and remains at that level until menses occur. Body temperature can be elevated in the postprandial state. Pregnancy and endocrinologic dysfunction also affect body temperature.

FEVER VERSUS HYPERTHERMIA

FEVER

Fever is an elevation of body temperature that exceeds the normal daily variation and occurs *in conjunction with an increase in the hypothalamic set point* [e.g., from 37°C to 39°C (98.6°F to 102.2°F)]. This shift of the set point from "normothermic" to febrile levels very much resembles the resetting of the home thermostat to a higher level to raise the ambient temperature in a room. Once the hypothalamic set point is raised, neurons in the vasomotor center are activated and vasoconstriction commences. The individual first notices vasoconstriction in the hands and feet. Shunting of blood away from the periphery to the internal organs essentially decreases heat loss from the skin, and the person feels cold. For most fevers, body temperature increases by 1°–2°C (33.8°–35.6°F). Shivering, which increases heat production from the muscles, may begin at this time; however, shivering is not required if heat conservation mechanisms raise blood temperature sufficiently. Nonshivering heat production from the liver also contributes to increasing core temperature. In humans, behavioral adjustments (e.g., putting on more clothing

or bedding) help raise body temperature by decreasing heat loss.

The processes of heat conservation (vasoconstriction) and heat production (shivering and increased nonshivering thermogenesis) continue until the temperature of the blood bathing the hypothalamic neurons matches the new thermostat setting. Once that point is reached, the hypothalamus maintains the temperature at the febrile level by the same mechanisms of heat balance that function in the afebrile state. When the hypothalamic set point is again reset downward (in response to either a reduction in the concentration of pyrogens or the use of antipyretics), the processes of heat loss through vasodilation and sweating are initiated. Loss of heat by sweating and vasodilation continues until the blood temperature at the hypothalamic level matches the lower setting. Behavioral changes (e.g., removal of clothing) facilitate heat loss.

A fever of >41.5°C (>106.7°F) is called *hyperpyrexia*. This extraordinarily high fever can develop in patients with severe infections but most commonly occurs in patients with central nervous system (CNS) hemorrhages. In the preantibiotic era, fever due to a variety of infectious diseases rarely exceeded 41.1°C (106°F), and there has been speculation that this natural "thermal ceiling" is mediated by neuropeptides that function as central antipyretics.

In rare cases, the hypothalamic set point is elevated as a result of local trauma, hemorrhage, tumor, or intrinsic hypothalamic malfunction. The term *hypothalamic fever* sometimes is used to describe elevated temperature caused by abnormal hypothalamic function. However, most patients with hypothalamic damage have *sub*normal, not *supra*normal, body temperatures.

TABLE 8-1

CAUSES OF HYPERTHERMIA SYNDROMES

Heat Stroke
Exertional: Exercise in higher than normal heat and/or humidity Nonexertional: Anticholinergics, including antihistamines; antiparkinsonian drugs; diuretics; phenothiazines
Drug-Induced Hyperthermia
Amphetamines, cocaine, phencyclidine (PCP), methylenedioxymethamphetamine (MDMA; "ecstasy"), lysergic acid diethylamide (LSD), salicylates, lithium, anticholinergics, sympathomimetics
Neuroleptic Malignant Syndrome
Phenothiazines; butyrophenones, including haloperidol and bromperidol; fluoxetine; loxapine; tricyclic dibenzodiazepines; metoclopramide; domperidone; thiothixene; molindone; withdrawal of dopaminergic agents
Serotonin Syndrome
Selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants
Malignant Hyperthermia
Inhalational anesthetics, succinylcholine
Endocrinopathy
Thyrotoxicosis, pheochromocytoma
Central Nervous System Damage
Cerebral hemorrhage, status epilepticus, hypothalamic injury

Source: After FJ Curley et al (eds): *Intensive Care Medicine*, 3rd ed. Boston, Little, Brown, 1996.

HYPERTHERMIA

Although most patients with elevated body temperature have fever, there are circumstances in which elevated temperature represents not fever but hyperthermia (also called heat stroke; **Table 8-1**). Hyperthermia is characterized by an uncontrolled increase in body temperature that exceeds the body's ability to lose heat. The setting of the hypothalamic thermoregulatory center is unchanged. In contrast to fever in infections, hyperthermia does not involve pyrogenic molecules (see "Pyrogens," below). Exogenous heat exposure and endogenous heat production are two mechanisms by which hyperthermia can result in dangerously high internal temperatures. Excessive heat production can easily cause hyperthermia despite physiologic and behavioral control of body temperature. For example, work or exercise in hot environments can produce heat faster than peripheral mechanisms can lose it.

Heat stroke in association with a warm environment may be categorized as exertional or nonexertional. *Exertional heat stroke* typically occurs in individuals exercising at elevated ambient temperatures and/or humidity. In a dry environment and at maximal efficiency, sweating can dissipate ~600 kcal/h, requiring the production of >1 L of sweat. Even in healthy individuals, dehydration or the use of common medications (e.g., over-the-counter antihistamines with anticholinergic side effects) may precipitate exertional heat stroke. *Nonexertional heat stroke* typically occurs in either very young or elderly individuals, particularly during heat waves. According to the Centers for Disease Control and Prevention, there were 7000 deaths attributed to heat injury in the United States from 1979 to 1997. The elderly, the bedridden, persons taking anticholinergic or antiparkinsonian drugs or diuretics, and individuals confined to poorly ventilated and non-air-conditioned environments are most susceptible.

Drug-induced hyperthermia has become increasingly common as a result of the increased use of prescription psychotropic drugs and illicit drugs. Drug-induced hyperthermia may be caused by monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants, and amphetamines and by the illicit use of phencyclidine (PCP), lysergic acid diethylamide (LSD), methylenedioxymethamphetamine (MDMA, "ecstasy"), or cocaine.

Malignant hyperthermia occurs in individuals with an inherited abnormality of skeletal-muscle sarcoplasmic reticulum that causes a rapid increase in intracellular calcium levels in response to halothane and other inhalational anesthetics or to succinylcholine. Elevated temperature, increased muscle metabolism, muscle rigidity, rhabdomyolysis, acidosis, and cardiovascular instability develop within minutes. This rare condition is often fatal. The *neuroleptic malignant syndrome* occurs in the setting of the use of neuroleptic agents (antipsychotic phenothiazines, haloperidol, prochlorperazine, metoclopramide) or the withdrawal of dopaminergic drugs and is characterized by "lead-pipe" muscle rigidity, extrapyramidal side effects, autonomic dysregulation, and hyperthermia. This disorder appears to be caused by the inhibition of central dopamine receptors in the hypothalamus, which results in increased heat generation and decreased heat dissipation. The *serotonin syndrome*, seen with selective serotonin uptake inhibitors (SSRIs), MAOIs, and other serotonergic medications, has many features that overlap with those of the neuroleptic malignant syndrome (including hyperthermia) but may be distinguished by the presence of diarrhea, tremor, and myoclonus rather than lead-pipe rigidity. Thyrotoxicosis and pheochromocytoma also can cause increased thermogenesis.

It is important to distinguish between fever and hyperthermia since hyperthermia can be rapidly fatal and characteristically does not respond to antipyretics. In an emergency situation, however, making this distinction can be difficult. For example, in systemic sepsis, fever (hyperpyrexia) can be rapid in onset, and temperatures can exceed 40.5°C (104.9°F). Hyperthermia often is diagnosed on the basis of the events immediately preceding the elevation of core temperature—e.g., heat exposure or treatment with drugs that interfere with thermoregulation. In patients with heat stroke syndromes and in those taking drugs that block sweating, the skin is hot but dry, whereas in fever the skin can be cold as a consequence of vasoconstriction. Antipyretics do not reduce the elevated temperature in hyperthermia, whereas in fever—and even in hyperpyrexia—adequate doses of either aspirin or acetaminophen usually result in some decrease in body temperature.

PATHOGENESIS OF FEVER

PYROGENS

The term *pyrogen* is used to describe any substance that causes fever. *Exogenous* pyrogens are derived from outside the patient; most are microbial products, microbial toxins, or whole microorganisms. The classic example of an exogenous pyrogen is the lipopolysaccharide (endotoxin) produced by all gram-negative bacteria. Pyrogenic products of gram-positive organisms include the enterotoxins of *Staphylococcus aureus* and the group A and B streptococcal toxins, also called *superantigens*. One staphylococcal toxin of clinical importance is that associated with isolates of *S. aureus* from patients with toxic shock syndrome. These products of staphylococci and streptococci cause fever in experimental animals when injected intravenously at concentrations of 1–10 μg/kg. Endotoxin is a highly pyrogenic molecule in humans: When it is injected intravenously into volunteers, a dose of 2–3 ng/kg produces fever, leukocytosis, acute-phase proteins, and generalized symptoms of malaise.

PYROGENIC CYTOKINES

Cytokines are small proteins (molecular mass, 10,000–20,000 Da) that regulate immune, inflammatory, and hematopoietic processes. For example, the elevated leukocytosis seen in several infections with an absolute neutrophilia is the result of the cytokines interleukin (IL) 1 and IL-6. Some cytokines also cause fever; formerly referred to as *endogenous pyrogens*, they are now called *pyrogenic cytokines*. The pyrogenic cytokines include IL-1, IL-6, tumor necrosis factor (TNF), ciliary neurotropic factor (CNTF), and interferon (IFN) α. (IL-18, a member of the IL-1 family, does not appear to be a pyrogenic cytokine.) Other pyrogenic cytokines probably exist. Each cytokine is encoded by a separate gene, and each pyrogenic cytokine has been shown to cause fever in laboratory animals and in humans. When injected into humans, IL-1 and TNF produce fever at low doses (10–100 ng/kg); in contrast, for IL-6, a dose of 1–10 μg/kg is required for fever production.

A wide spectrum of bacterial and fungal products induce the synthesis and release of pyrogenic cytokines, as do viruses. However, fever can be a manifestation of disease in the absence of microbial infection. For example, inflammatory processes, trauma, tissue necrosis, and antigen-antibody complexes can induce the production of IL-1, TNF, and/or IL-6, which—individually or in combination—trigger the hypothalamus to raise the set point to febrile levels.

ELEVATION OF THE HYPOTHALAMIC SET POINT BY CYTOKINES

During fever, levels of prostaglandin E_2 (PGE_2) are elevated in hypothalamic tissue and the third cerebral ventricle. The concentrations of PGE_2 are highest near the circumventricular vascular organs (organum vasculosum of lamina terminalis)—networks of enlarged capillaries surrounding the hypothalamic regulatory centers. Destruction of these organs reduces the ability of pyrogens to produce fever. Most studies in animals have failed to show, however, that pyrogenic cytokines pass from the circulation into the brain itself. Thus, it appears that both exogenous and endogenous pyrogens interact with the endothelium of these capillaries and that this interaction is the first step in initiating fever—i.e., in raising the set point to febrile levels.

The key events in the production of fever are illustrated in **Fig. 8-1**. As has been mentioned, several cell types can produce pyrogenic cytokines. Pyrogenic cytokines such as IL-1, IL-6, and TNF are released from the cells and enter the systemic circulation. Although

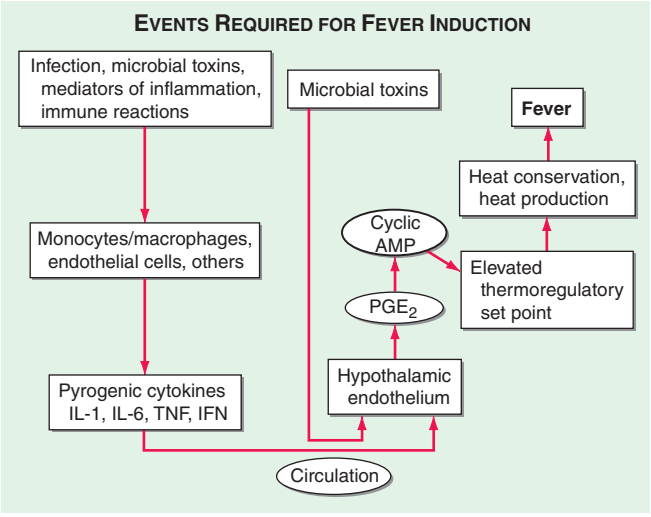


FIGURE 8-1
Chronology of events required for the induction of fever. AMP, adenosine 5′-monophosphate; IFN, interferon; IL, interleukin; PGE_2, prostaglandin E_2; TNF, tumor necrosis factor.

the systemic effects of these circulating cytokines lead to fever by inducing the synthesis of PGE_2, they also induce PGE_2 in peripheral tissues. The increase in PGE_2 in the periphery accounts for the nonspecific myalgias and arthralgias that often accompany fever. It is thought that some systemic PGE_2 escapes destruction by the lung and gains access to the hypothalamus via the internal carotid. However, it is the elevation of PGE_2 in the brain that starts the process of raising the hypothalamic set point for core temperature.

There are four receptors for PGE_2, and each signals the cell in different ways. Of the four receptors, the third (EP-3) is essential for fever: when the gene for this receptor is deleted in mice, no fever follows the injection of IL-1 or endotoxin. Deletion of the other PGE_2 receptor genes leaves the fever mechanism intact. Although PGE_2 is essential for fever, it is not a neurotransmitter. Rather, the release of PGE_2 from the brain side of the hypothalamic endothelium triggers the PGE_2 receptor on glial cells, and this stimulation results in the rapid release of cyclic adenosine 5′-monophosphate (cyclic AMP), which is a neurotransmitter. As shown in Fig. 8-1, the release of cyclic AMP from the glial cells activates neuronal endings from the thermoregulatory center that extend into the area. The elevation of cyclic AMP is thought to account for changes in the hypothalamic set point either directly or indirectly (by inducing the release of neurotransmitters). Distinct receptors for microbial products are located on the hypothalamic endothelium. These receptors are called *Toll-like receptors* and are similar in many ways to IL-1 receptors. The direct activation of Toll-like receptors also results in PGE_2 production and fever.

PRODUCTION OF CYTOKINES IN THE CNS

Cytokines produced in the brain may account for the hyperpyrexia of CNS hemorrhage, trauma, or infection. Viral infections of the CNS induce microglial and possibly neuronal production of IL-1, TNF, and IL-6. In experimental animals, the concentration of a cytokine required to cause fever is several orders of magnitude lower with direct injection into the brain substance or brain ventricles than with systemic injection. Therefore, cytokines produced in the CNS can raise the hypothalamic set point, bypassing the circumventricular organs. CNS cytokines probably account for the hyperpyrexia of CNS hemorrhage, trauma, or infection.

APPROACH TO THE PATIENT — Fever or Hyperthermia

PHYSICAL EXAMINATION The chronology of events preceding the fever (e.g., exposure to other infected individuals or to vectors of disease) should be ascertained. Electronic devices for measuring oral, tympanic membrane, and rectal temperatures are reliable, but the same site should be used consistently to monitor a febrile disease. Moreover, physicians should be aware that newborns, elderly patients, patients with chronic hepatic or renal failure, and patients taking glucocorticoids may have infections in the absence of fever.

LABORATORY TESTS The workup should include a complete blood count; a differential count should be performed manually or with an instrument sensitive to the identification of juvenile or band forms, toxic granulations, and Döhle bodies, which are suggestive of bacterial infection. Neutropenia may be present with some viral diseases.

Measurement of circulating cytokines in patients with fever is of little use since levels of pyrogenic cytokines in the circulation often are below the detection limit of the assay or do not coincide with fever. In patients with low-grade fevers, the most valuable measurements are C-reactive protein level and erythrocyte sedimentation rate. These markers of inflammatory processes are particularly helpful in detecting the possible presence of occult disease. Acute-phase reactants are discussed in Chap. 16.

FEVER IN RECIPIENTS OF ANTICYTOKINE THERAPY With the increasing use of anticytokines to reduce the activity of IL-1, IL-6, IL-12, or TNF in Crohn's disease, rheumatoid arthritis, or psoriasis, the potential of these therapies to blunt the febrile response must be considered. Chronic administration of anticytokines to block cytokine activity has the distinct clinical drawback of lowering the level of host defenses against both routine bacterial and opportunistic infections. The opportunistic infections reported in patients treated with agents that neutralize TNF-α are similar to those reported in the HIV-1-infected population (e.g., new infection with or reactivation of *Mycobacterium tuberculosis*, with dissemination). In nearly all reported cases of infection associated with anticytokine therapy, fever is among the presenting signs. However, the extent to which the febrile response is blunted in these patients remains unknown. This situation is similar

to that in patients receiving high-dose glucocorticoid therapy or anti-inflammatory agents such as ibuprofen. Therefore, low-grade fever is of considerable concern in patients receiving anticytokine therapies. The physician must undertake early and rigorous diagnostic evaluation of these patients.

TREATMENT Fever or Hyperthermia

THE DECISION TO TREAT FEVER Most fevers are associated with self-limited infections, such as common viral diseases. The use of antipyretics is not contraindicated in these infections: there is no significant clinical evidence that antipyretics delay the resolution of viral or bacterial infections, nor is there evidence that fever facilitates recovery from infection or acts as an adjuvant to the immune system. In short, routine treatment of fever and its symptoms with antipyretics does no harm and does not slow the resolution of common viral and bacterial infections.

However, with bacterial infections, withholding antipyretic therapy can be helpful in evaluating the effectiveness of a particular antibiotic, particularly in the absence of positive cultures of the infecting organism. Therefore, the routine use of antipyretics can mask an inadequately treated bacterial infection. Withholding antipyretics in some cases may facilitate the diagnosis of an unusual febrile disease. Temperature-pulse dissociation (relative bradycardia) occurs in typhoid fever, brucellosis, leptospirosis, some drug-induced fevers, and factitious fever. In newborns, the elderly, patients with chronic hepatic or renal failure, and patients taking glucocorticoids, fever may not be present despite infection. Hypothermia can be observed in patients with septic shock.

Some infections have characteristic patterns in which febrile episodes are separated by intervals of normal temperature. For example, *Plasmodium vivax* causes fever every third day, whereas fever occurs every fourth day with *P. malariae*. Another relapsing fever is related to *Borrelia* infection, with days of fever followed by a several-day afebrile period and then a relapse of days of fever. In the Pel-Ebstein pattern, fever lasting 3–10 days is followed by afebrile periods of 3–10 days; this pattern can be classic for Hodgkin's disease and other lymphomas. In cyclic neutropenia, fevers occur every 21 days and accompany the neutropenia. There is no periodicity of fever in patients with familial Mediterranean fever. However, these patterns have limited or no diagnostic value compared with specific and rapid laboratory tests.

ANTICYTOKINE THERAPY TO REDUCE FEVER IN AUTOIMMUNE AND AUTOINFLAMMATORY DISEASES Recurrent fever is documented at some point in most autoimmune diseases but in all autoinflammatory diseases. Although fever also can be a manifestation of autoimmune diseases, recurrent fevers are characteristic of autoinflammatory diseases. The autoinflammatory diseases (Table 8-2) include adult and juvenile Still's disease, familial Mediterranean fever, and hyper-IgD syndrome. In addition to recurrent fevers, neutrophilia and serosal inflammation characterize autoinflammatory diseases. The fevers associated with these illnesses are reduced dramatically by blocking of IL-1β activity. Anticytokines therefore reduce fever in autoimmune and autoinflammatory diseases. Although fevers in autoinflammatory diseases are mediated by IL-1β, these patients also respond to antipyretics.

MECHANISMS OF ANTIPYRETIC AGENTS The reduction of fever by lowering of the elevated hypothalamic set point is a direct function of reducing the level of PGE_2 in the thermoregulatory center. The synthesis of PGE_2 depends on the constitutively expressed enzyme cyclooxygenase. The substrate for cyclooxygenase is arachidonic acid released from the cell membrane, and this release is the rate-limiting step in the synthesis of PGE_2. Therefore, inhibitors of cyclooxygenase are potent antipyretics. The antipyretic potency of various drugs is directly correlated with the inhibition of brain cyclooxygenase. Acetaminophen is a poor cyclooxygenase inhibitor in peripheral tissue and lacks noteworthy anti-inflammatory activity; in the brain, however, acetaminophen is oxidized by the p450 cytochrome system, and the oxidized form inhibits cyclooxygenase activity. Moreover, in the brain, the inhibition of another enzyme, COX-3, by acetaminophen may account for the antipyretic effect of this agent. However, COX-3 is not found outside the CNS.

Oral aspirin and acetaminophen are equally effective in reducing fever in humans. Nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and specific inhibitors of COX-2 are also excellent antipyretics. Chronic high-dose therapy with antipyretics such as aspirin or any NSAID does not reduce normal core body temperature. Thus, PGE_2 appears to play no role in normal thermoregulation.

As effective antipyretics, glucocorticoids act at two levels. First, similar to the cyclooxygenase inhibitors, glucocorticoids reduce PGE_2 synthesis by inhibiting the

TABLE 8-2

AUTOINFLAMMATORY DISEASES
Adult and juvenile Still's disease
Cryopyrin-associated periodic syndromes (CAPS)
Familial Mediterranean fever
Hyper-IgD syndrome
Behçet's syndrome
Macrophage activation syndrome
Normocomplementemic urticarial vasculitis
Antisynthetase myositis
PAPA[a] syndrome
Blau syndrome
Gouty arthritis

[a]Pyogenic arthritis, pyoderma gangrenosum, and acne.

activity of phospholipase A_2, which is needed to release arachidonic acid from the cell membrane. Second, glucocorticoids block the transcription of the mRNA for the pyrogenic cytokines. Limited experimental evidence indicates that ibuprofen and COX-2 inhibitors reduce IL-1-induced IL-6 production and may contribute to the antipyretic activity of NSAIDs.

REGIMENS FOR THE TREATMENT OF FEVER The objectives in treating fever are first to reduce the elevated hypothalamic set point and second to facilitate heat loss. Reducing fever with antipyretics also reduces systemic symptoms of headache, myalgias, and arthralgias.

Oral aspirin and NSAIDs effectively reduce fever but can adversely affect platelets and the gastrointestinal tract. Therefore, use of acetaminophen is preferred as an antipyretic. In children, acetaminophen or oral ibuprofen must be used because aspirin increases the risk of Reye's syndrome. If the patient cannot take oral antipyretics, parenteral preparations of NSAIDs and rectal suppositories of various antipyretics can be used.

Treatment of fever in some patients is highly recommended. Fever increases the demand for oxygen (i.e., for every increase of 1°C over 37°C, there is a 13% increase in oxygen consumption) and can aggravate the condition of patients with preexisting impairment of cardiac, pulmonary, or CNS function. Children with a history of febrile or nonfebrile seizure should be treated aggressively to reduce fever. However, it is unclear what triggers the febrile seizure, and there is no correlation between absolute temperature elevation and onset of a febrile seizure in susceptible children.

In hyperpyrexia, the use of cooling blankets facilitates the reduction of temperature; however, cooling blankets should not be used without oral antipyretics. In hyperpyretic patients with CNS disease or trauma (CNS bleeding), reducing core temperature mitigates the detrimental effects of high temperature on the brain.

TREATING HYPERTHERMIA A high core temperature in a patient with an appropriate history (e.g., environmental heat exposure or treatment with anticholinergic or neuroleptic drugs, tricyclic antidepressants, succinylcholine, or halothane) along with appropriate clinical findings (dry skin, hallucinations, delirium, pupil dilation, muscle rigidity, and/or elevated levels of creatine phosphokinase) suggests hyperthermia. Antipyretics are of no use in treating hyperthermia. Physical cooling with sponging, fans, cooling blankets, and even ice baths should be initiated immediately in conjunction with the administration of IV fluids and appropriate pharmacologic agents (see below). If sufficient cooling is not achieved by external means, internal cooling can be achieved by gastric or peritoneal lavage with iced saline. In extreme circumstances, hemodialysis or even cardiopulmonary bypass with cooling of blood may be performed.

Malignant hyperthermia should be treated immediately with cessation of anesthesia and IV administration of dantrolene sodium. The recommended dose of dantrolene is 1–2.5 mg/kg given intravenously every 6 h for at least 24–48 h—until oral dantrolene can be administered, if needed. Dantrolene at similar doses is indicated in the neuroleptic malignant syndrome and in drug-induced hyperthermia and may even be useful in the hyperthermia of the serotonin syndrome and thyrotoxicosis. The neuroleptic malignant syndrome also may be treated with bromocriptine, levodopa, amantadine, or nifedipine or by induction of muscle paralysis with curare and pancuronium. Tricyclic antidepressant overdose may be treated with physostigmine.

CHAPTER 9

FEVER AND RASH

Elaine T. Kaye ■ Kenneth M. Kaye

The acutely ill patient with fever and rash often presents a diagnostic challenge for physicians. The distinctive appearance of an eruption in concert with a clinical syndrome may facilitate a prompt diagnosis and the institution of life-saving therapy or critical infection-control interventions. Representative images of many of the rashes discussed in this chapter are included in Chap. 11.

APPROACH TO THE PATIENT

Fever and Rash

A thorough history of patients with fever and rash includes the following relevant information: immune status, medications taken within the previous month, specific travel history, immunization status, exposure to domestic pets and other animals, history of animal (including arthropod) bites, existence of cardiac abnormalities, presence of prosthetic material, recent exposure to ill individuals, and exposure to sexually transmitted diseases. The history should also include the site of the onset of the rash and its direction and rate of spread.

A thorough physical examination entails close attention to the rash, with an assessment and precise definition of its salient features. First, it is critical to determine the *type* of lesions that make up the eruption. *Macules* are flat lesions defined by an area of changed color (i.e., a blanchable erythema). *Papules* are raised, solid lesions <5 mm in diameter; *plaques* are lesions >5 mm in diameter with a flat, plateau-like surface; and *nodules* are lesions >5 mm in diameter with a more rounded configuration. *Wheals* (urticaria, hives) are papules or plaques that are pale pink and may appear annular (ring-like) as they enlarge; classic (nonvasculitic) wheals are transient, lasting only 24 h in any defined area. *Vesicles* (<5 mm) and *bullae* (>5 mm) are circumscribed, elevated lesions containing fluid. *Pustules* are raised lesions containing purulent exudate; vesicular processes such as varicella or herpes simplex may evolve to pustules. *Nonpalpable purpura* is a flat lesion that is due to bleeding into the skin. If <3 mm in diameter, the purpuric lesions are termed *petechiae*; if >3 mm, they are termed *ecchymoses*. *Palpable purpura* is a raised lesion that is due to inflammation of the vessel wall (vasculitis) with subsequent hemorrhage. An *ulcer* is a defect in the skin extending at least into the upper layer of the dermis, and an *eschar* (tâche noire) is a necrotic lesion covered with a black crust.

Other pertinent features of rashes include their *configuration* (i.e., annular or target), the *arrangement* of their lesions, and their *distribution* (i.e., central or peripheral).

For further discussion, see Chap. 15.

CLASSIFICATION OF RASH

This chapter reviews rashes that reflect systemic disease, but it does not include localized skin eruptions (i.e., cellulitis, impetigo) that may also be associated with fever (Chap. 22). This chapter does not intend to be all-inclusive, but it covers the most important and most common diseases associated with fever and rash. Rashes are classified herein on the basis of the morphology and distribution of lesions. For practical purposes, this classification system is based on the most typical disease presentations. However, morphology may vary as rashes evolve, and the presentation of diseases with rashes is subject to many variations. For instance, the classic petechial rash of Rocky Mountain spotted fever (RMSF) (Chap. 79) may initially consist of blanchable erythematous macules distributed peripherally; at times, however, the rash associated with RMSF may not be predominantly acral or no rash may develop at all.

Diseases with fever and rash may be classified by type of eruption: centrally distributed maculopapular, peripheral, confluent desquamative erythematous, vesiculobullous, urticaria-like, nodular, purpuric, ulcerated, or eschar. Diseases are listed by these categories in **Table 9-1**, and many are highlighted in the text. However, for a more detailed discussion of each disease associated with a rash, the reader is referred to the chapter dealing with that specific disease. (Reference chapters are cited in the text and listed in Table 9-1.)

CENTRALLY DISTRIBUTED MACULOPAPULAR ERUPTIONS

Centrally distributed rashes, in which lesions are primarily truncal, are the most common type of eruption. The rash of *rubeola* (measles) starts at the hairline 2–3 days into the illness and moves down the body, sparing the palms and soles (Chap. 98). It begins as discrete erythematous lesions, which become confluent as the rash spreads. Koplik's spots (1- to 2-mm white or bluish lesions with an erythematous halo on the buccal mucosa) are pathognomonic for measles and are generally seen during the first 2 days of symptoms. They should not be confused with Fordyce's spots (ectopic sebaceous glands), which have no erythematous halos and are found in the mouth of healthy individuals. Koplik's spots may briefly overlap with the measles exanthem.

Rubella (German measles) also spreads from the hairline downward; unlike that of measles, however, the rash of rubella tends to clear from originally affected areas as it migrates, and it may be pruritic (Chap. 99). Forchheimer spots (palatal petechiae) may develop, but are nonspecific because they also develop in mononucleosis (Chap. 86) and scarlet fever (Chap. 39). Postauricular and suboccipital adenopathy and arthritis are common among adults with rubella. Exposure of pregnant women to ill individuals should be avoided, as rubella causes severe congenital abnormalities. Numerous strains of enteroviruses (Chap. 97), primarily echoviruses and coxsackieviruses, cause nonspecific syndromes of fever and eruptions that may mimic rubella or measles. Patients with infectious mononucleosis caused by Epstein-Barr virus (Chap. 86) or with primary infection caused by HIV (Chap. 93) may exhibit pharyngitis, lymphadenopathy, and a nonspecific maculopapular exanthem.

The rash of *erythema infectiosum* (fifth disease), which is caused by human parvovirus B19, primarily affects children 3–12 years old; it develops after fever has resolved as a bright blanchable erythema on the cheeks ("slapped cheeks") with perioral pallor (Chap. 89). A more diffuse rash (often pruritic) appears the next day on the trunk and extremities and then rapidly develops into a lacy reticular eruption that may wax and wane (especially with temperature change) over 3 weeks. Adults with fifth

TABLE 9-1

DISEASES ASSOCIATED WITH FEVER AND RASH

DISEASE	ETIOLOGY	DESCRIPTION	GROUP AFFECTED/ EPIDEMIOLOGIC FACTORS	CLINICAL SYNDROME	CHAPTER
Centrally Distributed Maculopapular Eruptions					
Acute meningococcemia[a]	—	—	—	—	48
Drug-induced hypersensitivity syndrome/ drug reaction with eosinophilia and systemic symptoms (DIHS/DRESS)[b]	—	—	—	—	11
Rubeola (measles, first disease)	Paramyxovirus	Discrete lesions that become confluent as rash spreads from hairline downward, sparing palms and soles; lasts ≥3 days; Koplik's spots	Nonimmune individuals	Cough, conjunctivitis, coryza, severe prostration	98
Rubella (German measles, third disease)	Togavirus	Spreads from hairline downward, clearing as it spreads; Forschheimer spots	Nonimmune individuals	Adenopathy, arthritis	99
Erythema infectiosum (fifth disease)	Human parvovirus B19	Bright-red "slapped-cheeks" appearance followed by lacy reticular rash that waxes and wanes over 3 weeks; rarely, papular-purpuric "gloves-and-socks" syndrome on hands and feet	Most common among children 3–12 years old; occurs in winter and spring	Mild fever; arthritis in adults; rash following resolution of fever	89
Exanthem subitum (roseola, sixth disease)	Human herpesvirus 6	Diffuse maculopapular eruption over trunk and neck; resolves within 2 days	Usually affects children <3 years old	Rash following resolution of fever; similar to Boston exanthem (echovirus 16); febrile seizures may occur	87
Primary HIV infection	HIV	Nonspecific diffuse macules and papules; less commonly, urticarial or vesicular oral or genital ulcers	Individuals recently infected with HIV	Pharyngitis, adenopathy, arthralgias	93
Infectious mononucleosis	Epstein-Barr virus	Diffuse maculopapular eruption (5% of cases; 90% if ampicillin is given); urticaria, petechiae in some cases; periorbital edema (50%); palatal petechiae (25%)	Adolescents, young adults	Hepatosplenomegaly, pharyngitis, cervical lymphadenopathy, atypical lymphocytosis, heterophile antibody	86
Other viral exanthems	Echoviruses 2, 4, 9, 11, 16, 19, 25; coxsackieviruses A9, B1, B5; etc.	Wide range of skin findings that may mimic rubella or measles	Affect children more commonly than adults	Nonspecific viral syndromes	97

(*continued*)

TABLE 9-1

DISEASES ASSOCIATED WITH FEVER AND RASH (*CONTINUED*)

DISEASE	ETIOLOGY	DESCRIPTION	GROUP AFFECTED/ EPIDEMIOLOGIC FACTORS	CLINICAL SYNDROME	CHAPTER
Centrally Distributed Maculopapular Eruptions (*continued*)					
Exanthematous drug-induced eruption	Drugs (antibiotics, anticonvulsants, diuretics, etc.)	Intensely pruritic, bright-red macules and papules, symmetric on trunk and extremities; may become confluent	Occurs 2–3 days after exposure in previously sensitized individuals; otherwise, after 2–3 weeks (but can occur anytime, even shortly after drug is discontinued)	Variable findings: fever and eosinophilia	—
Epidemic typhus	*Rickettsia prowazekii*	Maculopapular eruption appearing in axillae, spreading to trunk and later to extremities; usually spares face, palms, soles; evolves from blanchable macules to confluent eruption with petechiae; rash evanescent in recrudescent typhus (Brill-Zinsser disease)	Exposure to body lice; occurrence of recrudescent typhus as relapse after 30–50 years	Headache, myalgias; 10–40% mortality if untreated; milder clinical presentation in recrudescent form	79
Endemic (murine) typhus	*Rickettsia typhi*	Maculopapular eruption, usually sparing palms, soles	Exposure to rat or cat fleas	Headache, myalgias	79
Scrub typhus	*Orientia tsutsugamushi*	Diffuse macular rash starting on trunk; eschar at site of mite bite	Endemic in South Pacific, Australia, Asia; transmitted by mites	Headache, myalgias, regional adenopathy; mortality up to 30% if untreated	79
Rickettsial spotted fevers	*Rickettsia conorii* (boutonneuse fever), *Rickettsia australis* (North Queensland tick typhus), *Rickettsia sibirica* (Siberian tick typhus), and others	Eschar common at bite site; maculopapular (rarely, vesicular and petechial) eruption on proximal extremities, spreading to trunk and face	Exposure to ticks; *R. conorii* in Mediterranean region, India, Africa; *R. australis* in Australia; *R. sibirica* in Siberia, Mongolia	Headache, myalgias, regional adenopathy	79
Human monocytotropic ehrlichiosis[c]	*Ehrlichia chaffeensis*	Maculopapular eruption (40% of cases), involves trunk and extremities; may be petechial	Tickborne; most common in U.S. Southeast, southern Midwest, and mid-Atlantic regions	Headache, myalgias, leukopenia	79
Leptospirosis	*Leptospira interrogans*	Maculopapular eruption; conjunctivitis; scleral hemorrhage in some cases	Exposure to water contaminated with animal urine	Myalgias; aseptic meningitis; *fulminant form*: ictero-hemorrhagic fever (Weil's disease)	76

(*continued*)

TABLE 9-1

DISEASES ASSOCIATED WITH FEVER AND RASH (*CONTINUED*)

DISEASE	ETIOLOGY	DESCRIPTION	GROUP AFFECTED/ EPIDEMIOLOGIC FACTORS	CLINICAL SYNDROME	CHAPTER
Centrally Distributed Maculopapular Eruptions (*continued*)					
Lyme disease	*Borrelia burgdorferi*	Papule expanding to erythematous annular lesion with central clearing (erythema migrans; average diameter, 15 cm), sometimes with concentric rings, sometimes with indurated or vesicular center; multiple secondary erythema migrans lesions in some cases	Bite of tick vector	Headache, myalgias, chills, photophobia occurring acutely; CNS disease, myocardial disease, arthritis weeks to months later in some cases	78
Southern tick-associated rash illness (STARI, Master's disease)	*Borrelia lonestari*	Similar to erythema migrans of Lyme disease with several differences, including: multiple secondary lesions less likely; lesions tending to be smaller (average diameter, ~8 cm); central clearing more likely	Bite of tick vector *Amblyomma americanum* (Lone Star tick); often found in regions where Lyme disease is uncommon, including southern United States	Compared with Lyme disease: fewer constitutional symptoms, tick bite more likely to be recalled; other Lyme disease sequelae lacking	78
Typhoid fever	*Salmonella typhi*	Transient, blanchable erythematous macules and papules, 2–4 mm, usually on trunk (rose spots)	Ingestion of contaminated food or water (rare in U.S.)	Variable abdominal pain and diarrhea; headache, myalgias, hepatosplenomegaly	58
Dengue fever[d]	Dengue virus (4 serotypes; flaviviruses)	Rash in 50% of cases; initially diffuse flushing; midway through illness, onset of maculopapular rash, which begins on trunk and spreads centrifugally to extremities and face; pruritus, hyperesthesia in some cases; after defervescence, petechiae on extremities in some cases	Occurs in tropics and subtropics; transmitted by mosquito	Headache, musculoskeletal pain ("breakbone fever"); leukopenia; occasionally biphasic ("saddleback") fever	102
Ratbite fever (sodoku)	*Spirillum minus*	Eschar at bite site; then blotchy violaceous or red-brown rash involving trunk and extremities	Rat bite; primarily found in Asia; rare in U.S.	Regional adenopathy, recurrent fevers if untreated	35
Relapsing fever	*Borrelia* species	Central rash at end of febrile episode; petechiae in some cases	Exposure to ticks or body lice	Recurrent fever, headache, myalgias, hepatosplenomegaly	77

(*continued*)

TABLE 9-1

DISEASES ASSOCIATED WITH FEVER AND RASH (*CONTINUED*)

DISEASE	ETIOLOGY	DESCRIPTION	GROUP AFFECTED/ EPIDEMIOLOGIC FACTORS	CLINICAL SYNDROME	CHAPTER
Centrally Distributed Maculopapular Eruptions (*continued*)					
Erythema marginatum (rheumatic fever)	Group A *Streptococcus*	Erythematous annular papules and plaques occurring as polycyclic lesions in waves over trunk, proximal extremities; evolving and resolving within hours	Patients with rheumatic fever	Pharyngitis preceding polyarthritis, carditis, subcutaneous nodules, chorea	41
Systemic lupus erythematosus	Autoimmune disease	Macular and papular erythema, often in sun-exposed areas; discoid lupus lesions (local atrophy, scale, pigmentary changes); periungual telangiectasis; malar rash; vasculitis sometimes causing urticaria, palpable purpura; oral erosions in some cases	Most common in young to middle-aged women; flares precipitated by sun exposure	Arthritis; cardiac, pulmonary, renal, hematologic, and vasculitic disease	—
Still's disease	Autoimmune disease	Transient 2- to 5-mm erythematous papules appearing at height of fever on trunk, proximal extremities; lesions evanescent	Children and young adults	High spiking fever, polyarthritis, splenomegaly; erythrocyte sedimentation rate, >100 mm/h	—
African trypanosomiasis	*Trypanosoma brucei rhodesiense/ gambiense*	Blotchy or annular erythematous macular and papular rash (trypanid), primarily on trunk; pruritus; chancre at site of tsetse fly bite may precede rash by several weeks	Tsetse fly bite in East (*T. brucei rhodesiense)* or West *(T. brucei gambiense)* Africa	Hemolymphatic disease followed by meningoencephalitis; Winterbottom's sign (posterior cervical lymphadenopathy) *(T. brucei gambiense)*	123
Arcanobacterial pharyngitis	*Arcanobacterium (Corynebacterium) haemolyticum*	Diffuse, erythematous, maculopapular eruption involving trunk and proximal extremities; may desquamate	Children and young adults	Exudative pharyngitis, lymphadenopathy	42
Peripheral Eruptions					
Chronic meningococcemia, disseminated gonococcal infection,[a] human parvovirus B19 infection[e]	—	—	—	—	48, 49, 89
Rocky Mountain spotted fever	*Rickettsia rickettsii*	Rash beginning on wrists and ankles and spreading centripetally; appears on palms and soles later in disease; lesion evolution from blanchable macules to petechiae	Tick vector; widespread but more common in southeastern and southwest-central U.S.	Headache, myalgias, abdominal pain; mortality up to 40% if untreated	79

(*continued*)

TABLE 9-1

DISEASES ASSOCIATED WITH FEVER AND RASH (*CONTINUED*)

DISEASE	ETIOLOGY	DESCRIPTION	GROUP AFFECTED/ EPIDEMIOLOGIC FACTORS	CLINICAL SYNDROME	CHAPTER
Peripheral Eruptions (*continued*)					
Secondary syphilis	*Treponema pallidum*	Coincident primary chancre in 10% of cases; copper-colored, scaly papular eruption, diffuse but prominent on palms and soles; rash never vesicular in adults; condyloma latum, mucous patches, and alopecia in some cases	Sexually transmitted	Fever, constitutional symptoms	74
Chikungunya fever	Chikungunya virus	Maculopapular eruption; prominent on upper extremities and face, but can also occur on trunk and lower extremities	*Aedes aegypti* and *A. albopictus* mosquito bites; primarily in Africa and Indian Ocean region	Severe polyarticular, migratory arthralgias, especially involving small joints (e.g., hands, wrists, ankles)	102
Hand-foot-and-mouth disease	Coxsackievirus A16 most common cause	Tender vesicles, erosions in mouth; 0.25-cm papules on hands and feet with rim of erythema evolving into tender vesicles	Summer and fall; primarily children <10 years old; multiple family members	Transient fever	97
Erythema multiforme (EM)	Infection, drugs, idiopathic causes	Target lesions (central erythema surrounded by area of clearing and another rim of erythema) up to 2 cm; symmetric on knees, elbows, palms, soles; spreads centripetally; papular, sometimes vesicular; when extensive and involving mucous membranes, termed *EM major*	Herpes simplex virus or *Mycoplasma pneumoniae* infection; drug intake (i.e., sulfa, phenytoin, penicillin)	50% younger than 20 years old; fever more common in most severe form, EM major, which can be confused with Stevens-Johnson syndrome (but EM major lacks prominent skin sloughing)	—[f]
Rat-bite fever (Haverhill fever)	*Streptobacillus moniliformis*	Maculopapular eruption over palms, soles, and extremities; tends to be more severe at joints; eruption sometimes becoming generalized; may be purpuric; may desquamate	Rat bite, ingestion of contaminated food	Myalgias; arthritis (50%); fever recurrence in some cases	35
Bacterial endocarditis	*Streptococcus, Staphylococcus*, etc.	*Subacute course*: Osler's nodes (tender pink nodules on finger or toe pads); petechiae on skin and mucosa; splinter hemorrhages. *Acute course* (*Staphylococcus aureus*): Janeway lesions (painless erythematous or hemorrhagic macules, usually on palms and soles)	Abnormal heart valve *(Streptococcus)*, intravenous drug use	New or changing heart murmur	20

(*continued*)

TABLE 9-1

DISEASES ASSOCIATED WITH FEVER AND RASH (*CONTINUED*)

DISEASE	ETIOLOGY	DESCRIPTION	GROUP AFFECTED/ EPIDEMIOLOGIC FACTORS	CLINICAL SYNDROME	CHAPTER
Confluent Desquamative Erythemas					
Scarlet fever (second disease)	Group A *Streptococcus* (pyrogenic exotoxins A, B, C)	Diffuse blanchable erythema beginning on face and spreading to trunk and extremities; circumoral pallor; "sandpaper" texture to skin; accentuation of linear erythema in skin folds (Pastia's lines); enanthem of white evolving into red "strawberry" tongue; desquamation in second week	Most common among children 2–10 years old; usually follows group A streptococcal pharyngitis	Fever, pharyngitis, headache	39
Kawasaki disease	Idiopathic causes	Rash similar to scarlet fever (scarlatiniform) or erythema multiforme; fissuring of lips, strawberry tongue; conjunctivitis; edema of hands, feet; desquamation later in disease	Children <8 years old	Cervical adenopathy, pharyngitis, coronary artery vasculitis	—
Streptococcal toxic shock syndrome	Group A *Streptococcus* (associated with pyrogenic exotoxin A and/or B or certain M types)	When present, rash often scarlatiniform	May occur in setting of severe group A streptococcal infections (e.g., necrotizing fasciitis, bacteremia, pneumonia)	Multiorgan failure, hypotension; 30% mortality rate	39
Staphylococcal toxic shock syndrome	*S. aureus* (toxic shock syndrome toxin 1, enterotoxin B or C)	Diffuse erythema involving palms; pronounced erythema of mucosal surfaces; conjunctivitis; desquamation 7–10 days into illness	Colonization with toxin-producing *S. aureus*	Fever >39±C (>102°F), hypotension, multiorgan dysfunction	38
Staphylococcal scalded-skin syndrome	*S. aureus*, phage group II	Diffuse tender erythema, often with bullae and desquamation; Nikolsky's sign	Colonization with toxin-producing *S. aureus*; occurs in children <10 years old (termed "Ritter's disease" in neonates) or adults with renal dysfunction	Irritability; nasal or conjunctival secretions	38

(*continued*)

TABLE 9-1

DISEASES ASSOCIATED WITH FEVER AND RASH (*CONTINUED*)

DISEASE	ETIOLOGY	DESCRIPTION	GROUP AFFECTED/ EPIDEMIOLOGIC FACTORS	CLINICAL SYNDROME	CHAPTER
Confluent Desquamative Erythemas (*continued*)					
Exfoliative erythroderma syndrome	Underlying psoriasis, eczema, drug eruption, mycosis fungoides	Diffuse erythema (often scaling) interspersed with lesions of underlying condition	Usually occurs in adults over age 50; more common among men	Fever, chills (i.e., difficulty with thermoregulation); lymphadenopathy	—
DIHS/DRESS	Aromatic anticonvulsants; other drugs, including sulfonamides, minocycline	Maculopapular eruption (mimicking exanthematous drug rash) sometimes progressing to exfoliative erythroderma; profound edema, especially facial; pustules may occur	Individuals genetically unable to detoxify arene oxides (anticonvulsants), patients with slow *N*-acetylating capacity (sulfonamides)	Lymphadenopathy, multiorgan failure (especially hepatic), eosinophilia, atypical lymphocytes; mimics sepsis	—
Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN)	Drugs (80% of cases; often allopurinol, anticonvulsants, antibiotics), infection, idiopathic	Erythematous and purpuric macules, sometimes targetoid, or diffuse erythema progressing to bullae, with sloughing and necrosis of entire epidermis; Nikolsky's sign; involves mucosal surfaces; TEN (>30% epidermal necrosis) is maximal form; SJS involves <10%; SJS/TEN overlap involves 10–30% of epidermis	Uncommon among children; more common among patients with HIV infection, SLE, certain HLA types, or slow acetylators	Dehydration, sepsis sometimes resulting from lack of normal skin integrity; up to 30% mortality	—
Vesiculobullous or Pustular Eruptions					
Hand-foot-and-mouth syndrome[g]; staphylococcal scalded-skin syndrome; toxic epidermal necrolysis[b]; DIHS/DRESS[b]	—	—	—	—	—[f]
Varicella (chickenpox)	Varicella-zoster virus	Macules (2–3 mm) evolving into papules, then vesicles (sometimes umbilicated), on an erythematous base ("dewdrops on a rose petal"); pustules then forming and crusting; lesions appearing in crops; may involve scalp, mouth; intensely pruritic	Usually affects children; 10% of adults susceptible; most common in late winter and spring	Malaise; generally mild disease in healthy children; more severe disease with complications in adults and immunocompromised children	85

(*continued*)

TABLE 9-1

DISEASES ASSOCIATED WITH FEVER AND RASH (*CONTINUED*)

DISEASE	ETIOLOGY	DESCRIPTION	GROUP AFFECTED/ EPIDEMIOLOGIC FACTORS	CLINICAL SYNDROME	CHAPTER
Vesiculobullous or Pustular Eruptions (*continued*)					
Pseudomonas "hot-tub" folliculitis	*Pseudomonas aeruginosa*	Pruritic erythematous follicular, papular, vesicular, or pustular lesions that may involve axillae, buttocks, abdomen, and especially areas occluded by bathing suits; can mani fest as tender isolated nodules on palmar or plantar surfaces (the latter designated "*Pseudomonas* hot-foot syndrome")	Bathers in hot tubs or swimming pools; occurs in outbreaks	Earache, sore eyes and/or throat; generally self-limited	57
Variola (smallpox)	Variola major virus	Red macules on tongue, palate evolving to papules and vesicles; skin macules evolving to papules, then vesicles, then pustules over 1 week, with subsequent lesion crusting; lesions initially appearing on face and spreading centrifugally from trunk to extremities; differs from varicella in that (1) skin lesions in any given area are at same stage of development and (2) there is a prominent distribution of lesions on face and extremities (including palms, soles)	Nonimmune individuals exposed to smallpox	Prodrome of fever, headache, backache, myalgias; vomiting in 50% of cases	7
Primary herpes simplex virus (HSV) infection	HSV	Erythema rapidly followed by hallmark painful *grouped vesicles* that may evolve into pustules that ulcerate, especially on mucosal surfaces; lesions at site of inoculation: commonly gingivostomatitis for HSV-1 and genital lesions for HSV-2; recurrent disease milder (e.g., herpes labialis does not involve oral mucosa)	Primary infection most common among children and young adults for HSV-1 and among sexually active young adults for HSV-2; no fever in recurrent infection	Regional lymphadenopathy	84

(*continued*)

TABLE 9-1

DISEASES ASSOCIATED WITH FEVER AND RASH (*CONTINUED*)

DISEASE	ETIOLOGY	DESCRIPTION	GROUP AFFECTED/ EPIDEMIOLOGIC FACTORS	CLINICAL SYNDROME	CHAPTER
Vesiculobullous or Pustular Eruptions (*continued*)					
Disseminated herpesvirus infection	Varicella-zoster virus or HSV	Generalized vesicles that can evolve to pustules and ulcerations; individual lesions similar for varicella-zoster and HSV. *Zoster cutaneous dissemination*: >25 lesions extending outside involved dermatome. *HSV*: extensive, progressive mucocutaneous lesions that may occur in absence of dissemination, sometimes disseminate in eczematous skin (eczema herpeticum); HSV visceral dissemination may occur with only localized mucocutaneous disease; in disseminated neonatal disease, skin lesions diagnostically helpful when present, but rash absent in a substantial minority of cases	Patients with immunosuppression, eczema; neonates	Visceral organ involvement (especially liver) in some cases; neonatal disease particularly severe	84, 85, 31
Rickettsialpox	*Rickettsia akari*	Eschar found at site of mite bite; generalized rash involving face, trunk, extremities; may involve palms and soles; <100 papules and plaques (2–10 mm); tops of lesions developing vesicles that may evolve into pustules	Seen in urban settings; transmitted by mouse mites	Headache, myalgias, regional adenopathy; mild disease	79
Acute generalized eruptive pustulosis (AGEP)	Drugs (mostly anticonvulsants or antimicrobials); also viral	Tiny sterile nonfollicular pustules on erythematous, edematous skin; begins on face and in body folds, then becomes generalized	Appears 2–21 days after start of drug therapy, depending on whether previously sensitized	Acute fever, pruritus, leukocytosis	—
Disseminated *Vibrio vulnificus* infection	*V. vulnificus*	Erythematous lesions evolving into hemorrhagic bullae and then into necrotic ulcers	Patients with cirrhosis, diabetes, renal failure; exposure by ingestion of contaminated saltwater, seafood	Hypotension; 50% mortality	61
Ecthyma gangrenosum	*P. aeruginosa*, other gram-negative rods, fungi	Indurated plaque evolving into hemorrhagic bulla or pustule that sloughs, resulting in eschar formation; erythematous halo; most common in axillary, groin, perianal regions	Usually affects neutropenic patients; occurs in up to 28% of individuals with *Pseudomonas* bacteremia	Clinical signs of sepsis	57

(*continued*)

TABLE 9-1

DISEASES ASSOCIATED WITH FEVER AND RASH (*CONTINUED*)

DISEASE	ETIOLOGY	DESCRIPTION	GROUP AFFECTED/ EPIDEMIOLOGIC FACTORS	CLINICAL SYNDROME	CHAPTER
Urticaria-like Eruptions					
Urticarial vasculitis	Serum sickness, often due to infection (including hepatitis B, enteroviral, parasitic), drugs; connective tissue disease	Erythematous, edematous "urticaria-like" plaques, pruritic or burning; unlike urticaria: typical lesion duration >24 h (up to 5 days) and lack of complete lesion blanching with compression due to hemorrhage	Patients with serum sickness (including hepatitis B), connective tissue disease	Fever variable; arthralgias/arthritis	—[f]
Nodular Eruptions					
Disseminated infection	Fungi (e.g., candidiasis, histoplasmosis, cryptococcosis, sporotrichosis, coccidioidomycosis); mycobacteria	Subcutaneous nodules (up to 3 cm); fluctuance, draining common with mycobacteria; necrotic nodules (extremities, periorbital or nasal regions) common with *Aspergillus*, *Mucor*	Immunocompromised hosts (i.e., bone marrow transplant recipients, patients undergoing chemotherapy, HIV-infected patients, alcoholics)	Features vary with organism	—[f]
Erythema nodosum (septal panniculitis)	Infections (e.g., streptococcal, fungal, mycobacterial, yersinial); drugs (e.g., sulfas, penicillins, oral contraceptives); sarcoidosis; idiopathic causes	Large, violaceous, nonulcerative, subcutaneous nodules; exquisitely tender; usually on lower legs but also on upper extremities	More common among girls and women 15–30 years old	Arthralgias (50%); features vary with associated condition	—[f]
Sweet's syndrome (acute febrile neutrophilic dermatosis)	Yersinial infection; lymphoproliferative disorders; idiopathic causes	Tender red or blue edematous nodules giving impression of vesiculation; usually on face, neck, upper extremities; when on lower extremities, may mimic erythema nodosum	More common among women and among persons 30–60 years old; 20% of cases associated with malignancy (men and women equally affected in this group)	Headache, arthralgias, leukocytosis	—
Bacillary angiomatosis	*Bartonella henselae*, *B. quintana*	Many forms, including erythematous, smooth vascular nodules; friable, exophytic lesions; erythematous plaques (may be dry, scaly); subcutaneous nodules (may be erythematous)	Usually patients with HIV infection	Peliosis of liver and spleen in some cases; lesions sometimes involving multiple organs; bacteremia	65

(*continued*)

TABLE 9-1

DISEASES ASSOCIATED WITH FEVER AND RASH (*CONTINUED*)

DISEASE	ETIOLOGY	DESCRIPTION	GROUP AFFECTED/ EPIDEMIOLOGIC FACTORS	CLINICAL SYNDROME	CHAPTER
Purpuric Eruptions					
Rocky Mountain spotted fever, rat-bite fever, endocarditis[g]; epidemic typhus[e]; dengue fever[d]; human parvovirus B19 infection[e]	—	—	—	—	—[f]
Acute meningococcemia	*Neisseria meningitidis*	Initially pink maculopapular lesions evolving into petechiae; petechiae rapidly becoming numerous, sometimes enlarging and becoming vesicular; trunk, extremities most commonly involved; may appear on face, hands, feet; may include purpura fulminans (see next) reflecting disseminated intravascular coagulation	Most common among children, individuals with asplenia or terminal complement component deficiency (C5–C8)	Hypotension, meningitis (sometimes preceded by upper respiratory infection)	48
Purpura fulminans	Severe disseminated intravascular coagulation	Large ecchymoses with sharply irregular shapes evolving into hemorrhagic bullae and then into black necrotic lesions	Individuals with sepsis (e.g., involving *N. meningitidis*), malignancy, or massive trauma; asplenic patients at high risk for sepsis	Hypotension	16, 48
Chronic meningococcemia	*N. meningitidis*	Variety of recurrent eruptions, including pink maculopapular; nodular (usually on lower extremities); petechial (sometimes developing vesicular centers); purpuric areas with pale blue-gray centers	Individuals with complement deficiencies	Fevers, sometimes intermittent; arthritis, myalgias, headache	48
Disseminated gonococcal infection	*Neisseria gonorrhoeae*	Papules (1–5 mm) evolving over 1–2 days into hemorrhagic pustules with gray necrotic centers; hemorrhagic bullae occurring rarely; lesions (usually <40) distributed peripherally near joints (more commonly on upper extremities)	Sexually active individuals (more often females), some with complement deficiency	Low-grade fever, tenosynovitis, arthritis	49

(*continued*)

TABLE 9-1

DISEASES ASSOCIATED WITH FEVER AND RASH (*CONTINUED*)

DISEASE	ETIOLOGY	DESCRIPTION	GROUP AFFECTED/ EPIDEMIOLOGIC FACTORS	CLINICAL SYNDROME	CHAPTER
Purpuric Eruptions (*continued*)					
Enteroviral petechial rash	Usually echovirus 9 or coxsackievirus A9	Disseminated petechial lesions (may also be maculopapular, vesicular, or urticarial)	Often occurs in outbreaks	Pharyngitis, headache; aseptic meningitis with echovirus 9	97
Viral hemorrhagic fever	Arboviruses (including dengue) and arenaviruses	Petechial rash	Residence in or travel to endemic areas, other virus exposure	Triad of fever, shock, hemorrhage from mucosa or gastrointestinal tract	102, 103
Thrombotic thrombocytopenic purpura/hemolytic-uremic syndrome	Idiopathic, *Escherichia coli* O157:H7 (Shiga toxin), drugs	Petechiae	Individuals with *E. coli* O157:H7 gastroenteritis (especially children), cancer chemotherapy, HIV infection, autoimmune diseases; pregnant/postpartum women	Fever (not always present), hemolytic anemia, thrombocytopenia, renal dysfunction, neurologic dysfunction; coagulation studies normal	54, 59
Cutaneous small-vessel vasculitis (leukocytoclastic vasculitis)	Infections (including group A *Streptococcus*, viral hepatitis), drugs, chemicals, food allergens, idiopathic causes	Palpable purpuric lesions appearing in crops on legs or other dependent areas; may become vesicular or ulcerative; usually resolve over 3–4 weeks	Occurs in a wide spectrum of diseases, including connective tissue disease, cryoglobulinemia, malignancy, Henoch-Schönlein purpura (HSP); more common among children	Fever, malaise, arthralgias, myalgias; systemic vasculitis in some cases; renal, joint, and gastrointestinal involvement commonly seen in HSP	—
Eruptions with Ulcers and/or Eschars					
Scrub typhus, rickettsial spotted fevers, rat-bite fever[e]; rickettsialpox, ecthyma gangrenosum[h]	—	—	—	—	—[f]
Tularemia	*Francisella tularensis*	Ulceroglandular form: erythematous, tender papule evolves into necrotic, tender ulcer with raised borders; in 35% of cases, eruptions (maculopapular, vesiculopapular, acneiform, urticarial, erythema nodosum, or erythema multiforme) may occur	Exposure to ticks, biting flies, infected animals	Fever, headache, lymphadenopathy	63

(*continued*)

TABLE 9-1

DISEASES ASSOCIATED WITH FEVER AND RASH (*CONTINUED*)

DISEASE	ETIOLOGY	DESCRIPTION	GROUP AFFECTED/ EPIDEMIOLOGIC FACTORS	CLINICAL SYNDROME	CHAPTER
Eruptions with Ulcers and/or Eschars (*continued*)					
Anthrax	*Bacillus anthracis*	Pruritic papule enlarging and evolving into a 1- by 3-cm painless ulcer surrounded by vesicles and then developing a central eschar with edema; residual scar	Exposure to infected animals or animal products, other exposure to anthrax spores	Lymphadenopathy, headache	7

[a]See "Purpuric eruptions."
[b]See "Confluent desquamative erythemas."
[c]In human granulocytotropic ehrlichiosis or anaplasmosis (caused by *Anaplasma phagocytophila;* most common in the upper midwestern and northeastern regions of the United States), rash is rare.
[d]See "Viral hemorrhagic fever" under "Purpuric eruptions" for dengue hemorrhagic fever/dengue shock syndrome.
[e]See "Centrally distributed maculopapular eruptions."
[f]See etiology-specific chapters.
[g]See "Peripheral eruptions."
[h]See "Vesiculobullous or pustular eruptions."

disease often have arthritis, and fetal hydrops can develop in association with this condition in pregnant women.

Exanthem subitum (roseola) is caused by human herpesvirus 6 and is most common among children <3 years of age (Chap. 87). As in erythema infectiosum, the rash usually appears after fever has subsided. It consists of 2- to 3-mm rose-pink macules and papules that rarely coalesce, which occur initially on the trunk and sometimes on the extremities (sparing the face) and fade within 2 days.

Although drug reactions have many manifestations, including urticaria, exanthematous *drug-induced eruptions* are most common and are often difficult to distinguish from viral exanthems. Eruptions elicited by drugs are usually more intensely erythematous and pruritic than viral exanthems, but this distinction is not reliable. A history of new medications and an absence of prostration may help to distinguish a drug-related rash from an eruption of another etiology. Rashes may persist for up to two weeks after administration of the offending agent is discontinued. Certain populations are more prone than others to drug rashes. Of HIV-infected patients, 50–60% develop a rash in response to sulfa drugs; 90% of patients with mononucleosis due to Epstein-Barr virus develop a rash when given ampicillin.

Rickettsial illnesses (Chap. 79) should be considered in the evaluation of individuals with centrally distributed maculopapular eruptions. The usual setting for *epidemic typhus* is a site of war or natural disaster in which people are exposed to body lice. *Endemic typhus* or *leptospirosis* (the latter caused by a spirochete) (Chap. 76) may be seen in urban environments where rodents proliferate. Outside the United States, other rickettsial diseases cause a spotted-fever syndrome and should be considered in residents of or travelers to endemic areas. Similarly, *typhoid fever*, a nonrickettsial disease caused by *Salmonella typhi* (Chap. 58), is usually acquired during travel outside the United States. Dengue fever, caused by a mosquito-transmitted flavivirus, occurs in tropical and subtropical regions of the world (Chap. 102).

Some centrally distributed maculopapular eruptions have distinctive features. Erythema migrans, the rash of Lyme disease (Chap. 78), typically manifests as singular or multiple annular plaques. Untreated erythema migrans lesions usually fade within a month but may persist for more than a year. Southern tick-associated rash illness (STARI) has an erythema migrans–like rash but is less severe than Lyme disease and often occurs in regions where Lyme is not endemic. *Erythema marginatum*, the rash of acute rheumatic fever (Chap. 41), has a distinctive pattern of enlarging and shifting transient annular lesions.

Collagen vascular diseases may cause fever and rash. Patients with *systemic lupus erythematosus* typically develop a sharply defined, erythematous eruption in a butterfly distribution on the cheeks (malar rash) as well as many other skin manifestations. *Still's disease* presents as an evanescent, salmon-colored rash on the trunk and proximal extremities that coincides with fever spikes.

PERIPHERAL ERUPTIONS

These rashes are alike in that they are most prominent peripherally or begin in peripheral (acral) areas before spreading centripetally. Early diagnosis and therapy are critical in RMSF (Chap. 79) because of its grave prognosis if untreated. Lesions evolve from macular to petechial, start on the wrists and ankles, spread centripetally,

and appear on the palms and soles only later in the disease. The rash of *secondary syphilis* (Chap. 74), which may be generalized but is prominent on the palms and soles, should be considered in the differential diagnosis of pityriasis rosea, especially in sexually active patients. Chikungunya fever (Chap. 102), which is transmitted by mosquito bite in Africa and the Indian Ocean region, is associated with a maculopapular eruption and severe polyarticular small-joint arthralgias. *Hand-foot-and-mouth disease* (Chap. 97), most commonly caused by coxsackievirus A16, is distinguished by tender vesicles distributed peripherally and in the mouth; outbreaks commonly occur within families. The classic target lesions of *erythema multiforme* appear symmetrically on the elbows, knees, palms, soles, and face. In severe cases, these lesions spread diffusely and involve mucosal surfaces. Lesions may develop on the hands and feet in *endocarditis* (Chap. 20).

CONFLUENT DESQUAMATIVE ERYTHEMAS

These eruptions consist of diffuse erythema frequently followed by desquamation. The eruptions caused by group A *Streptococcus* or *Staphylococcus aureus* are toxin-mediated. *Scarlet fever* (Chap. 39) usually follows pharyngitis; patients have a facial flush, a "strawberry" tongue, and accentuated petechiae in body folds (Pastia's lines). *Kawasaki disease* presents in the pediatric population as fissuring of the lips, a strawberry tongue, conjunctivitis, adenopathy, and sometimes cardiac abnormalities. *Streptococcal toxic shock syndrome* (Chap. 39) manifests with hypotension, multiorgan failure, and, often, a severe group A streptococcal infection (e.g., necrotizing fasciitis). *Staphylococcal toxic shock syndrome* (Chap. 38) also presents with hypotension, and multiorgan failure, but usually only *S. aureus* colonization—not a severe *S. aureus* infection—is documented. *Staphylococcal scalded-skin syndrome* (Chap. 38) is seen primarily in children and in immunocompromised adults. Generalized erythema is often evident during the prodrome of fever and malaise; profound tenderness of the skin is distinctive. In the exfoliative stage, the skin can be induced to form bullae with light lateral pressure (Nikolsky's sign). In a mild form, a scarlatiniform eruption mimics scarlet fever, but the patient does not exhibit a strawberry tongue or circumoral pallor. In contrast to the staphylococcal scalded-skin syndrome, in which the cleavage plane is superficial in the epidermis, *toxic epidermal necrolysis* a maximal variant of Stevens-Johnson syndrome, involves sloughing of the entire epidermis, resulting in severe disease. *Exfoliative erythroderma syndrome* is a serious reaction associated with systemic toxicity that is often due to eczema, psoriasis, a drug reaction, or mycosis fungoides. Drug-induced hypersensitivity syndrome (DIHS) due to antiepileptic and antibiotic agents initially appears similar to an exanthematous drug reaction, but may progress to exfoliative erythroderma; it is accompanied by multiorgan failure and has an associated mortality rate of ~10%.

VESICULOBULLOUS OR PUSTULAR ERUPTIONS

Varicella (Chap. 85) is highly contagious, often occurring in winter or spring. At any point in time, within a given region of the body, varicella lesions are in different stages of development. In immunocompromised hosts, varicella vesicles may lack the characteristic erythematous base or may appear hemorrhagic. Lesions of *Pseudomonas* "hot-tub" folliculitis (Chap. 57) are also pruritic and may appear similar to those of varicella. However, hot-tub folliculitis generally occurs in outbreaks after bathing in hot tubs or swimming pools, and lesions occur in regions occluded by bathing suits. Lesions of *variola* (smallpox) (Chap. 7) also appear similar to those of varicella, but are all at the same stage of development in a given region of the body. Variola lesions are most prominent on the face and extremities, while varicella lesions are most prominent on the trunk. Herpes simplex virus infection (Chap. 84) is characterized by hallmark grouped vesicles on an erythematous base. Primary herpes infection is accompanied by fever and toxicity, while recurrent disease is milder. *Rickettsialpox* (Chap. 79) is often documented in urban settings and is characterized by vesicles followed by pustules. It can be distinguished from varicella by an eschar at the site of the mouse-mite bite and the papule/plaque base of each vesicle. Acute generalized eruptive pustulosis (AGEP) should be considered in individuals who are acutely febrile and are taking new medications, especially anticonvulsant or antimicrobial agents. Disseminated *Vibrio vulnificus* infection (Chap. 61) or *ecthyma gangrenosum* due to *Pseudomonas aeruginosa* (Chap. 57) should be considered in immunosuppressed individuals with sepsis and hemorrhagic bullae.

URTICARIA-LIKE ERUPTIONS

Individuals with classic urticaria ("hives") usually have a hypersensitivity reaction without associated fever. In the presence of fever, urticaria-like eruptions are usually due to *urticarial vasculitis*. Unlike individual lesions of classic urticaria, which last up to 24 h, these lesions may last 3–5 days. Etiologies include serum sickness (often induced by drugs such as penicillins, sulfas, salicylates, or barbiturates), connective-tissue disease (e.g., systemic lupus erythematosus or Sjögren's syndrome), and infection (e.g., with hepatitis B virus, enteroviruses, or parasites). Malignancy, especially lymphoma, may be associated with fever and chronic urticaria.

NODULAR ERUPTIONS

In immunocompromised hosts, nodular lesions often represent disseminated infection. Patients with disseminated *candidiasis* (often due to *Candida tropicalis*) may have a triad of fever, myalgias, and eruptive nodules (Chap. 110). Disseminated *cryptococcosis* lesions (Chap. 109) may resemble molluscum contagiosum (Chap. 88). Necrosis of nodules

should raise the suspicion of *aspergillosis* (Chap. 111) or *mucormycosis* (Chap. 112). *Erythema nodosum* presents with exquisitely tender nodules on the lower extremities. *Sweet's syndrome* should be considered in individuals with multiple nodules and plaques, often so edematous that they give the appearance of vesicles or bullae. Sweet's syndrome may affect either healthy individuals or persons with lymphoproliferative disease.

PURPURIC ERUPTIONS

Acute meningococcemia (Chap. 48) classically presents in children as a petechial eruption, but initial lesions may appear as blanchable macules or urticaria. RMSF should be considered in the differential diagnosis of acute meningococcemia. *Echovirus 9 infection* (Chap. 97) may mimic acute meningococcemia; patients should be treated as if they have bacterial sepsis because prompt differentiation of these conditions may be impossible. Large ecchymotic areas of *purpura fulminans* (Chaps. 16 and 48) reflect severe underlying disseminated intravascular coagulation, which may be due to infectious or noninfectious causes. The lesions of *chronic meningococcemia* (Chap. 48) may have a variety of morphologies, including petechial. Purpuric nodules may develop on the legs and resemble erythema nodosum but lack its exquisite tenderness. Lesions of *disseminated gonococcemia* (Chap. 49) are distinctive, sparse, countable hemorrhagic pustules, usually located near joints. The lesions of chronic meningococcemia and those of gonococcemia may be indistinguishable in terms of appearance and distribution. *Viral hemorrhagic fever* (Chaps. 102 and 103) should be considered in patients with an appropriate travel history and a petechial rash. *Thrombotic thrombocytopenic purpura* and *hemolytic-uremic syndrome* (Chaps. 54 and 59) are closely related and are noninfectious causes of fever and petechiae. *Cutaneous small-vessel vasculitis* (*leukocytoclastic vasculitis*) typically manifests as palpable purpura and has a wide variety of causes.

ERUPTIONS WITH ULCERS OR ESCHARS

The presence of an ulcer or eschar in the setting of a more widespread eruption can provide an important diagnostic clue. For example, the presence of an eschar may suggest the diagnosis of scrub typhus or rickettsialpox (Chap. 79) in the appropriate setting. In other illnesses (e.g., anthrax) (Chap. 7), an ulcer or eschar may be the only skin manifestation.

CHAPTER 10

FEVER OF UNKNOWN ORIGIN

Jeffrey A. Gelfand ■ Michael V. Callahan

DEFINITION AND CLASSIFICATION

Fever of unknown origin (FUO) was defined by Petersdorf and Beeson in 1961 as (1) temperatures of >38.3°C (>101°F) on several occasions; (2) a duration of fever of >3 weeks; and (3) failure to reach a diagnosis despite 1 week of inpatient investigation. While this classification has stood for more than 30 years, Durack and Street have proposed a revised system for classification of FUO that better accounts for nonendemic and emerging diseases, improved diagnostic technologies, and adverse reactions to new therapeutic interventions. This updated classification includes (1) classic FUO, (2) nosocomial FUO, (3) neutropenic FUO, and (4) FUO associated with HIV infection.

Classic FUO corresponds closely to the earlier definition of FUO, differing only with regard to the prior requirement for 1 week's study in the hospital. The newer definition is broader, stipulating three outpatient visits or 3 days in the hospital without elucidation of a cause or 1 week of "intelligent and invasive" ambulatory investigation. In *nosocomial FUO*, a temperature of ≥38.3°C (≥101°F) develops on several occasions in a hospitalized patient who is receiving acute care and in whom infection was not manifest or incubating on admission. Three days of investigation, including at least 2 days' incubation of cultures, is the minimum requirement for this diagnosis. *Neutropenic FUO* is defined as a temperature of ≥38.3°C (≥101°F) on several occasions

in a patient whose neutrophil count is <500/μL or is expected to fall to that level in 1–2 days. The diagnosis of neutropenic FUO is invoked if a specific cause is not identified after 3 days of investigation, including at least 2 days' incubation of cultures. *HIV-associated FUO* is defined by a temperature of ≥38.3°C (≥101°F) on several occasions over a period of >4 weeks for outpatients or >3 days for hospitalized patients with HIV infection. This diagnosis is invoked if appropriate investigation over 3 days, including 2 days' incubation of cultures, reveals no source.

Adoption of these categories of FUO in the literature has allowed a more rational compilation of data regarding these disparate groups. In the remainder of this chapter, the discussion will focus on classic FUO in the adult patient unless otherwise specified.

CAUSES OF CLASSIC FUO

Table 10-1 summarizes the findings of several large studies of FUO carried out since the advent of the antibiotic era, including a prospective study of 167 adult patients with FUO encompassing all eight university hospitals in the Netherlands and using a standardized protocol in which the first author reviewed every patient's case. Coincident with the widespread use of antibiotics, increasingly useful diagnostic technologies—both noninvasive and invasive—have been developed. Newer studies reflect not only changing patterns of disease but also the impact of diagnostic techniques that make it possible to eliminate many patients with specific illness from the FUO category. The ubiquitous use of potent broad-spectrum antibiotics may have decreased the number of infections causing FUO. The wide availability of ultrasonography, CT, MRI, radionuclide scanning, and positron emission tomography (PET) scanning has enhanced the detection of localized infections and of occult neoplasms and lymphomas in patients previously thought to have FUO. Likewise, the widespread availability of highly specific and sensitive immunologic testing has reduced the number of undetected cases of adult Still's disease, systemic lupus erythematosus, and polyarteritis nodosa.

Infections such as extrapulmonary tuberculosis and—in endemic areas—typhoid fever and malaria remain a leading diagnosable cause of FUO. Prolonged mononucleosis syndromes caused by Epstein-Barr virus, cytomegalovirus (CMV), or HIV are conditions whose consideration as a cause of FUO are sometimes confounded by delayed antibody responses. Intraabdominal abscesses (sometimes poorly localized) and renal, retroperitoneal, and paraspinal abscesses continue to be difficult to diagnose. Renal malacoplakia, with submucosal plaques or nodules involving the urinary tract, may cause fatal FUO if untreated; it is associated with intracellular bacterial infection, is seen in patients with defects of intracellular bacterial killing, and is treated with fluoroquinolones or trimethoprim-sulfamethoxazole. Occasionally, other organs may be involved. Osteomyelitis, especially where prosthetic devices have been implanted, must be considered. Although true culture-negative infective endocarditis is rare, one may be misled by cryptic endocarditis caused by indolent, slow-growing microorganisms of the HACEK group (*Haemophilus aphrophilus*, *Aggregatibacter* [formerly *Actinobacillus*] *actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella*

TABLE 10-1

CLASSIC FUO IN ADULTS

AUTHORS (YEAR OF PUBLICATION)	YEARS OF STUDY	NO. OF CASES	INFECTIONS (%)	NEOPLASMS (%)	NONINFECTIOUS INFLAMMATORY DISEASES (%)	MISCELLANEOUS CAUSES (%)	UNDIAGNOSED CAUSES (%)
Petersdorf and Beeson (1961)	1952–1957	100	36	19	19[a]	19[a]	7
Larson and Featherstone (1982)	1970–1980	105	30	31	16[a]	11[a]	12
Knockaert and Vanneste (1992)	1980–1989	199	22.5	7	23[a]	21.5[a]	25.5
de Kleijn et al. (1997, Part I)	1992–1994	167	26	12.5	24	8	30
Bleeker-Rovers et al. (2007)	2003–2005	73	16	7	22[b]	4	51

[a]Authors' raw data retabulated to conform to altered diagnostic categories.
[b]Connective tissue diseases.
Source: Modified from EM de Kleijn et al: Fever of unknown origin (FUO): I. A prospective multicenter study of 167 patients with FUO, using fixed epidemiologic entry criteria. Medicine 76:392, 1997.

kingae), *Bartonella* spp. (previously *Rochalimaea*), *Legionella* spp., *Coxiella burnetii*, *Chlamydophila psittaci*, and fungi. Prostatitis, dental abscesses, sinusitis, and cholangitis continue to be sources of occult fever.

Fungal diseases, most notably histoplasmosis involving the reticuloendothelial system, may cause FUO, particularly outside of the endemic regions where these diseases may be more readily recognized. FUO following travel to neotropical regions and the desert southwest of the United States, even for very limited periods, should prompt evaluation for paracoccidioidomycosis and coccidioidomycosis, respectively. The rising popularity of adventure travel among citizens of Western countries has increased the incidence in these nations of presentation for FUO due to otherwise uncommon endemic vector-borne infections, notably chikungunya fever and scrub typhus. FUO with headache should prompt examination of spinal fluid for *Cryptococcus neoformans, Mycobacterium tuberculosis*, and travel-acquired trypanosomes. Malaria (which may result from transfusion, failure to take a prescribed prophylactic agent, or infection with a drug-resistant *Plasmodium* strain) continues to be a cause of FUO, particularly of the asynchronous variety. A related protozoan infection, babesiosis, may cause FUO and is increasing in geographic distribution and in incidence, especially among the elderly and the immunosuppressed.

In most earlier series, neoplasms were the next most common cause of FUO after infections (Table 10-1). In more recent series, a decrease in the percentage of FUO cases due to malignancy was attributed to improvement in diagnostic technologies—in particular, high-resolution tomography, MRI, PET scanning, and tumor antigen assays. This observation does not diminish the importance of considering neoplasia in the initial diagnostic evaluation of a patient with fever. A number of patients in these series had temporal arteritis, adult Still's disease, drug-related fever, and factitious fever. In recent series, ~25–50% of cases of FUO have remained undiagnosed. The general term *noninfectious inflammatory diseases* applies to systemic rheumatologic or vasculitic diseases such as polymyalgia rheumatica, lupus, and adult Still's disease as well as to granulomatous diseases such as sarcoidosis, Crohn's disease, and granulomatous hepatitis.

In the elderly, multisystem disease is the most frequent cause of FUO, giant-cell arteritis being the leading etiologic entity in this category. In patients >50 years of age, this disease accounts for 15–20% of FUO cases. Tuberculosis is the most common infection causing FUO in the elderly, and colon cancer is an important cause of FUO with malignancy in this age group.

Many diseases have been grouped in the various studies as "miscellaneous." On this list are drug fever, pulmonary embolism, factitious fever, the hereditary periodic fever syndromes [familial Mediterranean fever, hyper-IgD syndrome, tumor necrosis factor (TNF) receptor–associated periodic syndrome (also known as TRAPS or familial Hibernian fever), familial cold urticaria, and the Muckle-Wells syndrome)], and congenital lysosomal storage diseases such as Gaucher's and Fabry's disease.

A drug-related etiology must be considered in any case of prolonged fever. Any febrile pattern may be elicited by a drug. Virtually all classes of drugs can cause fever, but antimicrobial agents (especially β-lactam antibiotics), cardiovascular drugs (e.g., quinidine), antineoplastic drugs, and drugs acting on the central nervous system (e.g., phenytoin) are particularly common causes. The use of TNF inhibitors for treatment of inflammatory diseases has led to atypical presentations of tuberculosis, histoplasmosis, coccidioidomycosis, and JC virus infection associated with FUO.

It is axiomatic that, as the duration of fever increases, the likelihood of an infectious cause decreases, even for the more indolent infectious etiologies (e.g., brucellosis, paracoccidioidomycosis, malaria due to *Plasmodium malariae*). In a series of 347 patients referred to the National Institutes of Health from 1961 to 1977, only 6% had an infection **(Table 10-2)**. A significant proportion (9%) had factitious fevers—i.e., fevers due either to false elevations of temperature or to self-induced disease. A substantial number of these factitious cases were in young women in the health professions. It is worth noting that 8% of the patients with prolonged fevers (some of whom had completely normal liver function studies) had granulomatous hepatitis, and 6% had adult Still's disease. After prolonged investigation, 19% of cases still had no specific diagnosis. A total of 27% of patients had no actual fever during inpatient observation or had an exaggerated circadian temperature rhythm without chills, elevated pulse, or other abnormalities.

GLOBAL CONSIDERATIONS

More than 200 conditions may be considered in the differential diagnosis of classic FUO in adults; the most common of these are listed in **Table 10-3**. This list applies predominantly to

TABLE 10-2

CAUSES OF FUO LASTING >6 MONTHS

CAUSE	CASES, %
None identified	19
Miscellaneous causes	13
Factitious causes	9
Granulomatous hepatitis	8
Neoplasm	7
Still's disease	6
Infection	6
Collagen vascular disease	4
Familial Mediterranean fever	3
No fever[a]	27

[a]No actual fever observed during 2–3 weeks of inpatient observation. Includes patients with exaggerated circadian rhythm.

Source: From a study of 347 patients referred to the National Institutes of Health from 1961–1977 with a presumptive diagnosis of FUO of >6 months' duration. (Data from R Aduan et al: Prolonged fever of unknown origin. Clin Res 26:558A, 1978.)

TABLE 10-3

CAUSES OF FUO IN ADULTS IN THE UNITED STATES

Infections

Localized pyogenic infections
- Appendicitis
- Cat-scratch disease
- Cholangitis
- Cholecystitis
- Dental abscess
- Diverticulitis/abscess
- Lesser sac abscess
- Liver abscess
- Mesenteric lymphadenitis
- Osteomyelitis
- Pancreatic abscess
- Pelvic inflammatory disease
- Perinephric/intrarenal abscess
- Prostatic abscess
- Renal malacoplakia
- Sinusitis
- Subphrenic abscess
- Suppurative thrombophlebitis
- Tuboovarian abscess

Intravascular infections
- Bacterial aortitis
- Bacterial endocarditis
- Vascular catheter infection

Systemic bacterial infections
- Bartonellosis
- Brucellosis
- *Campylobacter* infection
- Cat-scratch disease/bacillary angiomatosis (*B. henselae*)
- Gonococcemia
- Legionnaires' disease
- Leptospirosis
- Listeriosis
- Lyme disease
- Melioidosis
- Meningococcemia
- Rat-bite fever
- Relapsing fever
- Salmonellosis
- Syphilis
- Tularemia
- Typhoid fever
- Vibriosis
- *Yersinia* infection

Mycobacterial infections
- *M. avium/M. intracellulare* infections
- Other atypical mycobacterial infections
- Tuberculosis

Other bacterial infections
- Actinomycosis
- Bacillary angiomatosis
- Nocardiosis
- Whipple's disease

Rickettsial infections
- Anaplasmosis
- Ehrlichiosis
- Murine typhus
- Q fever
- Rickettsialpox
- Rocky Mountain spotted fever
- Scrub typhus

Mycoplasmal infections

Chlamydial infections
- Lymphogranuloma venereum
- Psittacosis
- TWAR (*C. pneumoniae*) infection

Viral infections
- Chikungunya fever
- Colorado tick fever
- Coxsackievirus group B infection
- Cytomegalovirus infection
- Dengue
- Epstein-Barr virus infection
- Hepatitis A, B, C, D, and E
- HIV infection
- Human herpesvirus 6 infection
- Lymphocytic choriomeningitis
- Parvovirus B19 infection
- Picornavirus infection

Fungal infections
- Aspergillosis
- Blastomycosis
- Candidiasis
- Coccidioidomycosis
- Cryptococcosis
- Histoplasmosis
- Mucormycosis
- Paracoccidioidomycosis
- *Pneumocystis* infection
- Sporotrichosis

Parasitic infections
- Amebiasis
- Babesiosis
- Chagas' disease
- Leishmaniasis
- Malaria
- Strongyloidiasis
- Toxocariasis
- Toxoplasmosis
- Trichinellosis

Presumed infections, agent undetermined
- Kawasaki's disease (mucocutaneous lymph node syndrome)
- Kikuchi's necrotizing lymphadenitis

Neoplasms

Malignant
- Colon cancer
- Gall bladder carcinoma
- Hepatoma
- Hodgkin's lymphoma
- Immunoblastic T-cell lymphoma
- Leukemia
- Lymphomatoid granulomatosis
- Malignant histiocytosis
- Non-Hodgkin's lymphoma
- Pancreatic cancer
- Renal cell carcinoma
- Sarcoma

Benign
- Atrial myxoma
- Castleman's disease
- Renal angiomyolipoma

Habitual Hyperthermia
- (Exaggerated circadian rhythm)

Collagen Vascular/Hypersensitivity Diseases
- Adult Still's disease
- Behçet's disease
- Erythema multiforme
- Erythema nodosum
- Giant-cell arteritis/polymyalgia rheumatica
- Hypersensitivity pneumonitis
- Hypersensitivity vasculitis
- Mixed connective-tissue disease
- Polyarteritis nodosa
- Relapsing polychondritis
- Rheumatic fever
- Rheumatoid arthritis
- Schnitzler's syndrome
- Systemic lupus erythematosus
- Takayasu's aortitis
- Weber-Christian disease
- Granulomatosis with polyangiitis

Granulomatous Diseases
- Crohn's disease
- Granulomatous hepatitis
- Midline granuloma
- Sarcoidosis

Miscellaneous Conditions
- Aortic dissection
- Drug fever
- Gout
- Hematomas
- Hemoglobinopathies
- Laennec's cirrhosis
- PFPA syndrome: periodic fever, adenitis, pharyngitis, aphthae
- Postmyocardial infarction syndrome
- Recurrent pulmonary emboli
- Subacute thyroiditis (de Quervain's)
- Tissue infarction/necrosis

Inherited and Metabolic Diseases
- Adrenal insufficiency
- Cyclic neutropenia
- Deafness, urticaria, and amyloidosis
- Fabry disease
- Familial cold urticaria
- Familial Mediterranean fever
- Hyperimmunoglobulinemia D and periodic fever
- Muckle-Wells syndrome
- Tumor necrosis factor receptor–associated periodic syndrome (familial Hibernian fever)
- Type V hypertriglyceridemia

Thermoregulatory Disorders

Central
- Brain tumor
- Cerebrovascular accident
- Encephalitis
- Hypothalamic dysfunction

Peripheral
- Hyperthyroidism
- Pheochromocytoma

Factitious Fevers

"Afebrile" FUO [<38.3°C (100.94°F)]

Source: Modified from RK Root, RG Petersdorf, in JD Wilson et al (eds): *Harrison's Principles of Internal Medicine*, 12th ed. New York, McGraw-Hill, 1991.

Western nations such as the United States. The workup of FUO must take into careful consideration the patient's country of origin, recent and remote travel (including past service in foreign wars), unusual environmental exposures associated with travel or hobbies (e.g., caving, hunting, and safaris), and pets. The increasing number of returning sojourners with exotic travel itineraries underscores the need for a detailed history of travel and associated activities in the setting of undiagnosed fever, as do the changing demographics of the travelers themselves. For example, increasing numbers of travelers are immunosuppressed, are undergoing disease-modifying interventions such as TNF-α suppression, or have recently reconstituted immunity. Immigrants with unexplained fever, including naturalized citizens who have left their countries of origin decades previously, should be carefully interviewed with regard to childhood exposures, including immunization with nonstandard or unidentified live vaccines. In both foreign-born individuals and veterans of foreign wars, subclinical infections may be unmasked decades after exposure by new malignancies or immunosuppressive conditions. The differential diagnosis of FUO must also take into account changes in the range of arthropod vectors or the possibility that local permissive vectors have become infected with previously nonendemic pathogens. Evaluation of FUO in under-resourced medical settings requires increased reliance on history and clinical examination. Patients, family members, and close occupational contacts may need to be interviewed. If specialized laboratory and imaging studies cannot be conducted, diagnosis may be facilitated by maximizing the quality and precision of locally available approaches (e.g., culture of lysed, centrifuged blood cultures and microscopic examination by an experienced technician). Emerging infectious diseases may include FUO first presenting as clusters of cases in remote regions; insight may be gained from contacting local epidemiologists.

The possibility of international and domestic terrorist activity involving the intentional release of infectious agents, many of which cause illnesses presenting with prolonged fever, underscores the need for obtaining an insightful environmental, occupational, and professional history, with early notification of public health authorities in cases of suspicious etiology (Chap. 7). Moreover, the global spread of genetic engineering technologies raises the possibility that traditional agents—including Centers for Disease Control Categories A, B, and C agents; see Table 7-2)—that circumvent vaccine-acquired immunity could be developed or that novel recombinant organisms could be engineered to produce clinical or laboratory responses that defy current diagnostic approaches.

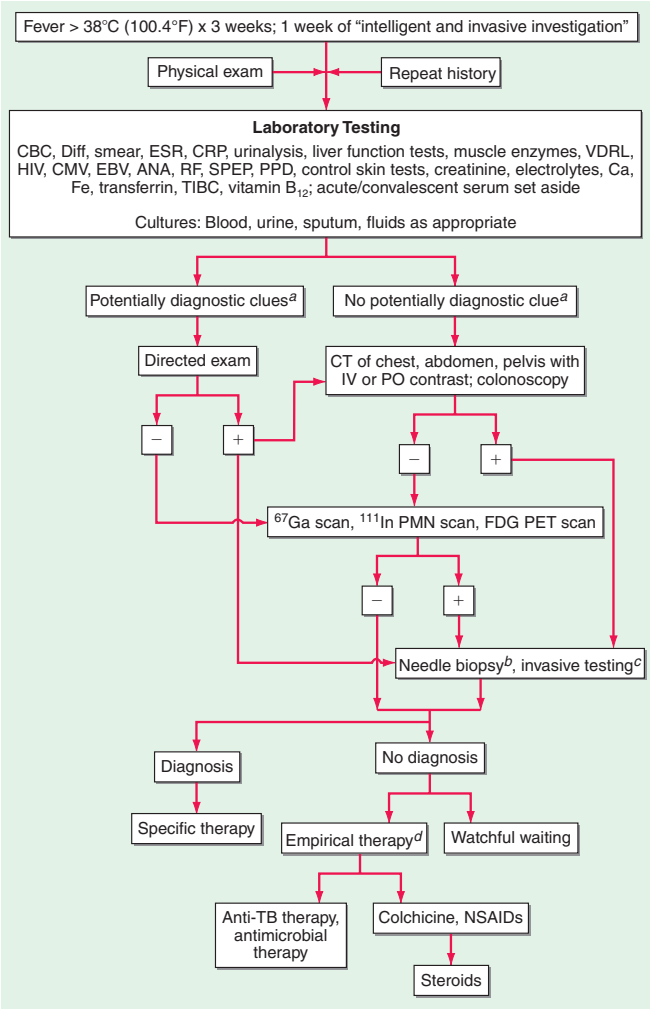


FIGURE 10-1

Approach to the patient with classic FUO. [a]"Potentially diagnostic clues," as outlined by de Kleijn and colleagues (1997, Part II), may be key findings in the history, localizing signs, or key symptoms. [b]Needle biopsy of liver as well as any other tissue indicated by "potentially diagnostic clues." [c]Invasive testing could involve laparoscopy. [d]Empirical therapy is a last resort, given the good prognosis of most patients with FUO persisting without a diagnosis. *Abbreviations:* ANA, antinuclear antibody; CBC, complete blood count; CMV, cytomegalovirus; CRP, C-reactive protein; CT, computed tomography; Diff, differential; EBV, Epstein-Barr virus; ESR, erythrocyte sedimentation rate; FDG, fluorodeoxyglucose F18; NSAIDs, nonsteroidal anti-inflammatory drugs; PET, positron emission tomography; PMN, polymorphonuclear leukocyte; PPD, purified protein derivative; RF, rheumatoid factor; SPEP, serum protein electrophoresis; TB, tuberculosis; TIBC, total iron-binding capacity; VDRL, Venereal Disease Research Laboratory test.

SPECIALIZED DIAGNOSTIC STUDIES

Classic FUO

A stepwise flow chart depicting the diagnostic workup and therapeutic management of FUO is provided in Fig. 10-1. In this flow chart, reference is made to "potentially diagnostic clues," as outlined by de Kleijn and colleagues; these clues may be key findings in the history (e.g., travel), localizing signs, or key symptoms. Certain specific diagnostic maneuvers become critical in dealing with prolonged fevers. If factitious fever is suspected, temperature-taking should be supervised, and simultaneous urine and body temperatures should be measured. Thick blood smears should be examined

for *Plasmodium*; thin blood smears, prepared with proper technique and quality stains and subjected to expert microscopy, should be used to speciate *Plasmodium* and to identify *Babesia*, *Trypanosoma*, *Leishmania*, *Leptospira*, *Rickettsia*, and *Borrelia*. Specialized staining of mononuclear cells and granulocytes can help to identify intracellular bacteria, protozoal amastigotes, and the inclusion bodies of ehrlichiosis and anaplasmosis. Any tissue removed during prior relevant surgery should be reexamined; slides should be requested, and, if necessary, paraffin blocks of fixed pathologic material should be reexamined and additional special studies performed. Relevant x-rays should be reexamined; review of prior radiologic reports may be insufficient. Serum should be set aside in the laboratory as soon as possible and retained for future examination for rising antibody titers.

Febrile agglutinins is a vague term that, in most laboratories, refers to serologic studies for salmonellosis, brucellosis, and rickettsial diseases. These studies are seldom useful, having low sensitivity and variable specificity. Multiple blood samples (no fewer than three and rarely more than six, including samples for anaerobic culture) should be cultured in the laboratory—with and without increased CO_2—for 2 to 3 weeks to ensure ample growth time for any HACEK organisms (Chap. 51). It is critical to inform the laboratory of the intent to test for unusual organisms. Specialized media should be used if an exposure or travel history suggests uncommon causes of endocarditis, such as *Histoplasma*, *Chlamydophila*, *Mycoplasma*, *Bartonella*, *Coxiella*, or *Tropheryma whipplei*. Blood culture media should be supplemented with L-cysteine or pyridoxal to assist in the isolation of nutritionally variant streptococci. Lysis-centrifugation blood culture techniques should be employed when prior antimicrobial therapy or fungal or atypical mycobacterial infection is suspected. It should be noted that sequential cultures positive for multiple organisms may reflect self-injection of contaminated substances. Cultures of sinus fluid and pulmonary secretions on multiple permissive cell lines may prove helpful in identifying new respiratory viruses implicated in FUO. Urine cultures, including cultures for mycobacteria, fungi, and CMV, are indicated. In the setting of recurrent fevers with lymphocytic meningitis (Mollaret's meningitis), cerebrospinal fluid can be tested for herpesvirus, with use of the polymerase chain reaction (PCR) to amplify and detect viral nucleic acid (Chap. 84). A highly multiplexed oligonucleotide microarray using PCR amplification and containing probes for all recognized virus species hosted by vertebrates and up to 135 bacterial, 73 fungal, and 63 parasitic genera and species has been developed but has not yet been approved for clinical use. The continued clinical validation of such microarrays will further diminish rates of undiagnosed FUO of infectious etiology.

In any FUO workup, the erythrocyte sedimentation rate (ESR) should be determined. Striking elevation of the ESR and anemia of chronic disease are frequently seen in association with giant cell arteritis or polymyalgia rheumatica—common causes of FUO in patients >50 years of age. Still's disease is suggested by elevations of ESR, leukocytosis, and anemia and is often accompanied by arthralgias, polyserositis (pleuritis, pericarditis), lymphadenopathy, splenomegaly, and rash. The C-reactive protein level may be a useful cross-reference for the ESR and is a more sensitive and specific indicator of an "acute-phase" inflammatory metabolic response. Antinuclear antibody, antineutrophil cytoplasmic antibody, rheumatoid factor, and serum cryoglobulins should be measured to rule out other collagen vascular diseases and vasculitis. Elevated levels of angiotensin-converting enzyme in serum may point to sarcoidosis. With rare exceptions, the intermediate-strength purified protein derivative (PPD) skin test should be used to screen patients with classic FUO for tuberculosis. Concurrent control tests, such as the mumps skin test antigen (Aventis-Pasteur, Swiftwater, PA), should be employed. It should be kept in mind that both the PPD tuberculin skin test (TST) and control tests may yield false-negative results in patients with miliary tuberculosis, sarcoidosis, Hodgkin's disease, malnutrition, or AIDS. Two interferon γ–release assays have been approved by the U.S. Food and Drug Administration for the diagnosis of tuberculosis. These tests—the QuantiFERON-TB Gold In-Tube (QFT-GIT) assay and the T-SPOT TB assay—measure the production of interferon γ by T lymphocytes upon exposure to antigens of *M. tuberculosis*. In direct comparisons, the sensitivity of the QFT-GIT test was statistically similar to that of the TST for detecting infection in persons with untreated, culture-confirmed tuberculosis. The QFT-GIT test is more specific, is less influenced by previous infection with nontuberculous mycobacteria, and is not affected by prior vaccination with bacille Calmette-Guérin (BCG); TSTs are variably affected by these factors. Repeating the QFT-GIT test does not boost the in vitro response, while injection of PPD for the TST can boost subsequent TST responses, primarily in persons who have been infected with nontuberculous mycobacteria or vaccinated with BCG. Negative results in the QFT-GIT test—as in the TST—do not definitively exclude a diagnosis of tuberculosis.

Noninvasive procedures should include an upper gastrointestinal contrast study with small-bowel follow-through and colonoscopy to examine the terminal ileum and cecum for early evidence of lymphoma or subclinical Crohn's disease. Colonoscopy is especially strongly indicated in the elderly. Chest x-rays should be repeated if new symptoms arise. Sputum should be induced with an ultrasonic nebulizer for cultures, cytology, and molecular diagnostic testing. If there are pulmonary signs or symptoms, bronchoscopy with bronchoalveolar lavage for cultures, PCR, and cytology should be considered. High-resolution spiral CT of the chest and abdomen should be performed with both IV and oral contrast. If a spinal or paraspinal lesion is suspected, however, MRI is preferred. MRI may be superior to CT in demonstrating intraabdominal abscesses and aortic dissection, but the comparative utility of MRI and CT in the diagnosis of FUO is unknown. At present, abdominal CT with contrast should be used unless MRI is specifically indicated. Arteriography may be useful for patients in whom systemic

necrotizing vasculitis is suspected. Saccular aneurysms may be seen, most commonly in renal or hepatic vessels, and may permit diagnosis of arteritis when biopsy is difficult. Ultrasonography of the abdomen is useful for investigation of the hepatobiliary tract, kidneys, spleen, and pelvis. Echocardiography may be helpful in an evaluation for bacterial endocarditis, pericarditis, nonbacterial thrombotic endocarditis, and atrial myxomas. Transesophageal echocardiography is preferred for these lesions.

Radionuclide scanning procedures using technetium (Tc) 99m sulfur colloid, gallium (Ga) 67 citrate, or indium (In) 111–labeled leukocytes may be useful in identifying and/or localizing inflammatory processes such as aortitis or abscess. In one study, Ga scintigraphy yielded useful diagnostic information in almost one-third of cases, and it was suggested that this procedure might actually be used before other imaging techniques if no specific organ is suspected of being abnormal. It is likely that PET scanning, which provides quicker results (hours vs days), will prove even more sensitive and specific than ^{67}Ga scanning in FUO. ^{99m}Tc bone scan should be undertaken to look for osteomyelitis or bony metastases; ^{67}Ga scan may be used to identify sarcoidosis or *Pneumocystis* infection (Chap. 114) in the lungs or Crohn's disease in the abdomen. ^{111}In-labeled white blood cell (WBC) scan may be used to locate abscesses. With these scans, false-positive and false-negative findings are common. Fluorodeoxyglucose F18 (FDG) PET scanning appears to be superior to other forms of nuclear imaging. The FDG used in PET scans accumulates in tumors and at sites of inflammation and has even been shown to accumulate reliably at sites of vasculitis. Where available, FDG PET scanning should therefore be chosen over ^{67}Ga scanning in the diagnosis of FUO.

Biopsy of the liver and bone marrow should be considered in the workup of FUO if the studies mentioned earlier are unrevealing and if fever is prolonged. Granulomatous hepatitis has been diagnosed by liver biopsy, even when liver enzymes are normal and no other diagnostic clues point to liver disease. All biopsy specimens should be cultured for bacteria, mycobacteria, and fungi. Likewise, in the absence of clues pointing to the bone marrow, bone marrow biopsy (not simple aspiration) for histology and culture has yielded diagnoses late in the workup. When possible, a section of the tissue block should be retained for further sections or stains. At some research centers, PCR technology makes it possible in some cases to identify and speciate mycobacterial DNA in paraffin-embedded, fixed tissues. Thus, a retrospective diagnosis can sometimes be made on the basis of studies of long-fixed pathologic tissues. In a patient over age 50 (or occasionally in a younger patient) with the appropriate symptoms and laboratory findings, "blind biopsy" of one or both temporal arteries may yield a diagnosis of arteritis. Tenderness or decreased pulsation, if noted, should guide the selection of a site for biopsy. Lymph node biopsy may be helpful if nodes are enlarged, but inguinal nodes are often palpable and are seldom diagnostically useful.

Exploratory laparotomy has been performed when all other diagnostic procedures fail but has largely been replaced by imaging and guided-biopsy techniques. Peritoneal lavage may be used as a minimally invasive approach to peritoneal cytology studies. Laparoscopic biopsy may provide more adequate guided sampling of lymph nodes or liver, with less invasive morbidity.

Nosocomial FUO

(See also Chap. 14) The primary considerations in diagnosing nosocomial FUO are the underlying susceptibility of the patient coupled with the potential complications of hospitalization. The original surgical or procedural field is the place to begin a directed physical and laboratory examination for abscesses, hematomas, or infected foreign bodies. More than 50% of patients with nosocomial FUO are infected. Intravascular lines, septic phlebitis, and prostheses are all suspect. In this setting, the best approach is to focus on sites where occult infections may be sequestered, such as the sinuses of intubated patients or a prostatic abscess in a man with a urinary catheter. *Clostridium difficile* colitis may be associated with fever and leukocytosis before the onset of diarrhea. In ~25% of patients with nosocomial FUO, the fever has a noninfectious cause. Among these causes are acalculous cholecystitis, deep-vein thrombophlebitis, and pulmonary embolism. Drug fever, transfusion reactions, alcohol/drug withdrawal, adrenal insufficiency, thyroiditis, pancreatitis, gout, and pseudogout are among the many possible causes to consider. As in classic FUO, repeated meticulous physical examinations, coupled with focused diagnostic techniques, are imperative. Multiple blood, wound, and fluid cultures are mandatory. The pace of diagnostic tests is accelerated, and the threshold for procedures—CT scans, ultrasonography, ^{111}In WBC scans, noninvasive venous studies—is low. Even so, 20% of cases of nosocomial FUO may go undiagnosed.

Like diagnostic measures, therapeutic maneuvers must be swift and decisive, as many patients are already critically ill. IV lines must be changed (and cultured), drugs stopped for 72 hours, and empirical therapy started if bacteremia, fungemia, or persistently high virus loads are a threat. In many hospital settings, empirical antibiotic therapy for nosocomial FUO now includes vancomycin for coverage of methicillin-resistant *Staphylococcus aureus* as well as broad-spectrum gram-negative coverage with piperacillin/tazobactam, ticarcillin/clavulanate, imipenem, or meropenem. Practice guidelines covering many of these issues have been published jointly by the Infectious Diseases Society of America (IDSA) and the American College of Critical Care Medicine and can be accessed on the IDSA website (*www.journals.uchicago.edu/IDSA/guidelines*).

Neutropenic FUO

(See also Chap. 12) Neutropenic patients are susceptible to focal bacterial and fungal infections, to bacteremic infections, to infections involving catheters (including septic thrombophlebitis), and to perianal infections. *Candida* and *Aspergillus* infections are common. Infections due to herpes simplex virus or CMV

are sometimes causes of FUO in this group. While the duration of illness may be short in these patients, the consequences of untreated infection may be catastrophic; 50–60% of febrile neutropenic patients are infected, and 20% are bacteremic. The IDSA has published extensive practice guidelines covering these critically ill neutropenic patients (*www.journals.uchicago.edu/IDSA/guidelines*). In these patients, severe mucositis, quinolone prophylaxis, colonization with methicillin-resistant *S. aureus*, obvious catheter-related infection, or hypotension dictates the use of vancomycin plus ceftazidime, cefepime, or a carbapenem with or without an aminoglycoside to provide empirical coverage for bacterial sepsis.

HIV-Associated FUO

HIV infection alone may be a cause of fever. The infectious etiology varies with the extent of immunosuppression and the geographic region. Infection due to *Mycobacterium avium* or *M. intracellulare*, tuberculosis, toxoplasmosis, CMV infection, *Pneumocystis* infection, salmonellosis, cryptococcosis, histoplasmosis, strongyloidiasis, non-Hodgkin's lymphoma, and (of particular importance) drug fever are all possible causes of FUO. Mycobacterial infection can be diagnosed by blood cultures and by liver, bone marrow, and lymph node biopsies. Chest CT should be performed to identify enlarged mediastinal nodes. Serologic studies may reveal cryptococcal antigen, and ^{67}Ga scan may help identify *Pneumocystis* pulmonary infection. FUO has an infectious etiology in >80% of HIV-infected patients, but drug fever and lymphoma remain important considerations. Treatment of HIV-associated FUO depends on many factors and is discussed in Chap. 93.

TREATMENT **Fever of Unknown Origin**

The focus here is on classic FUO. Other modifiers of FUO—neutropenia, HIV infection, a nosocomial setting—all vastly affect the risk equation and dictate therapy based on the probability of various causes of fever and on the calculated risks and benefits of a guided empirical approach. The age and physical state of the patient are factors as well: the frail, elderly patient may merit a trial of empirical therapy earlier than the robust young adult.

The emphasis in patients with classic FUO is on continued observation and examination, with the avoidance of "shotgun" empirical therapy. Antibiotic therapy (even that for tuberculosis) may irrevocably alter the ability to culture fastidious bacteria or mycobacteria and delineate ultimate cause. However, vital-sign instability or neutropenia is an indication for empirical therapy with a fluoroquinolone plus piperacillin or the regimen mentioned earlier (see "Nosocomial FUO" , earlier in the chapter).), for example. Cirrhosis, asplenia, disease-modifying biologic therapy, intercurrent immunosuppressive drug use, or exotic travel or environmental exposures (e.g., cave interiors) may all tip the balance toward earlier empirical anti-infective therapy. If the TST is positive or if granulomatous hepatitis or other granulomatous disease is present with anergy (and sarcoid seems unlikely), then a therapeutic trial for tuberculosis should be undertaken, with treatment usually continued for up to 6 weeks. A failure of the fever to respond over this period suggests an alternative diagnosis.

The response of rheumatic fever and Still's disease to aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) may be dramatic. The effects of glucocorticoids on temporal arteritis, polymyalgia rheumatica, and granulomatous hepatitis are equally dramatic. Colchicine is highly effective in preventing attacks of familial Mediterranean fever but is of little use once an attack is well under way. The ability of glucocorticoids and NSAIDs to mask fever while permitting the spread of infection dictates that their use be avoided unless infection has been largely ruled out and unless inflammatory disease is both probable and debilitating or threatening.

When no underlying source of FUO is identified after prolonged observation (>6 months), the prognosis is generally good, however vexing the fever may be to the patient. Under such circumstances, debilitating symptoms are treated with NSAIDs, and glucocorticoids are the last resort. The initiation of empirical therapy does not mark the end of the diagnostic workup; rather, it commits the physician to continued thoughtful reexamination and evaluation. Patience, compassion, equanimity, vigilance, and intellectual flexibility are indispensable attributes for the clinician in dealing successfully with FUO.

ACKNOWLEDGMENTS

Sheldon M. Wolff, MD, now deceased, was an author of a previous version of this chapter. It is to his memory that the chapter is dedicated. The substantial contributions of Charles A. Dinarello, MD, to this chapter in previous editions of Harrison's Principles of Internal Medicine are gratefully acknowledged.

CHAPTER 11

ATLAS OF RASHES ASSOCIATED WITH FEVER

Kenneth M. Kaye ■ Elaine T. Kaye

Given the extremely broad differential diagnosis, the presentation of a patient with fever and rash often poses a thorny diagnostic challenge for even the most astute and experienced clinician. Rapid narrowing of the differential by prompt recognition of a rash's key features can result in appropriate and sometimes life-saving therapy. This atlas presents high-quality images of a variety of rashes that have an infectious etiology and are commonly associated with fever.

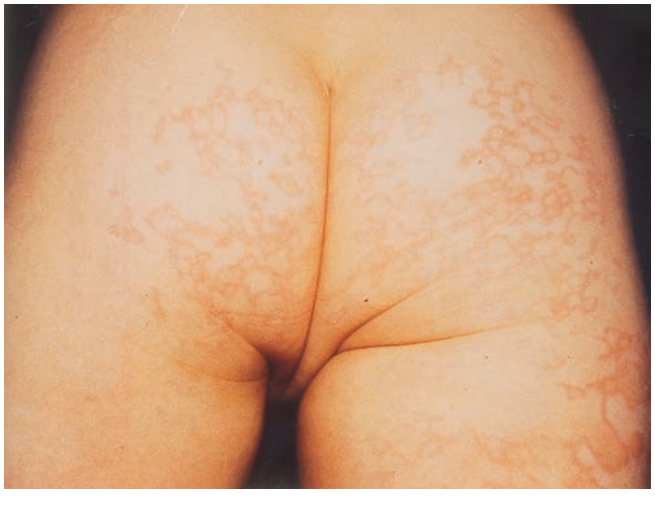


FIGURE 11-1
Lacy reticular rash of **erythema infectiosum** (fifth disease) caused by parvovirus B19.

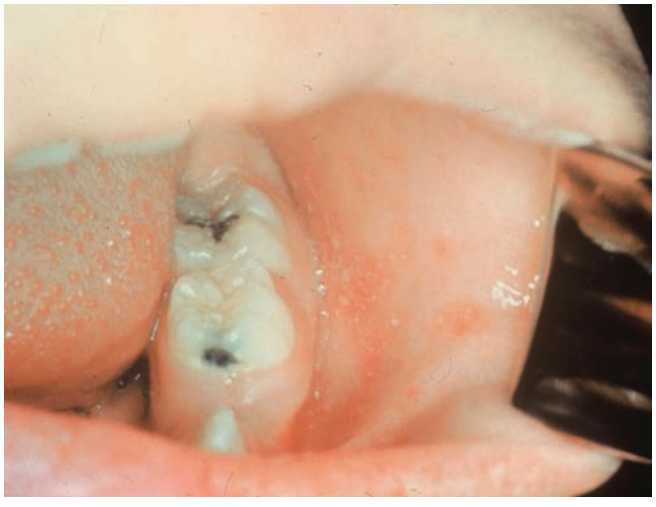


FIGURE 11-2
Koplik's spots, which manifest as white or bluish lesions with an erythematous halo on the buccal mucosa, usually occur in the first two days of measles symptoms and may briefly overlap the measles exanthem. The presence of the erythematous halo differentiates Koplik's spots from Fordyce's spots (ectopic sebaceous glands), which occur in the mouths of healthy individuals. (*Source: Centers for Disease Control and Prevention.*)

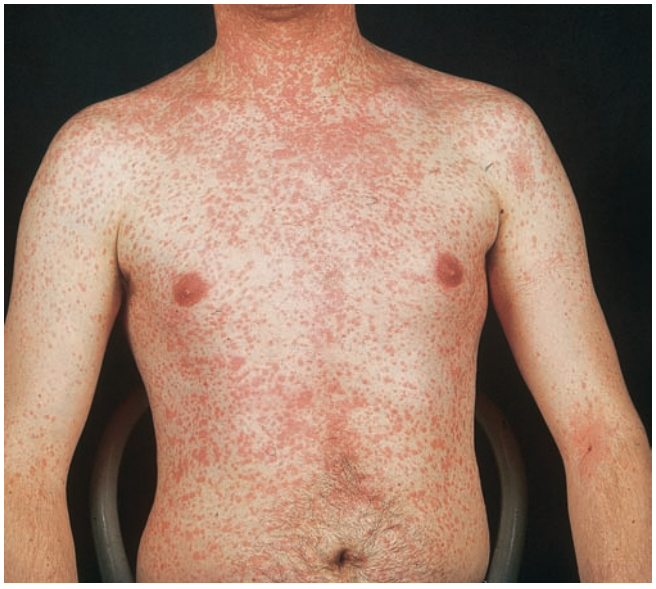


FIGURE 11-3
In **measles**, discrete erythematous lesions become confluent on the face and neck over 2–3 days as the rash spreads downward to the trunk and arms, where lesions remain discrete. (*Reprinted from K Wolff, RA Johnson: Color Atlas & Synopsis of Clinical Dermatology, 5th ed. New York, McGraw-Hill, 2005, p 788.*)

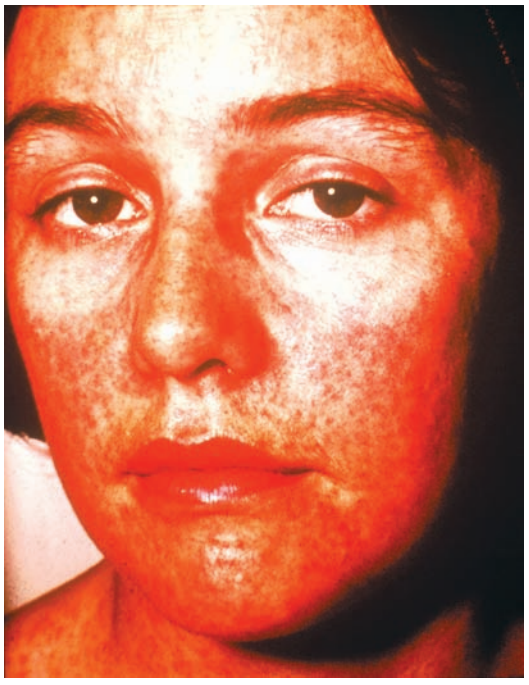


FIGURE 11-4
In **rubella**, an erythematous exanthem spreads from the hairline downward and clears as it spreads. (*Courtesy of Stephen E. Gellis, MD; with permission.*)

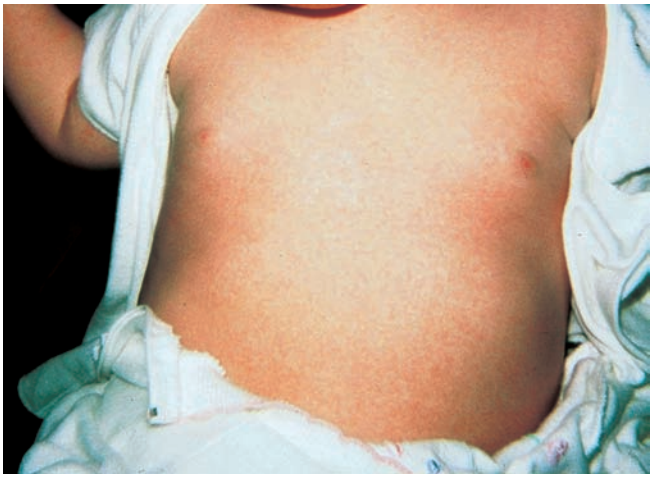


FIGURE 11-5
Exanthem subitum (roseola) occurs most commonly in young children. A diffuse maculopapular exanthem follows resolution of fever. (*Courtesy of Stephen E. Gellis, MD; with permission.*)

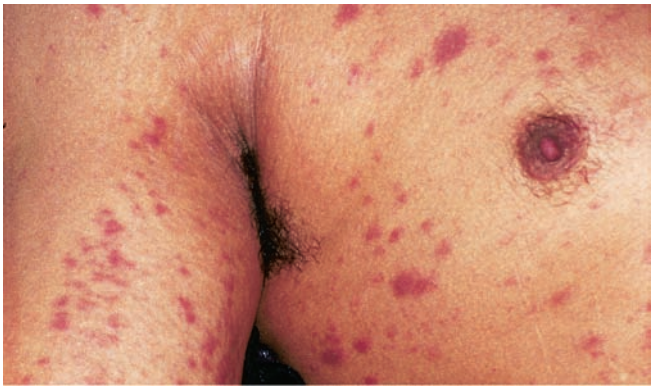


FIGURE 11-6
Erythematous macules and papules are apparent on the trunk and arm of this patient with **primary HIV infection**. (*Reprinted from K Wolff, RA Johnson: Color Atlas & Synopsis of Clinical Dermatology, 5th ed. New York, McGraw-Hill, 2005.*)

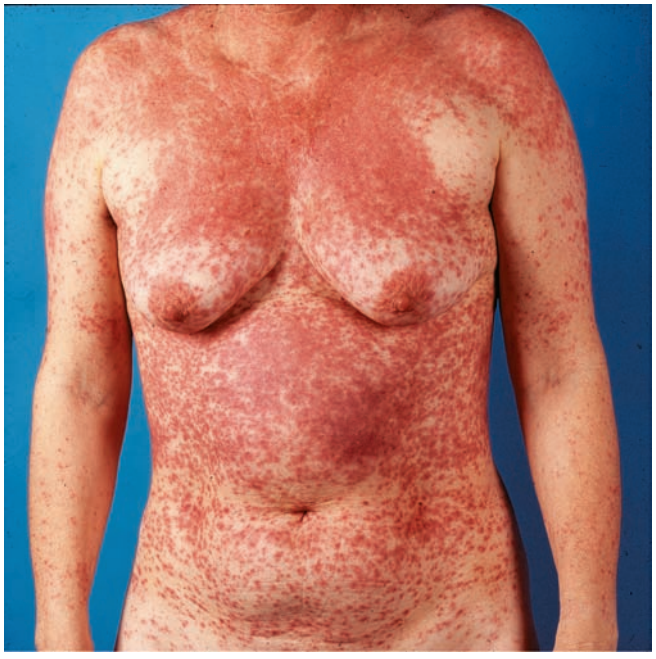


FIGURE 11-7
This **exanthematous, drug-induced eruption** consists of brightly erythematous macules and papules, some of which are confluent, distributed symmetrically on the trunk and extremities. Ampicillin caused this rash. (*Reprinted from K Wolff, RA Johnson: Color Atlas & Synopsis of Clinical Dermatology, 5th ed. New York, McGraw-Hill, 2005.*)

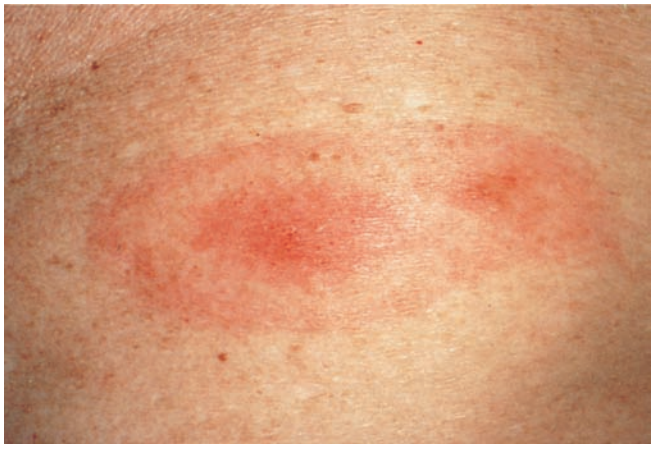


FIGURE 11-8
Erythema migrans is the early cutaneous manifestation of Lyme disease and is characterized by erythematous annular patches, often with a central erythematous papule at the tick-bite site. (*Courtesy of Yale Resident's Slide Collection; with permission.*)

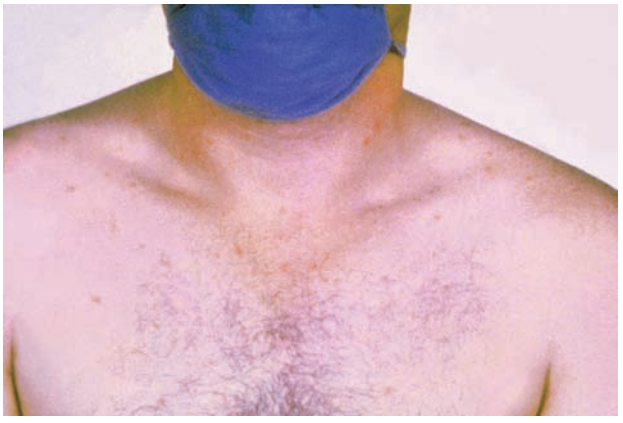


FIGURE 11-9
Rose spots are evident as erythematous macules on the trunk of this patient with **typhoid fever**. (*Source: Centers for Disease Control and Prevention.*)

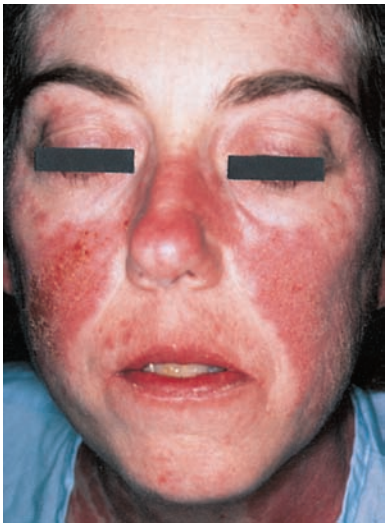


FIGURE 11-10
Systemic lupus erythematosus showing prominent, scaly, malar erythema. Involvement of other sun-exposed sites is also common.

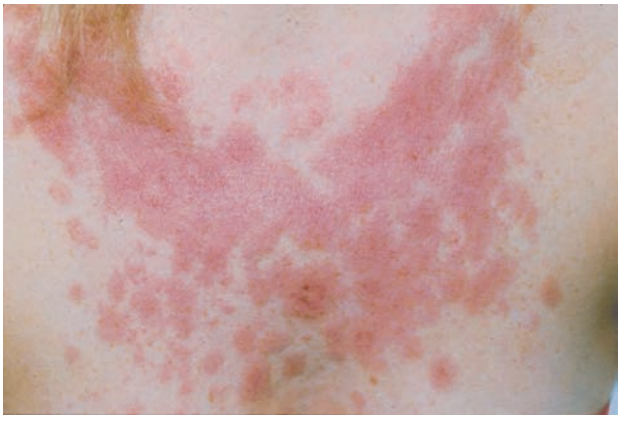


FIGURE 11-11
Acute lupus erythematosus on the upper chest, with brightly erythematous and slightly edematous coalescent papules and plaques. (*Courtesy of Robert Swerlick, MD; with permission.*)

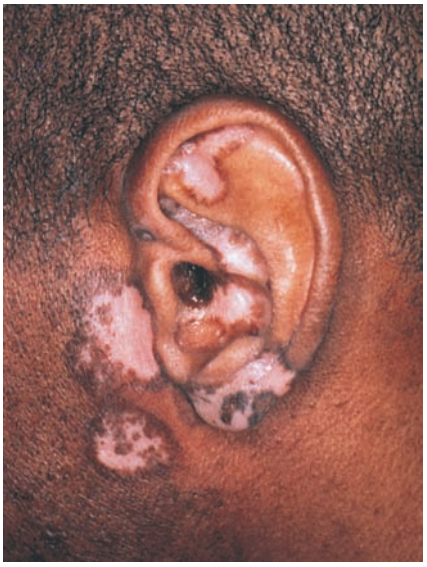


FIGURE 11-12
Discoid lupus erythematosus. Violaceous, hyperpigmented, atrophic plaques, often with evidence of follicular plugging (which may result in scarring), are characteristic of this cutaneous form of lupus. (*Courtesy of Marilynne McKay, MD; with permission.*)

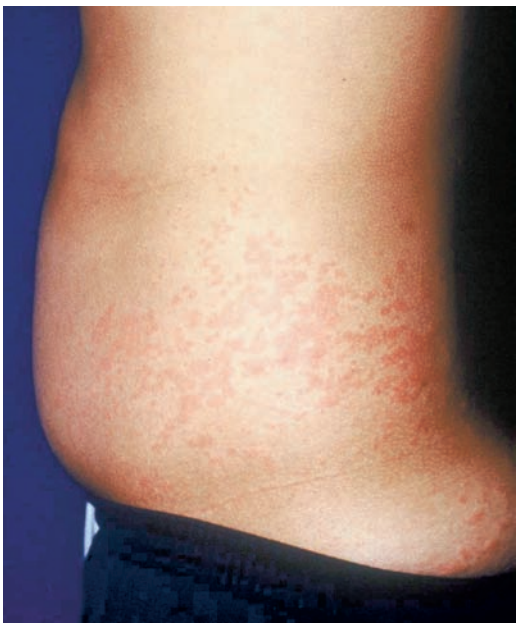


FIGURE 11-13
The rash of **Still's disease** typically exhibits evanescent, erythematous papules that appear at the height of fever on the trunk and proximal extremities. (*Courtesy of Stephen E. Gellis, MD; with permission.*)

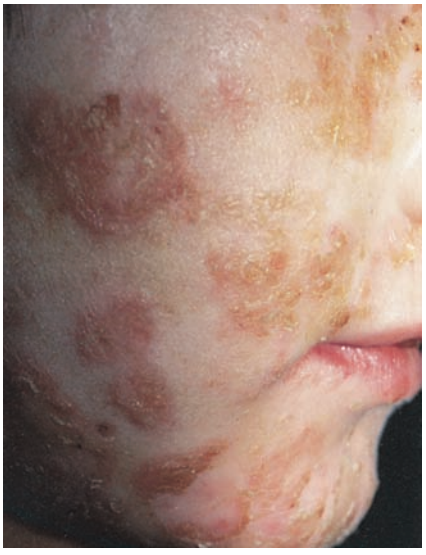


FIGURE 11-14
Impetigo is a superficial group A streptococcal or *Staphylococcus aureus* infection consisting of honey-colored crusts and erythematous weeping erosions. Occasionally, bullous lesions may be seen. (*Courtesy of Mary Spraker, MD; with permission.*)

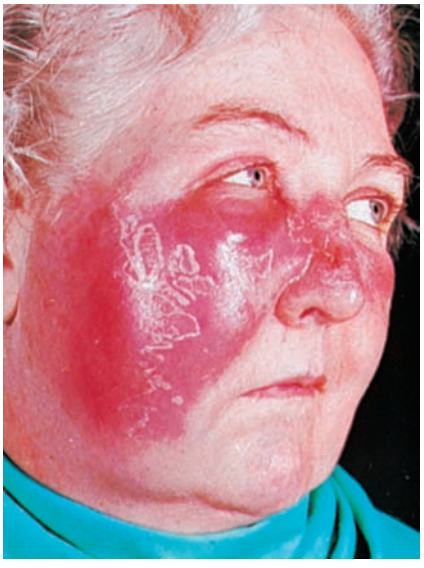
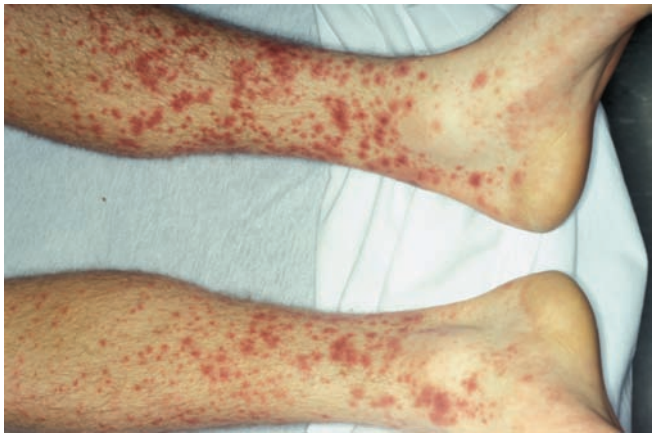


FIGURE 11-15
Erysipelas is a group A streptococcal infection of the superficial dermis and consists of well-demarcated, erythematous, edematous, warm plaques.



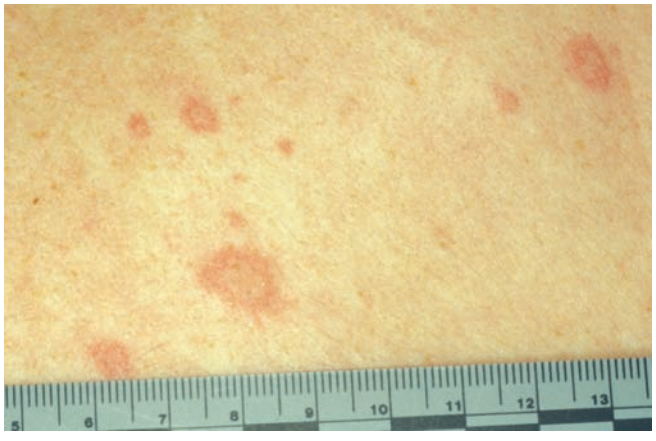


FIGURE 11-16
Top: Petechial lesions of **Rocky Mountain spotted fever** on the lower legs and soles of a young, otherwise healthy patient. ***Bottom:*** Close-up of lesions from the same patient. (*Courtesy of Lindsey Baden, MD; with permission.*)

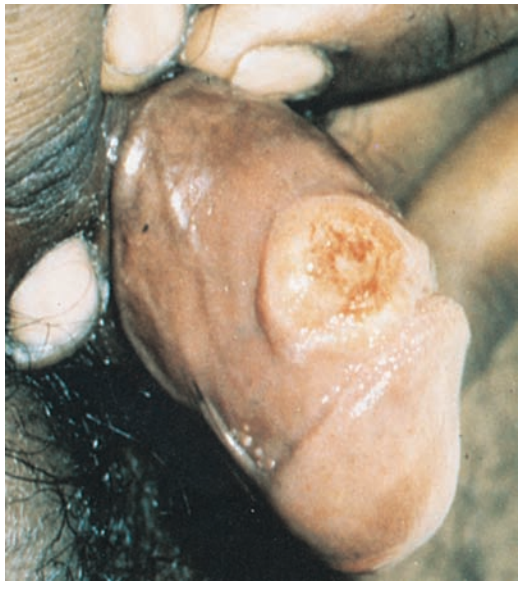


FIGURE 11-17
Primary syphilis with a firm, nontender chancre.

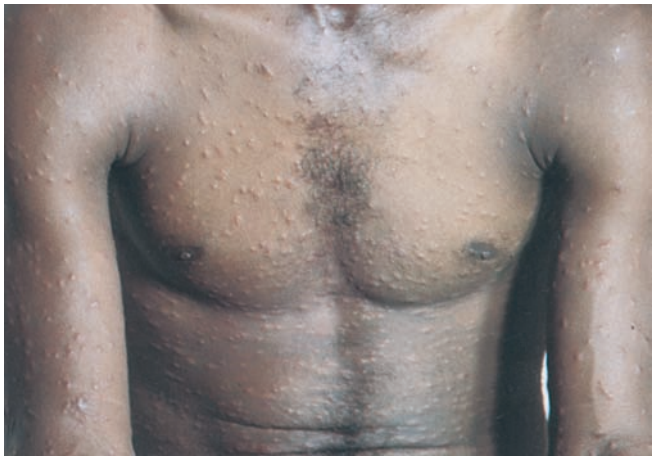


FIGURE 11-18
Secondary syphilis, demonstrating the papulosquamous truncal eruption.

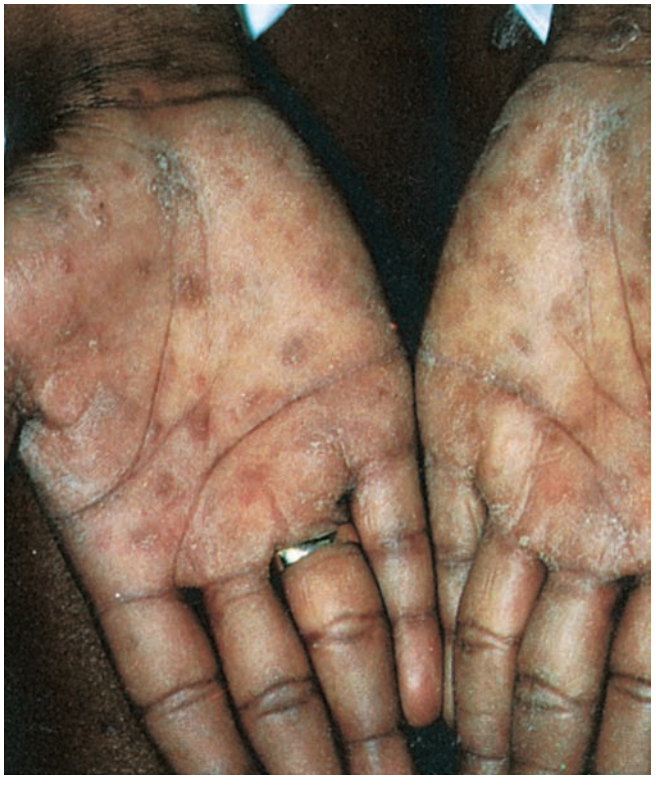


FIGURE 11-19
Secondary syphilis commonly affects the palms and soles with scaling, firm, red-brown papules.

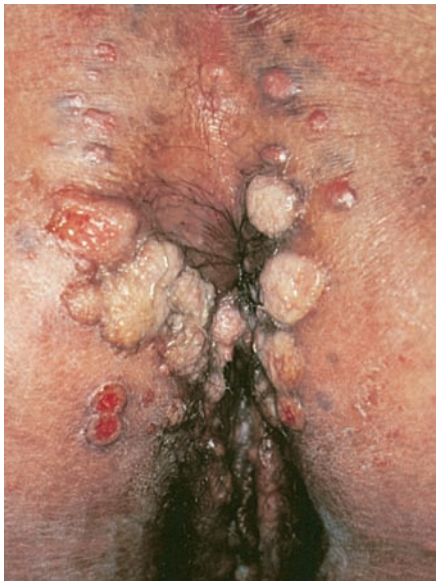


FIGURE 11-20
Condylomata lata are moist, somewhat verrucous intertriginous plaques seen in secondary syphilis.

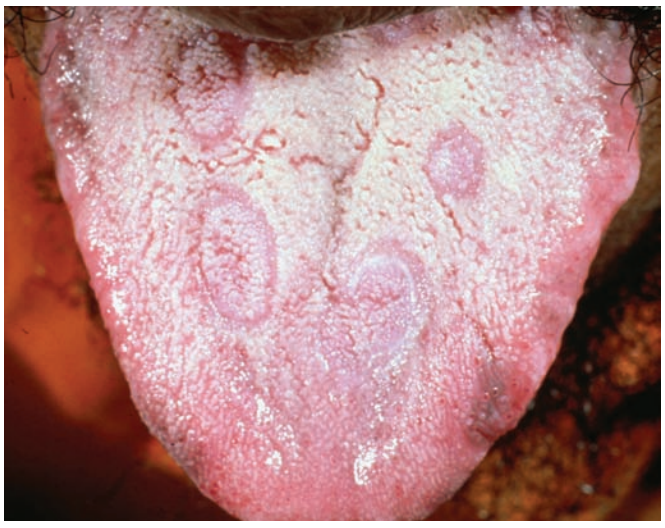


FIGURE 11-21
Mucous patches on the tongue of a patient with **secondary syphilis**. (*Courtesy of Ron Roddy; with permission.*)

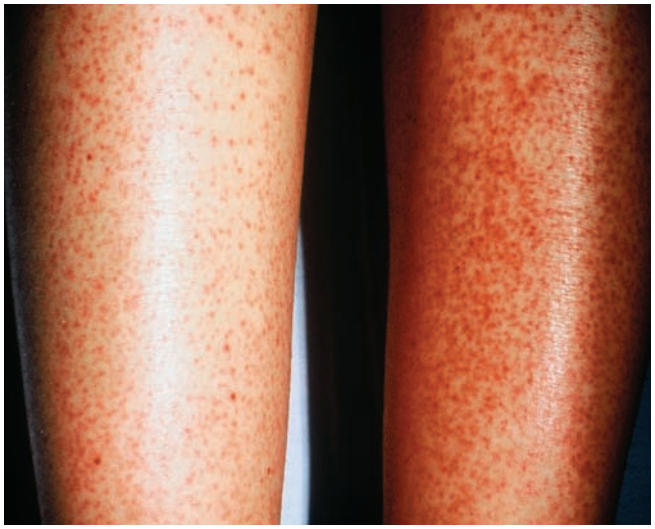


FIGURE 11-22
Petechial lesions in a patient with **atypical measles**. (*Courtesy of Stephen E. Gellis, MD; with permission.*)

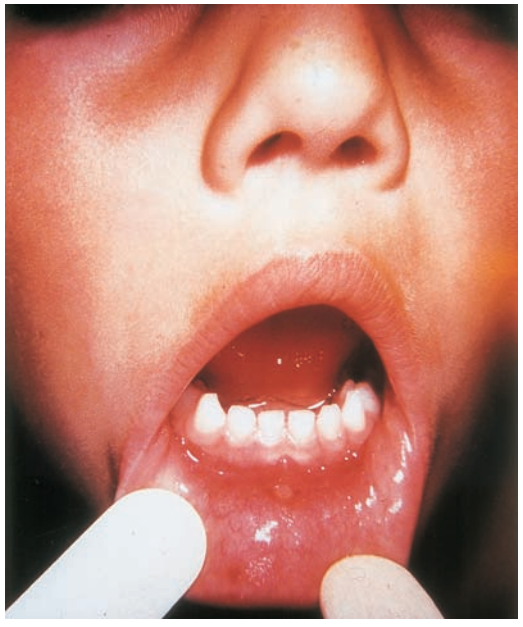


FIGURE 11-23
Tender vesicles and erosions in the mouth of a patient with **hand-foot-and-mouth disease**. (*Courtesy of Stephen E. Gellis, MD; with permission.*)

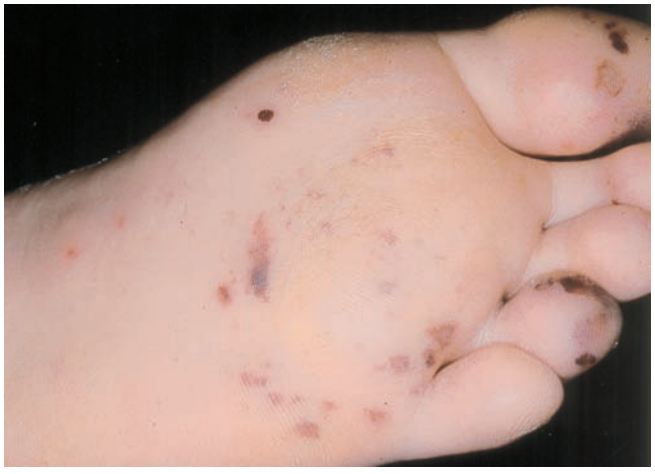


FIGURE 11-24
Septic emboli with hemorrhage and infarction due to acute *Staphylococcus aureus* **endocarditis**. (*Courtesy of Lindsey Baden, MD; with permission.*)

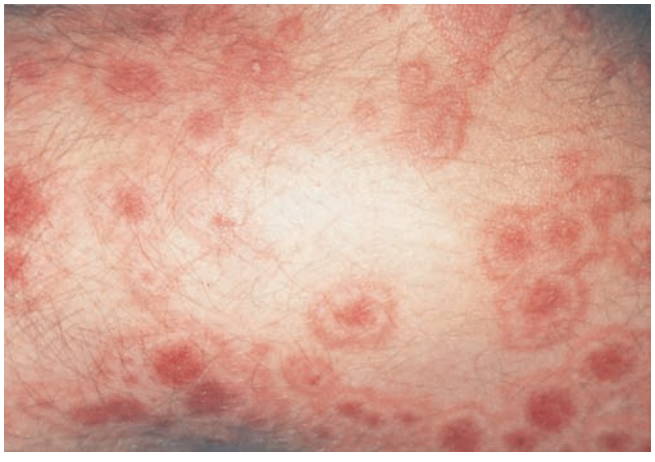


FIGURE 11-25
Erythema multiforme is characterized by multiple erythematous plaques with a target or iris morphology and usually represents a hypersensitive reaction to drugs or infections (especially herpes simplex virus). (*Courtesy of the Yale Resident's Slide Collection; with permission.*)

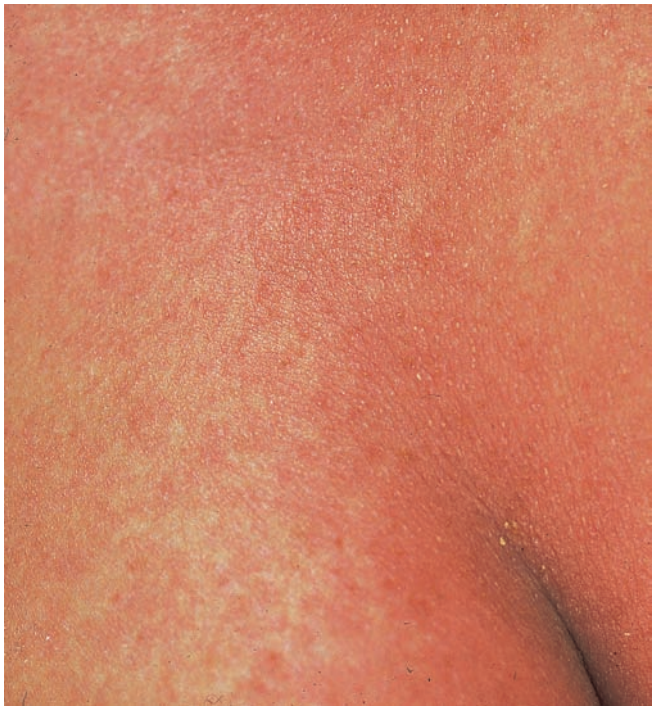


FIGURE 11-26
Scarlet fever exanthem. Finely punctuated erythema has become confluent (scarlatiniform); accentuation of linear erythema in body folds (Pastia's lines) is seen here. (*Reprinted from K Wolff, RA Johnson: Color Atlas & Synopsis of Clinical Dermatology, 6th ed. New York, McGraw-Hill, 2009.*)

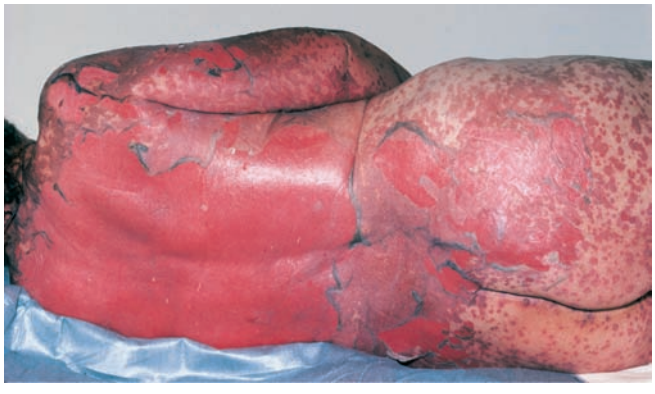


FIGURE 11-27
Erythema progressing to bullae with resulting sloughing of the entire thickness of the epidermis occurs in **toxic epidermal necrolysis**. This reaction was due to a sulfonamide. (*Reprinted from K Wolff, RA Johnson: Color Atlas & Synopsis of Clinical Dermatology, 5th ed. New York, McGraw-Hill, 2005.*)

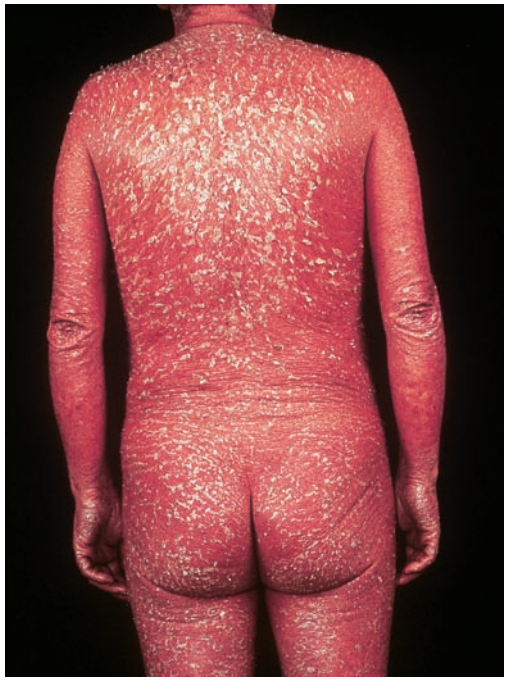


FIGURE 11-28
Diffuse erythema and scaling are present in this patient with psoriasis and the **exfoliative erythroderma syndrome**. (*Reprinted from K Wolff, RA Johnson: Color Atlas & Synopsis of Clinical Dermatology, 6th ed. New York, McGraw-Hill, 2009.*)

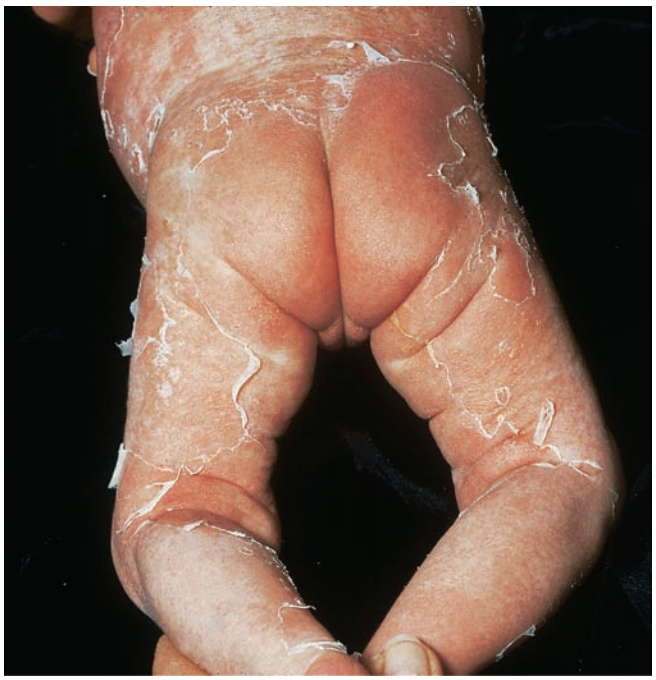


FIGURE 11-29
This infant with **staphylococcal scalded skin syndrome** demonstrates generalized desquamation. (*Reprinted from K Wolff, RA Johnson: Color Atlas & Synopsis of Clinical Dermatology, 6th ed. New York, McGraw-Hill, 2009.*)

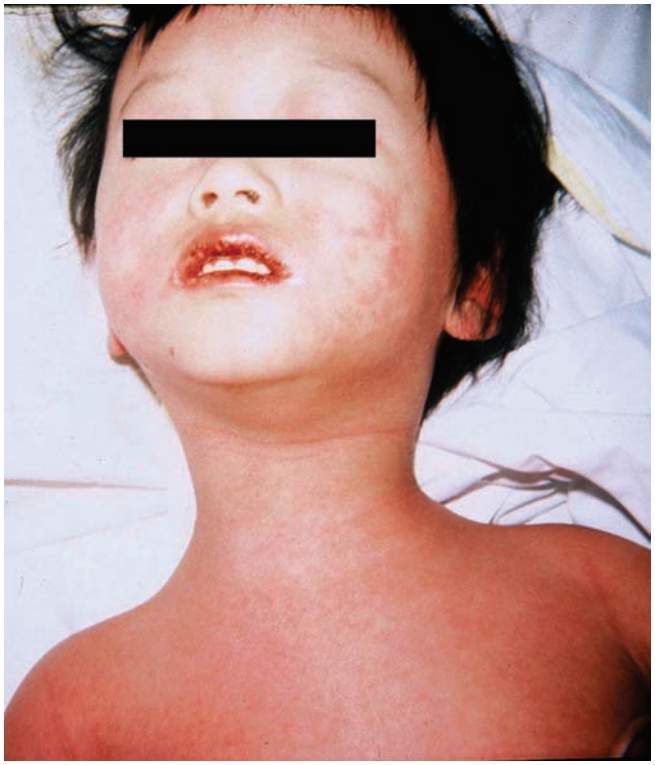


FIGURE 11-30
Fissuring of the lips and an erythematous exanthem are evident in this patient with **Kawasaki's disease**. (*Courtesy of Stephen E. Gellis, MD; with permission.*)

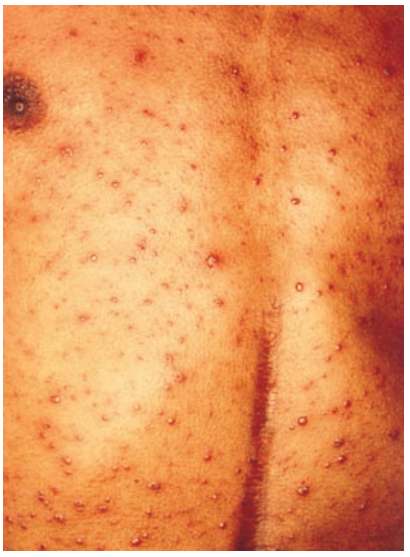


FIGURE 11-31
Numerous **varicella** lesions at various stages of evolution: vesicles on an erythematous base, umbilicated vesicles, and crusting lesions. (*Courtesy of R. Hartman; with permission.*)

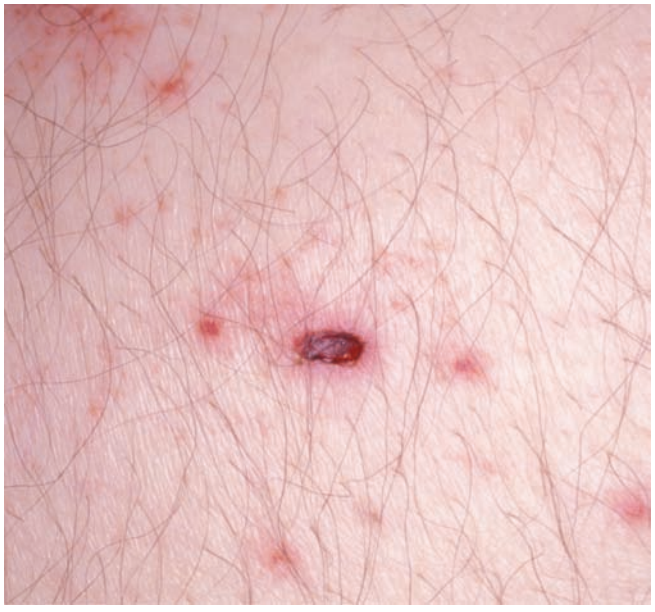


FIGURE 11-32
Close-up of lesions of **disseminated zoster**. Note lesions at different stages of evolution, including pustules and crusting. (*Courtesy of Lindsey Baden, MD; with permission.*)

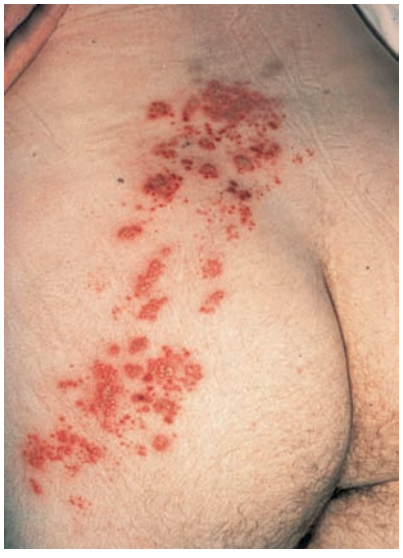


FIGURE 11-33
Herpes zoster is seen in this HIV-infected patient as hemorrhagic vesicles and pustules on an erythematous base grouped in a dermatomal distribution.

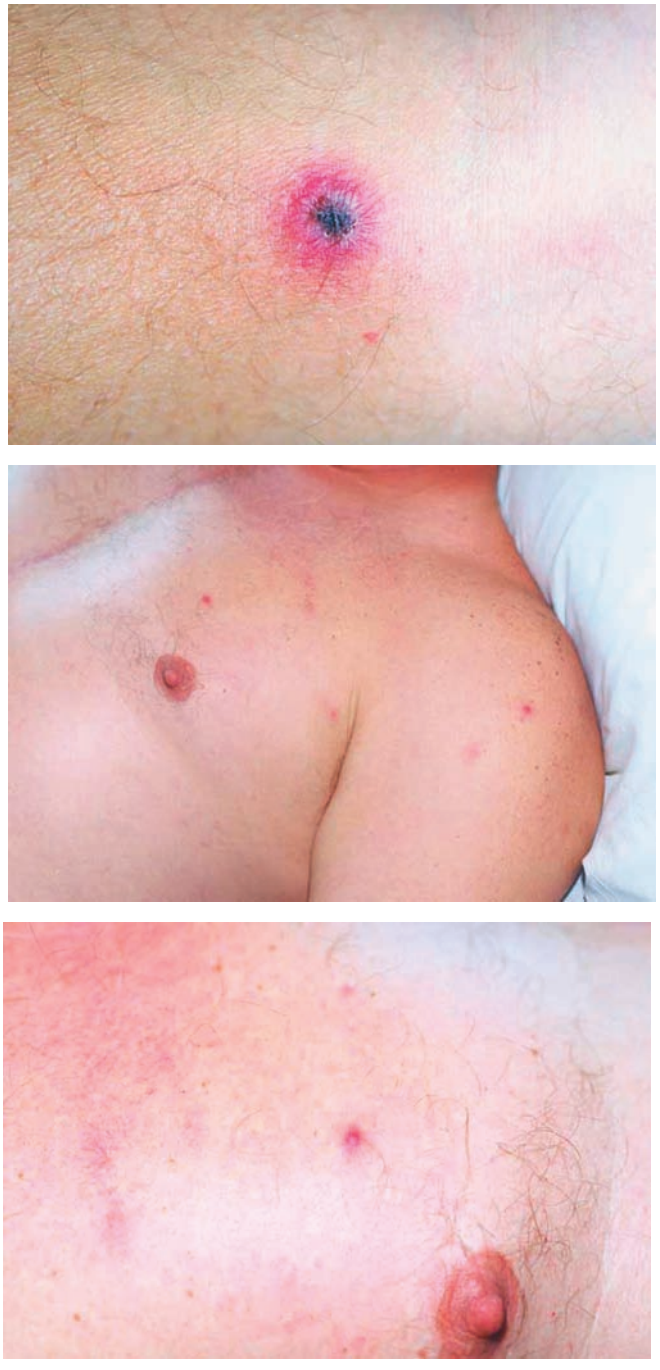


FIGURE 11-34
Top: Eschar at the site of the mite bite in a patient with **rickettsialpox**. ***Middle:*** Papulovesicular lesions on the trunk of the same patient. ***Bottom:*** Close-up of lesions from the same patient. (*Reprinted from A Krusell et al: Emerg Infect Dis 8:727, 2002.*)

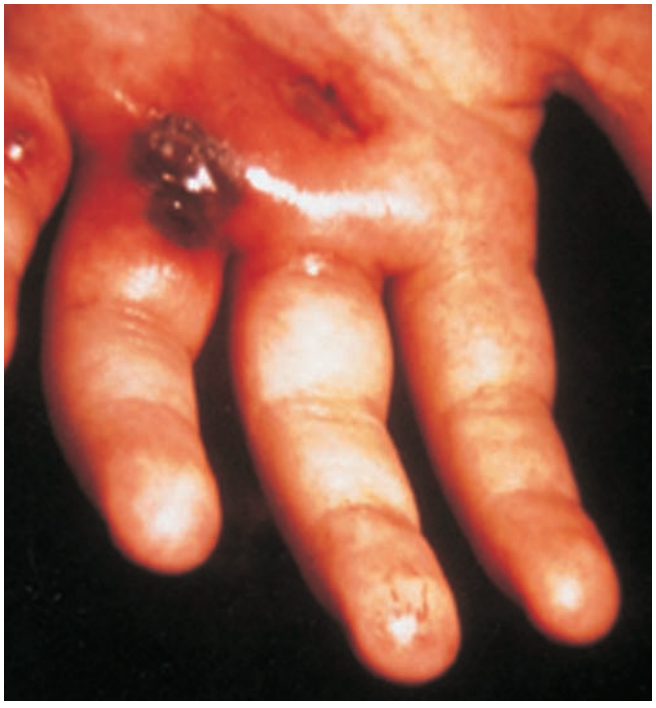


FIGURE 11-35
Ecthyma gangrenosum in a neutropenic patient with *Pseudomonas aeruginosa* bacteremia.

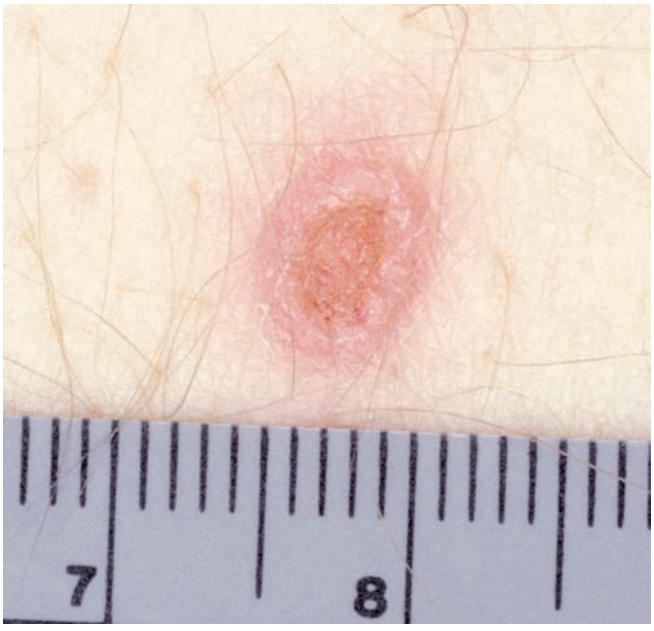


FIGURE 11-37
Disseminated cryptococcal infection. A liver-transplant recipient developed six cutaneous lesions similar to the one shown. Biopsy and serum-antigen testing demonstrated *Cryptococcus.* Important features of the lesion include a benign-appearing fleshy papule with central umbilication resembling molluscum contagiosum. (*Courtesy of Lindsey Baden, MD; with permission.*)

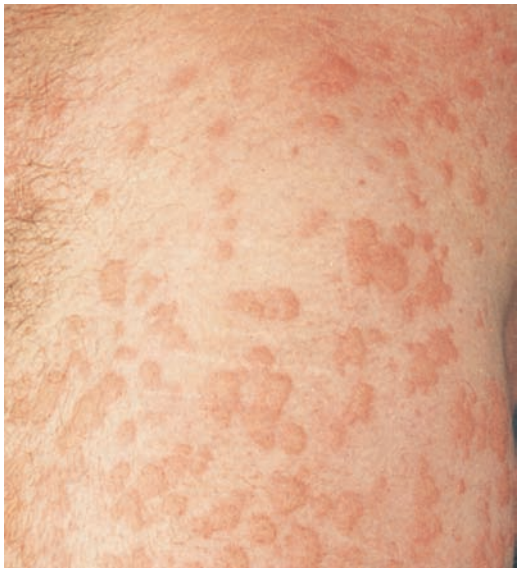


FIGURE 11-36
Urticaria showing characteristic discrete and confluent, edematous, erythematous papules and plaques.

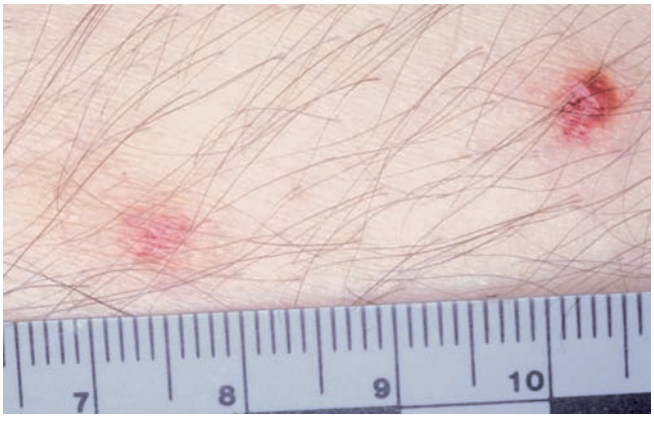


FIGURE 11-38
Disseminated candidiasis. Tender, erythematous, nodular lesions developed in a neutropenic patient with leukemia who was undergoing induction chemotherapy. (*Courtesy of Lindsey Baden, MD; with permission.*)

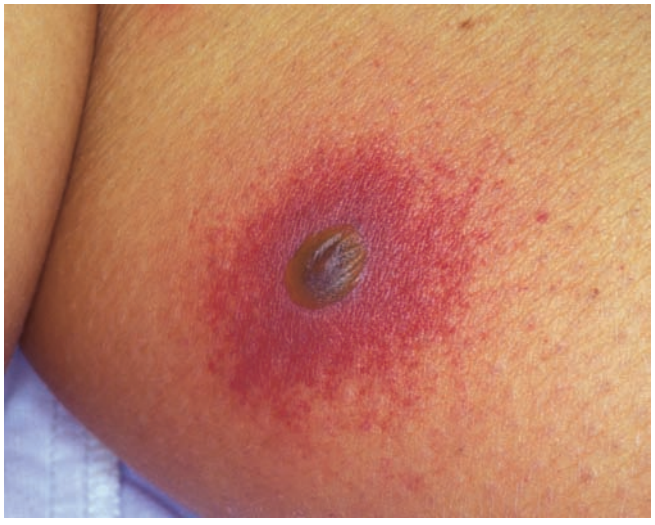


FIGURE 11-39
Disseminated *Aspergillus* infection. Multiple necrotic lesions developed in this neutropenic patient undergoing hematopoietic stem cell transplantation. The lesion in the photograph is on the inner thigh and is several centimeters in diameter. Biopsy demonstrated infarction caused by *Aspergillus fumigatus.* (*Courtesy of Lindsey Baden, MD; with permission.*)

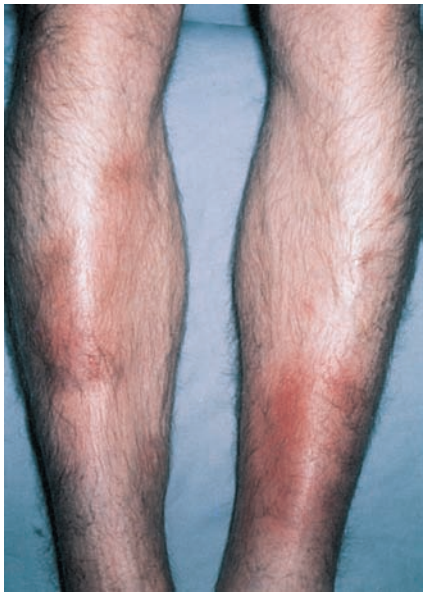


FIGURE 11-40
Erythema nodosum is a panniculitis characterized by tender, deep-seated nodules and plaques usually located on the lower extremities. (*Courtesy of Robert Swerlick, MD; with permission.*)

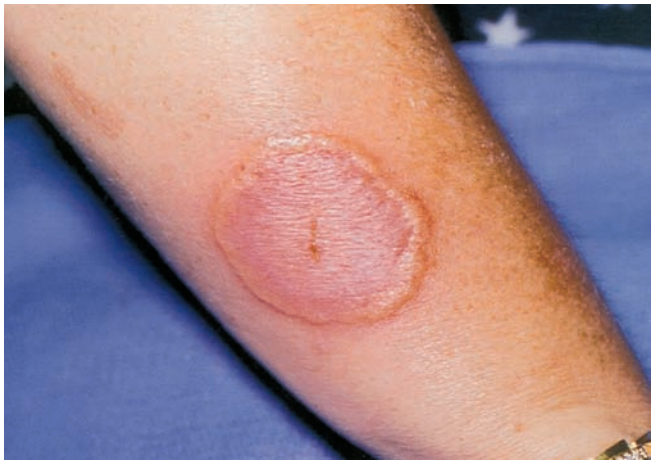


FIGURE 11-41
Sweet's syndrome: an erythematous indurated plaque with a pseudovesicular border. (*Courtesy of Robert Swerlick, MD; with permission.*)

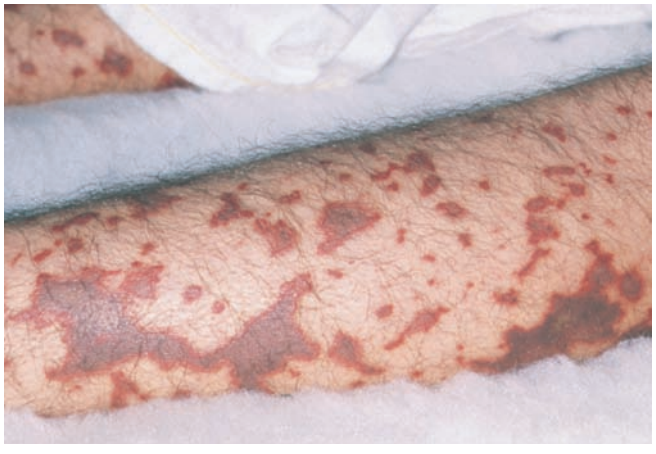


FIGURE 11-42
Fulminant meningococcemia with extensive angular purpuric patches. (*Courtesy of Stephen E. Gellis, MD; with permission.*)

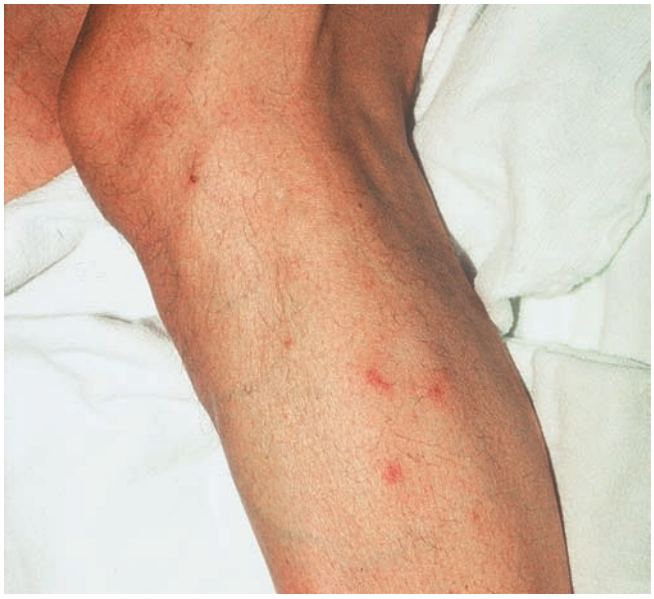


FIGURE 11-43
Erythematous papular lesions are seen on the leg of this patient with **chronic meningococcemia**.

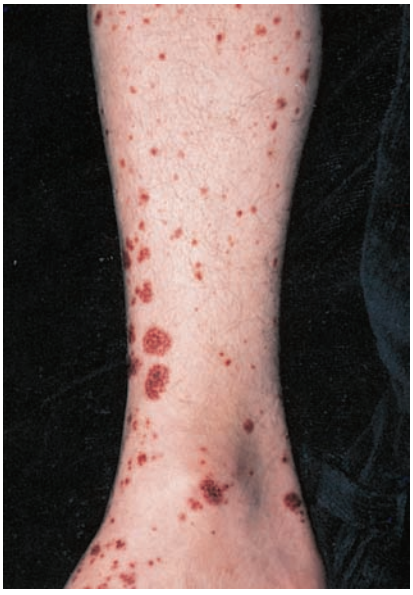


FIGURE 11-45
Palpable purpuric papules on the lower legs are seen in this patient with **cutaneous small-vessel vasculitis**. (*Courtesy of Robert Swerlick, MD; with permission.*)

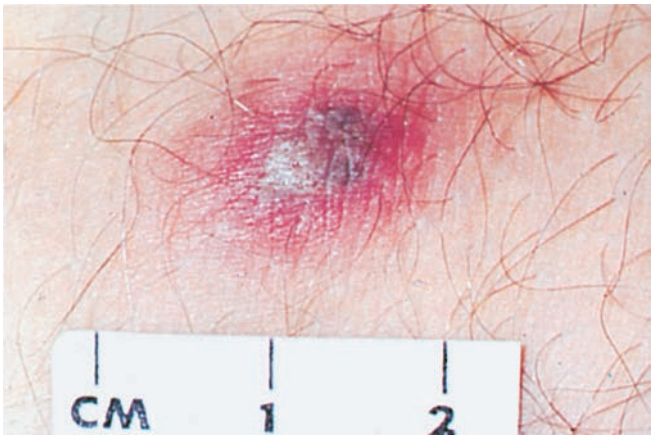


FIGURE 11-44
Disseminated gonococcemia in the skin is seen as hemorrhagic papules and pustules with purpuric centers in a centrifugal distribution. (*Courtesy of Daniel M. Musher, MD; with permission.*)

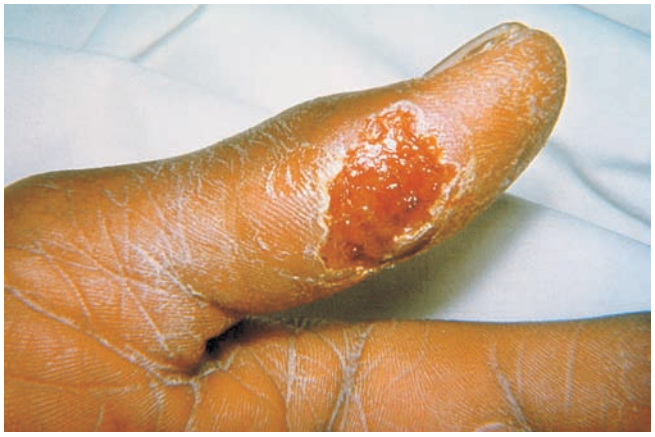


FIGURE 11-46
The thumb of a patient with a necrotic ulcer of **tularemia**. (*Source: Centers for Disease Control and Prevention.*)

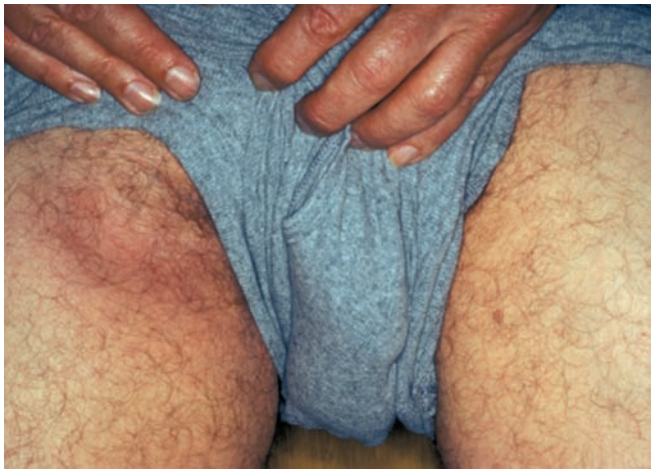


FIGURE 11-47
This 50-year-old man developed high fever and massive inguinal lymphadenopathy after a small ulcer healed on his foot. **Tularemia** was diagnosed. (*Courtesy of Lindsey Baden, MD; with permission.*)

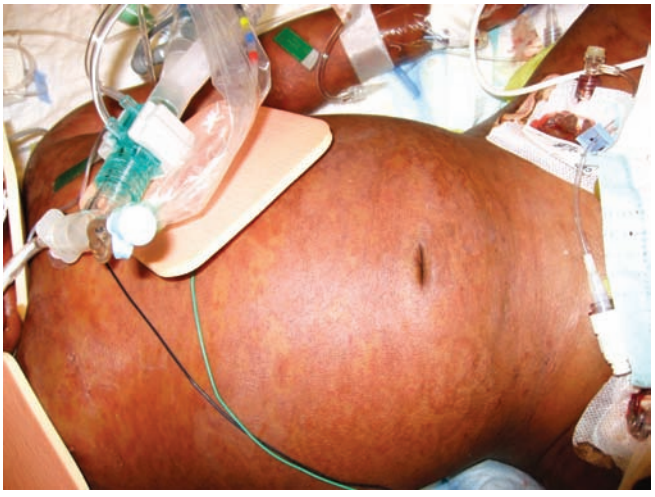


FIGURE 11-49
Drug-induced hypersensitivity syndrome (DIHS/DRESS): This patient developed a progressive eruption exhibiting early desquamation after taking phenobarbital. There was also associated lymphadenopathy and hepatomegaly. (*Courtesy of Peter Lio, MD; with permission.*)

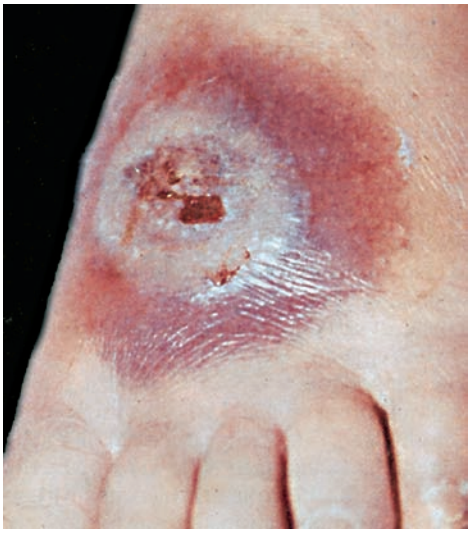


FIGURE 11-48
This painful **trypanosomal chancre** developed at the site of a tsetse-fly bite on the dorsum of the foot. *Trypanosoma brucei* was diagnosed from an aspirate of the ulcer. (*Courtesy of Edward T. Ryan, MD. N Engl J Med 346: 2069, 2002; with permission.*)

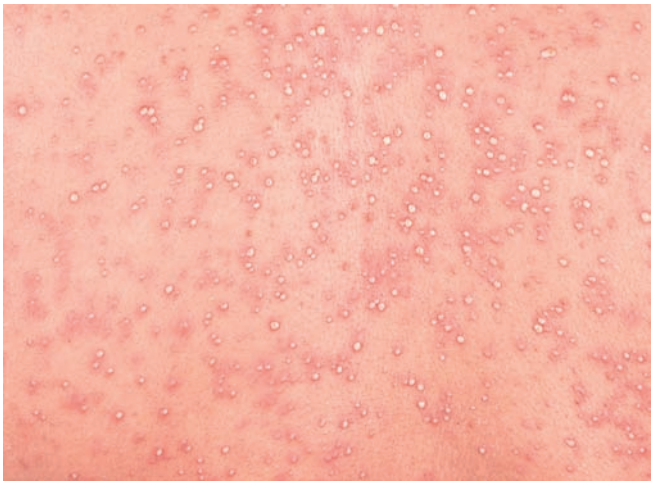


FIGURE 11-50
Many small, nonfollicular pustules are seen against a background of erythema in this patient with **acute generalized eruptive pustulosis (AGEP)**. The rash began in body folds and progressed to cover the trunk and face. (*Reprinted from K Wolff, RA Johnson: Color Atlas & Synopsis of Clinical Dermatology, 6th ed. New York, McGraw-Hill, 2009, p. 561.*)

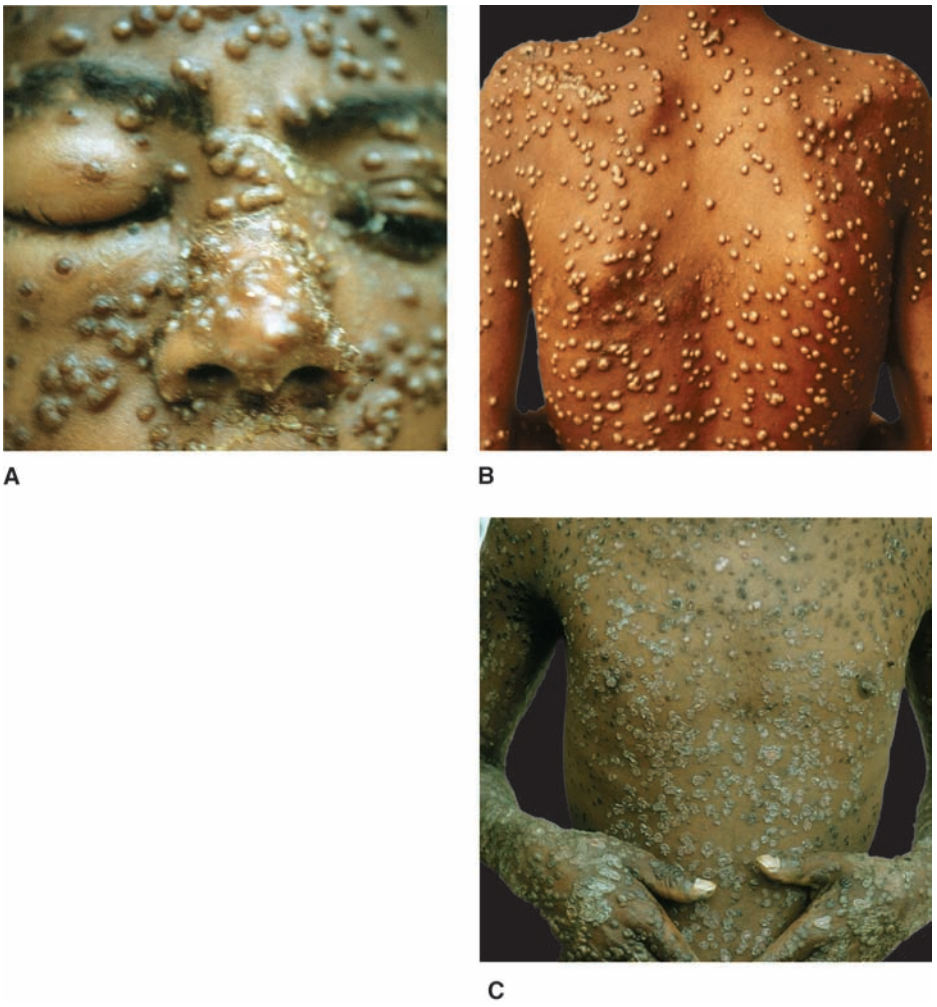


FIGURE 11-51
Smallpox is shown with many pustules on the face, becoming confluent (A), and on the trunk (B). Pustules are all in the same stage of development. In (C), crusting, healing lesions are noted on the trunk, arms, and hands. (*Reprinted from K Wolff, RA Johnson: Color Atlas & Synopsis of Clinical Dermatology, 6th ed. New York, McGraw-Hill, 2009, p. 780.*)

CHAPTER 12

INFECTIONS IN PATIENTS WITH CANCER

Robert Finberg

Infections are a common cause of death and an even more common cause of morbidity in patients with a wide variety of neoplasms. Autopsy studies show that most deaths from acute leukemia and half of deaths from lymphoma are caused directly by infection. With more intensive chemotherapy, patients with solid tumors have also become more likely to die of infection. Fortunately, an evolving approach to prevention and treatment of infectious complications of cancer has decreased infection-associated mortality rates and will probably continue to do so. This accomplishment has resulted from three major steps:

1. The concept of "early empirical" antibiotics reduced mortality rates among patients with leukemia and bacteremia from 84% in 1965 to 44% in 1972. This dramatic improvement is attributed to early intervention with appropriate antimicrobial therapy.
2. "Empirical" antifungal therapy has lowered the incidence of disseminated fungal infection; in trial settings, mortality rates now range from 7% to 21%. An antifungal agent is administered—on the basis of likely fungal infection—to neutropenic patients who, after 4–7 days of antibiotic therapy, remain febrile but have no positive cultures. In one study, the 7-day survival rate was ~85% among patients who had fever and neutropenia as a result of cancer chemotherapy and who required antifungal therapy.
3. Use of antibiotics for afebrile neutropenic patients as broad-spectrum prophylaxis against infections has decreased both mortality and morbidity even further. The current approach to treatment of severely neutropenic patients (e.g., those receiving high-dose chemotherapy for leukemia or high-grade lymphomas) is based on initial prophylactic therapy at the onset of neutropenia, with subsequent "empirical" antibacterial therapy targeting the organisms whose involvement is likely in light of physical findings (most often fever alone), and finally "empirical" antifungal therapy based on the known likelihood that fungal infection will become a serious issue after 4–7 days of broad-spectrum antibacterial therapy.

A physical predisposition to infection in patients with cancer **(Table 12-1)** can be a result of the neoplasm's production of a break in the skin. For example, a squamous cell carcinoma may cause local invasion of the epidermis, which allows bacteria to gain access to the subcutaneous tissue and permits the development of cellulitis. The artificial closing of a normally patent orifice can also predispose to infection; for example, obstruction of a ureter by a tumor can cause urinary tract infection, and obstruction of the bile duct can cause cholangitis. Part of the host's normal defense against infection depends on the continuous emptying of a viscus; without emptying, a few bacteria that are present as a result of bacteremia or local transit can multiply and cause disease.

A similar problem can affect patients whose lymph node integrity has been disrupted by radical surgery, particularly patients who have had radical node dissections. A common clinical problem following radical mastectomy is the development of cellulitis (usually caused by streptococci or staphylococci) because of lymphedema and/or inadequate lymph drainage. In most cases, this problem can be addressed by local measures designed to prevent fluid accumulation and breaks in the skin, but antibiotic prophylaxis has been necessary in refractory cases.

A life-threatening problem common to many cancer patients is the loss of the reticuloendothelial capacity to clear microorganisms after splenectomy, which may be performed as part of the management of hairy cell leukemia, chronic lymphocytic leukemia (CLL), and chronic myelocytic leukemia (CML) and in Hodgkin's disease. Even after curative therapy for the underlying disease, the lack of a spleen predisposes such patients to rapidly fatal infections. The loss of the spleen through trauma similarly predisposes the normal host to overwhelming infection throughout life. The splenectomized patient should be counseled about the risks of infection with certain organisms, such as the protozoan *Babesia* (Chap. 120) and *Capnocytophaga canimorsus*, a bacterium carried in the mouths of animals (Chaps. 35 and 51). Since encapsulated bacteria

TABLE 12-1

DISRUPTION OF NORMAL BARRIERS THAT MAY PREDISPOSE TO INFECTIONS IN PATIENTS WITH CANCER

TYPE OF DEFENSE	SPECIFIC LESION	CELLS INVOLVED	ORGANISM	CANCER ASSOCIATION	DISEASE
Physical barrier	Breaks in skin	Skin epithelial cells	Staphylococci, streptococci	Head and neck, squamous cell carcinoma	Cellulitis, extensive skin infection
Emptying of fluid collections	Occlusion of orifices: ureters, bile duct, colon	Luminal epithelial cells	Gram-negative bacilli	Renal, ovarian, biliary tree, metastatic diseases of many cancers	Rapid, overwhelming bacteremia; urinary tract infection
Lymphatic function	Node dissection	Lymph nodes	Staphylococci, streptococci	Breast cancer surgery	Cellulitis
Splenic clearance of microorganisms	Splenectomy	Splenic reticuloendothelial cells	*Streptococcus pneumoniae, Haemophilus influenzae, Neisseria meningitidis, Babesia, Capnocytophaga canimorsus*	Hodgkin's disease, leukemia, idiopathic thrombocytopenic purpura	Rapid, overwhelming sepsis
Phagocytosis	Lack of granulocytes	Granulocytes (neutrophils)	Staphylococci, streptococci, enteric organisms, fungi	Hairy cell, acute myelocytic, and acute lymphocytic leukemias	Bacteremia
Humoral immunity	Lack of antibody	B cells	*S. pneumoniae, H. influenzae, N. meningitidis*	Chronic lymphocytic leukemia, multiple myeloma	Infections with encapsulated organisms, sinusitis, pneumonia
Cellular immunity	Lack of T cells	T cells and macrophages	*Mycobacterium tuberculosis, Listeria,* herpesviruses, fungi, intracellular parasites	Hodgkin's disease, leukemia, T cell lymphoma	Infections with intracellular bacteria, fungi, parasites

(*Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis*) are the organisms most commonly associated with postsplenectomy sepsis, splenectomized persons should be vaccinated (and revaccinated; **Table 12-2** and Chap. 4) against the capsular polysaccharides of these organisms. Many clinicians recommend giving splenectomized patients a small supply of antibiotics effective against *S. pneumoniae*, *N. meningitidis*, and *H. influenzae* to avert rapid, overwhelming sepsis in the event that they cannot present for medical attention immediately after the onset of fever or other signs or symptoms of bacterial infection. A few amoxicillin/clavulanic acid tablets are a reasonable choice for this purpose.

The level of suspicion of infections with certain organisms should depend on the type of cancer diagnosed **(Table 12-3)**. Diagnosis of multiple myeloma or CLL should alert the clinician to the possibility of hypogammaglobulinemia. While immunoglobulin replacement therapy can be effective, in most cases prophylactic antibiotics are a cheaper, more convenient method of eliminating bacterial infections in CLL patients with hypogammaglobulinemia. Patients with acute lymphocytic leukemia (ALL), patients with non-Hodgkin's lymphoma, and all cancer patients treated with high-dose glucocorticoids (or glucocorticoid-containing chemotherapy regimens) should receive antibiotic prophylaxis for *Pneumocystis* infection (Table 12-3) for the duration of their chemotherapy. In addition to exhibiting susceptibility to certain infectious organisms, patients with cancer are likely to manifest their infections in characteristic ways. For example, fever—generally a sign of infection in normal hosts—continues to be a reliable indicator in neutropenic patients. In contrast, patients receiving glucocorticoids and agents that impair T cell function and cytokine secretion may have serious infections in the absence of fever. Similarly, neutropenic patients commonly present with cellulitis without purulence and with pneumonia without sputum or even x-ray findings (see next).

The use of monoclonal antibodies that target B and T cells as well as drugs that interfere with lymphocyte

TABLE 12-2

VACCINATION OF CANCER PATIENTS RECEIVING CHEMOTHERAPY[a]

	USE IN INDICATED PATIENTS		
VACCINE	**INTENSIVE CHEMOTHERAPY**	**HODGKIN'S DISEASE**	**HEMATOPOIETIC STEM CELL TRANSPLANTATION**
Diphtheria-tetanus[b]	Primary series and boosters as necessary	No special recommendation	3 doses given 6–12 months after transplantation
Poliomyelitis[c]	Complete primary series and boosters	No special recommendation	3 doses given 6–12 months after transplantation
Haemophilus influenzae type b conjugate	Primary series and booster for children	Immunization before treatment and booster 3 months afterward	3 doses given 6–12 months after transplantation
Human papillomavirus	3 doses for girls and women through 26 years of age	3 doses for girls and women through 26 years of age	3 doses for girls and women through 26 years of age
Hepatitis A	As indicated for normal hosts based on occupation and lifestyle	As indicated for normal hosts based on occupation and lifestyle	As indicated for normal hosts based on occupation and lifestyle
Hepatitis B	Same as for normal hosts	As indicated for normal hosts based on occupation and lifestyle	3 doses given 6–12 months after transplantation
23-Valent pneumococcal polysaccharide[d]	Every 5 years	Immunization before treatment and booster 3 months afterward	1 or 2 doses given 6–12 months after transplantation
4-Valent meningococcal vaccine[e]	Should be administered to splenectomized patients and patients living in endemic areas, including college students in dormitories	Should be administered to splenectomized patients and patients living in endemic areas, including college students in dormitories	Should be administered to splenectomized patients and patients living in endemic areas, including college students in dormitories
Influenza	Seasonal immunization	Seasonal immunization	Seasonal immunization
Measles/mumps/rubella	Contraindicated	Contraindicated during chemotherapy	After 24 months in patients without graft-versus-host disease
Varicella-zoster virus[f]	Contraindicated[g]	Contraindicated	Contraindicated

[a]The latest recommendations by the Advisory Committee on Immunization Practices and the CDC guidelines can be found at *http://www.cdc.gov/vaccines.*
[b]The Td (tetanus-diphtheria) combination was recommended for adults. Pertussis vaccine was not recommended for people >6 years of age in the past. However, recent data indicate that the Tdap (tetanus–diphtheria–acellular pertussis) product is both safe and efficacious in adults. A single Tdap booster is now recommended for adults.
[c]Live-virus vaccine is contraindicated; inactivated vaccine should be used.
[d]The 7- and 13-valent pneumococcal conjugate vaccines are currently recommended for children.
[e]Meningococcal conjugate vaccine (MCV4) is recommended for adults ≤55 years old and meningococcal polysaccharide vaccine (MPSV4) for those ≥56 years old.
[f]Includes both varicella vaccine for children and zoster vaccine for adults.
[g]Contact the manufacturer for more information on use in children with acute lymphocytic leukemia.

signal transduction events is associated with reactivation of latent infections. The use of rituximab, the antibody to CD20 (a B–cell surface protein), is associated with the development of reactivation tuberculosis as well as hepatitis B, cytomegalovirus (CMV) infection, and other latent infections. Like organ transplant recipients (Chap. 13), patients with positive purified protein derivative tests and underlying viral infection should be carefully monitored for reactivation disease.

SYSTEM-SPECIFIC SYNDROMES

SKIN-SPECIFIC SYNDROMES

Skin lesions are common in cancer patients, and the appearance of these lesions may permit the diagnosis of systemic bacterial or fungal infection. While cellulitis caused by skin organisms such as *Streptococcus* or *Staphylococcus* is common, neutropenic patients—i.e.,

TABLE 12-3

INFECTIONS ASSOCIATED WITH SPECIFIC TYPES OF CANCER

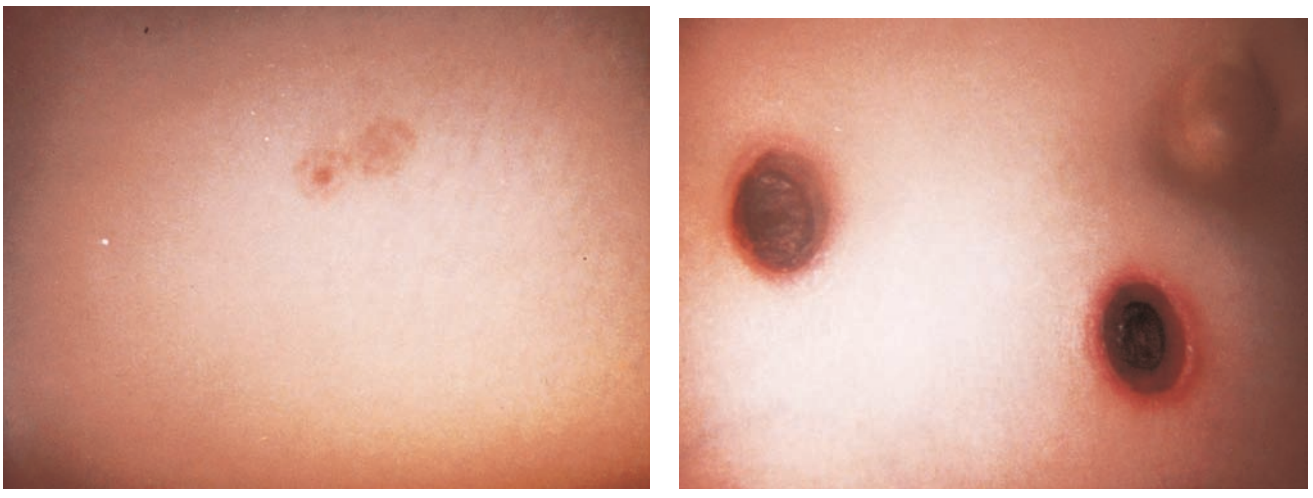
CANCER	UNDERLYING IMMUNE ABNORMALITY	ORGANISMS CAUSING INFECTION
Multiple myeloma	Hypogammaglobulinemia	*Streptococcus pneumoniae, Haemophilus influenzae, Neisseria meningitidis*
Chronic lymphocytic leukemia	Hypogammaglobulinemia	*S. pneumoniae, H. influenzae, N. meningitidis*
Acute myelocytic or lymphocytic leukemia	Granulocytopenia, skin and mucous-membrane lesions	Extracellular gram-positive and gram-negative bacteria, fungi
Hodgkin's disease	Abnormal T cell function	Intracellular pathogens *(Mycobacterium tuberculosis, Listeria, Salmonella, Cryptococcus, Mycobacterium avium)*
Non-Hodgkin's lymphoma and acute lymphocytic leukemia	Glucocorticoid chemotherapy, T and B cell dysfunction	*Pneumocystis*
Colon and rectal tumors	Local abnormalities[a]	*Streptococcus bovis* (bacteremia)
Hairy cell leukemia	Abnormal T cell function	Intracellular pathogens (*M. tuberculosis, Listeria, Cryptococcus, M. avium*)

[a]The reason for this association is not well defined.

those with <500 functional polymorphonuclear leukocytes (PMNs)/μL—and patients with impaired blood or lymphatic drainage may develop infections with unusual organisms. Innocent-looking macules or papules may be the first sign of bacterial or fungal sepsis in immunocompromised patients **(Fig. 12-1)**. In the neutropenic host, a macule progresses rapidly to ecthyma gangrenosum (Fig. 11-35), a usually painless, round, necrotic lesion consisting of a central black or gray-black eschar with surrounding erythema. Ecthyma gangrenosum, which is located in nonpressure areas (as distinguished from necrotic lesions associated with lack of circulation), is often associated with *Pseudomonas aeruginosa* bacteremia (Chap. 57) but may be caused by other bacteria.

Candidemia (Chap. 110) is also associated with a variety of skin conditions (Fig. 11-38) and commonly presents as a maculopapular rash. Punch biopsy of the skin may be the best method for diagnosis.

Cellulitis, an acute spreading inflammation of the skin, is most often caused by infection with group A *Streptococcus* or *Staphylococcus aureus*, virulent organisms normally found on the skin (Chap. 22). Although cellulitis tends to be circumscribed in normal hosts, it may spread rapidly in neutropenic patients. A tiny break in the skin may lead to spreading cellulitis, which is characterized by pain and erythema; in the affected patients, signs of infection (e.g., purulence) are often lacking. What might be a furuncle in a normal host may require amputation



A ***B***

FIGURE 12-1

A. **Papules related to *Escherichia coli*** bacteremia in a neutropenic patient with acute lymphocytic leukemia.
B. The same lesion the following day.

because of uncontrolled infection in a patient presenting with leukemia. A dramatic response to an infection that might be trivial in a normal host can mark the first sign of leukemia. Fortunately, granulocytopenic patients are likely to be infected with certain types of organisms (Table 12-4); thus, the selection of an antibiotic regimen is somewhat easier than it might otherwise be (see "Antibacterial Therapy," later in the chapter.). It is essential to recognize cellulitis early and to treat it aggressively. Patients who are neutropenic or have previously received antibiotics for other reasons may develop cellulitis with unusual organisms (e.g., *Escherichia coli*, *Pseudomonas*, or fungi). Early treatment, even of innocent-looking lesions, is essential to prevent necrosis and loss of tissue. Debridement to prevent spread may sometimes be necessary early in the course of disease, but it can often be performed after chemotherapy, when the PMN count increases.

Sweet's syndrome, or *febrile neutrophilic dermatosis*, was originally described in women with elevated white blood cell (WBC) counts. The disease is characterized by the presence of leukocytes in the lower dermis, with edema of the papillary body. Ironically, this disease now is usually seen in neutropenic patients with cancer, most often in association with acute leukemia but also in association with a variety of other malignancies. Sweet's syndrome usually presents as red or bluish-red papules or nodules that may coalesce and form sharply bordered plaques (Fig. 11-41). The edema may suggest vesicles, but on palpation the lesions are solid, and vesicles probably never arise in this disease. The lesions are most common on the face, neck, and arms. On the legs, they may be confused with erythema nodosum (Fig. 11-40).

TABLE 12-4

ORGANISMS LIKELY TO CAUSE INFECTIONS IN GRANULOCYTOPENIC PATIENTS

Gram-positive cocci
Staphylococcus epidermidis
Staphylococcus aureus
Viridans *Streptococcus*
Enterococcus faecalis
Streptococcus pneumoniae
Gram-negative bacilli
Escherichia coli
Klebsiella spp.
Pseudomonas aeruginosa
Non-*aeruginosa Pseudomonas* spp.[a]
Enterobacter spp.
Serratia spp.
Acinetobacter spp.[a]
Citrobacter spp.
Gram-positive bacilli
Diphtheroids
JK bacillus[a]
Fungi
Candida spp.
Aspergillus spp.

[a]Often associated with intravenous catheters.

The development of lesions is often accompanied by high fevers and an elevated erythrocyte sedimentation rate. Both the lesions and the temperature elevation respond dramatically to glucocorticoid administration. Treatment begins with high doses of glucocorticoids (60 mg/d of prednisone) followed by tapered doses over the next 2–3 weeks.

Data indicate that *erythema multiforme* (Fig. 11-25) with mucous membrane involvement is often associated with herpes simplex virus (HSV) infection and is distinct from Stevens-Johnson syndrome, which is associated with drugs and tends to have a more widespread distribution. Since cancer patients are both immunosuppressed (and therefore susceptible to herpes infections) and heavily treated with drugs (and therefore subject to Stevens-Johnson syndrome), both of these conditions are common in this population.

Cytokines, which are used as adjuvants or primary treatments for cancer, can themselves cause characteristic rashes, further complicating the differential diagnosis. This phenomenon is a particular problem in bone marrow transplant recipients (Chap. 13), who, in addition to having the usual chemotherapy-, antibiotic-, and cytokine-induced rashes, are plagued by graft-versus-host disease.

CATHETER-RELATED INFECTIONS

Because IV catheters are commonly used in cancer chemotherapy and are prone to infection (Chap. 14), they pose a major problem in the care of patients with cancer. Some catheter-associated infections can be treated with antibiotics, while in others the catheter must be removed (Table 12-5). If the patient has a "tunneled" catheter (which consists of an entrance site, a subcutaneous tunnel, and an exit site), a red streak over the subcutaneous part of the line (the tunnel) is grounds for immediate device removal. Failure to remove catheters under these circumstances may result in extensive cellulitis and tissue necrosis.

More common than tunnel infections are exit-site infections, often with erythema around the area where the line penetrates the skin. Most authorities (Chap. 38) recommend treatment (usually with vancomycin) for an exit-site infection caused by coagulase-negative *Staphylococcus*. Treatment of coagulase-positive staphylococcal infection is associated with a poorer outcome, and it is advisable to remove the catheter if possible. Similarly, many clinicians remove catheters associated with infections due to *P. aeruginosa* and *Candida* species, since such infections are difficult to treat and bloodstream infections with these organisms are likely to be deadly. Catheter infections caused by *Burkholderia cepacia*, *Stenotrophomonas* spp., *Agrobacterium* spp., and *Acinetobacter baumannii* as well as *Pseudomonas* spp. other than *aeruginosa* are likely to be very difficult to eradicate with antibiotics alone. Similarly, isolation of *Bacillus*, *Corynebacterium*, and *Mycobacterium* spp. should prompt removal of the catheter.

TABLE 12-5

APPROACH TO CATHETER INFECTIONS IN IMMUNOCOMPROMISED PATIENTS

CLINICAL PRESENTATION	CATHETER REMOVAL	ANTIBIOTICS	COMMENTS
Evidence of Infection, Negative Blood Cultures			
Exit-site erythema	Not necessary if infection responds to treatment	Usually begin treatment for gram-positive cocci.	Coagulase-negative staphylococci are most common.
Tunnel-site erythema	Required	Treat for gram-positive cocci pending culture results.	Failure to remove the catheter may lead to complications.
Blood Culture–Positive Infections			
Coagulase-negative staphylococci	Line removal optimal but may be unnecessary if patient is clinically stable and responds to antibiotics	Usually start with vancomycin. (Linezolid, quinupristin/dalfopristin, and daptomycin are all appropriate.)	If there are no contraindications to line removal, this course of action is optimal. If the line is removed, antibiotics may not be necessary.
Other gram-positive cocci (e.g., *Staphylococcus aureus, Enterococcus*); gram-positive rods (*Bacillus, Corynebacterium* spp.)	Recommended	Treat with antibiotics to which the organism is sensitive, with duration based on the clinical setting.	The incidence of metastatic infections following *S. aureus* infection and the difficulty of treating enterococcal infection make line removal the recommended course of action. In addition, gram-positive rods do not respond readily to antibiotics alone.
Gram-negative bacteria	Recommended	Use an agent to which the organism is shown to be sensitive.	Organisms like *Stenotrophomonas, Pseudomonas,* and *Burkholderia* are notoriously hard to treat.
Fungi	Recommended	—	Fungal infections of catheters are extremely difficult to treat.

GASTROINTESTINAL TRACT–SPECIFIC SYNDROMES

Upper gastrointestinal tract disease

Infections of the mouth

The oral cavity is rich in aerobic and anaerobic bacteria (Chap. 69) that normally live in a commensal relationship with the host. The antimetabolic effects of chemotherapy cause a breakdown of host defenses, leading to ulceration of the mouth and the potential for invasion by resident bacteria. Mouth ulcerations afflict most patients receiving cytotoxic chemotherapy and have been associated with viridans streptococcal bacteremia. *Candida* infections of the mouth are very common. Fluconazole is clearly effective in the treatment of both local infections (thrush) and systemic infections (esophagitis) due to *Candida albicans*. Other azoles (e.g., voriconazole) as well as echinocandins offer similar efficacy as well as activity against the fluconazole-resistant organisms that are associated with extensive fluconazole treatment (Chap. 110).

Noma (*cancrum oris*), commonly seen in malnourished children, is a penetrating disease of the soft and hard tissues of the mouth and adjacent sites, with resulting necrosis and gangrene. It has a counterpart in immunocompromised patients and is thought to be due to invasion of the tissues by *Bacteroides*, *Fusobacterium*, and other normal inhabitants of the mouth. Noma is associated with debility, poor oral hygiene, and immunosuppression.

Viruses, particularly HSV, are a prominent cause of morbidity in immunocompromised patients, in whom they are associated with severe mucositis. The use of acyclovir, either prophylactically or therapeutically, is of value.

Esophageal infections

The differential diagnosis of esophagitis (usually presenting as substernal chest pain upon swallowing) includes herpes simplex and candidiasis, both of which are readily treatable.

Lower gastrointestinal tract disease

Hepatic candidiasis (Chap. 110) results from seeding of the liver (usually from a gastrointestinal source) in neutropenic patients. It is most common among patients being treated for acute leukemia and usually presents symptomatically around the time the neutropenia resolves. The characteristic picture is that of persistent fever unresponsive to antibiotics, abdominal pain and tenderness or nausea, and elevated serum levels of alkaline phosphatase in a patient with hematologic malignancy who has recently recovered from neutropenia. The diagnosis of this disease (which may present in an indolent manner and persist for several months) is based on the finding of yeasts or pseudohyphae in granulomatous lesions. Hepatic ultrasound or CT may reveal bull's-eye lesions. In some cases, MRI reveals small lesions not visible by other imaging modalities. The pathology (a granulomatous response) and the timing (with resolution of neutropenia and an elevation in granulocyte count) suggest that the host response to *Candida* is an important component of the manifestations of disease. In many cases, although organisms are visible, cultures of biopsied material may be negative. The designation *hepatosplenic candidiasis* or *hepatic candidiasis* is a misnomer because the disease often involves the kidneys and other tissues; the term *chronic disseminated candidiasis* may be more appropriate. Because of the risk of bleeding with liver biopsy, diagnosis is often based on imaging studies (MRI, CT). Treatment should be directed to the causative agent (usually *C. albicans* but sometimes *C. tropicalis* or other less common *Candida* spp).

Typhlitis

Typhlitis (also referred to as necrotizing colitis, neutropenic colitis, necrotizing enteropathy, ileocecal syndrome, and cecitis) is a clinical syndrome of fever and right-lower-quadrant tenderness in an immunosuppressed host. This syndrome is classically seen in neutropenic patients after chemotherapy with cytotoxic drugs. It may be more common among children than among adults and appears to be much more common among patients with acute myelocytic leukemia (AML) or ALL than among those with other types of cancer; a similar syndrome has been reported in patients infected with HIV type 1. Physical examination reveals right-lower-quadrant tenderness, with or without rebound tenderness. Associated diarrhea (often bloody) is common, and the diagnosis can be confirmed by the finding of a thickened cecal wall on CT, MRI, or ultrasonography. Plain films may reveal a right-lower-quadrant mass, but CT with contrast or MRI is a much more sensitive means of diagnosis. Although surgery is sometimes attempted to avoid perforation from ischemia, most cases resolve with medical therapy alone. The disease is sometimes associated with positive blood cultures (which usually yield aerobic gram-negative bacilli), and therapy is recommended for a broad spectrum of bacteria (particularly gram-negative bacilli, which are likely to be found in the bowel flora). Surgery is indicated in the case of perforation.

Clostridium difficile–induced diarrhea

Patients with cancer are predisposed to the development of *C. difficile* diarrhea (Chap. 47) as a consequence of chemotherapy alone. Thus, they may have positive toxin tests before receiving antibiotics. Obviously, such patients are also subject to *C. difficile*–induced diarrhea as a result of antibiotic pressure. *C. difficile* should always be considered as a possible cause of diarrhea in cancer patients who have received antibiotics.

CENTRAL NERVOUS SYSTEM–SPECIFIC SYNDROMES

Meningitis

The presentation of meningitis in patients with lymphoma or CLL, patients receiving chemotherapy (particularly with glucocorticoids) for solid tumors, and patients who have received bone marrow transplants suggests a diagnosis of cryptococcal or listerial infection. As noted previously, splenectomized patients are susceptible to rapid, overwhelming infection with encapsulated bacteria (including *S. pneumoniae*, *H. influenzae*, and *N. meningitidis*). Similarly, patients who are antibody-deficient (e.g., those with CLL, those who have received intensive chemotherapy, or those who have undergone bone marrow transplantation) are likely to have infections caused by these bacteria. Other cancer patients, however, because of their defective cellular immunity, are likely to be infected with other pathogens (Table 12-3).

Encephalitis

The spectrum of disease resulting from viral encephalitis is expanded in immunocompromised patients. A predisposition to infections with intracellular organisms similar to those encountered in patients with AIDS (Chap. 93) is seen in cancer patients receiving (1) high-dose cytotoxic chemotherapy, (2) chemotherapy affecting T cell function (e.g., fludarabine), or (3) antibodies that eliminate T cells (e.g., anti-CD3, alemtuzumab, anti-CD52) or cytokine activity (anti-tumor necrosis factor agents or interleukin 1 receptor antagonists). Infection with varicella-zoster virus (VZV) has been associated with encephalitis that may be caused by VZV-related vasculitis. Chronic viral infections may also be associated with dementia and encephalitic presentations, and a diagnosis of progressive multifocal leukoencephalopathy (Chap. 31) should be considered when a patient who has received chemotherapy presents with dementia **(Table 12-6)**. Other abnormalities of the central nervous system (CNS) that may be confused with infection include normal-pressure hydrocephalus and vasculitis resulting from CNS irradiation. It may be possible to differentiate these conditions by MRI.

TABLE 12-6

DIFFERENTIAL DIAGNOSIS OF CENTRAL NERVOUS SYSTEM INFECTIONS IN PATIENTS WITH CANCER

	UNDERLYING PREDISPOSITION	
FINDINGS ON CT OR MRI	**PROLONGED NEUTROPENIA**	**DEFECTS IN CELLULAR IMMUNITY[a]**
Mass lesions	*Aspergillus, Nocardia,* or *Cryptococcus* brain abscess	Toxoplasmosis EBV-LPD
Diffuse encephalitis	PML (JC virus)	Infection with VZV, CMV, HSV, HHV-6, JC virus (PML), *Listeria*

[a]High-dose glucocorticoid therapy, cytotoxic chemotherapy.
Abbreviations: CMV, cytomegalovirus; EBV-LPD, Epstein-Barr virus lymphoproliferative disease; HHV-6, human herpesvirus type 6; HSV, herpes simplex virus; PML, progressive multifocal leukoencephalopathy; VZV, varicella-zoster virus.

Brain masses

Mass lesions of the brain most often present as headache with or without fever or neurologic abnormalities. Infections associated with mass lesions may be caused by bacteria (particularly *Nocardia*), fungi (particularly *Cryptococcus* or *Aspergillus*), or parasites (*Toxoplasma*). Epstein-Barr virus (EBV)–associated lymphoproliferative disease may also present as single or multiple mass lesions of the brain. A biopsy may be required for a definitive diagnosis.

PULMONARY INFECTIONS

Pneumonia (Chap. 18) in immunocompromised patients may be difficult to diagnose because conventional methods of diagnosis depend on the presence of neutrophils. Bacterial pneumonia in neutropenic patients may present without purulent sputum—or, in fact, without any sputum at all—and may not produce physical findings suggestive of chest consolidation (rales or egophony).

In granulocytopenic patients with persistent or recurrent fever, the chest x-ray pattern may help to localize an infection and thus to determine which investigative tests and procedures should be undertaken and which therapeutic options should be considered **(Table 12-7)**. In this setting, a simple chest x-ray is a screening tool; because the impaired host response results in less evidence of consolidation or infiltration, high-resolution CT is recommended for the diagnosis of pulmonary infections. The difficulties encountered in the management of pulmonary infiltrates relate in part to the difficulties of performing diagnostic procedures on the patients involved. When platelet counts can be increased to adequate levels by transfusion, microscopic and microbiologic evaluation of the fluid obtained by endoscopic bronchial lavage is often diagnostic. Lavage fluid should be cultured for *Mycoplasma*, *Chlamydia*, *Legionella*, *Nocardia*, more common bacterial pathogens, and fungi. In addition, the possibility of *Pneumocystis* pneumonia should be considered, especially in patients with ALL or lymphoma who have not received prophylactic trimethoprim-sulfamethoxazole (TMP-SMX). The characteristics of the infiltrate may be helpful in decisions about further diagnostic and therapeutic maneuvers. Nodular infiltrates suggest fungal pneumonia (e.g., that caused by *Aspergillus* or *Mucor*). Such lesions may best be approached by visualized biopsy procedures.

Aspergillus species (Chap. 111) can colonize the skin and respiratory tract or cause fatal systemic illness. Although this fungus may cause aspergillomas in a previously existing cavity or may produce allergic bronchopulmonary disease, the major problem posed by this genus in neutropenic patients is invasive disease due to *A. fumigatus* or *A. flavus*. The organisms enter the host following colonization of the respiratory tract, with subsequent invasion of blood vessels. The disease is likely to present as a thrombotic or embolic event because of this ability of the fungi to invade blood vessels. The risk of infection with *Aspergillus* correlates directly with the duration of neutropenia. In prolonged neutropenia, positive surveillance cultures for nasopharyngeal colonization with *Aspergillus* may predict the development of disease.

Patients with *Aspergillus* infection often present with pleuritic chest pain and fever, which are sometimes accompanied by cough. Hemoptysis may be an ominous sign. Chest x-rays may reveal new focal infiltrates or nodules. Chest CT may reveal a characteristic halo consisting of a mass-like infiltrate surrounded by an area of low attenuation. The presence of a "crescent sign" on chest x-ray or chest CT, in which the mass progresses to central cavitation, is characteristic of invasive *Aspergillus* infection but may develop as the lesions are resolving.

TABLE 12-7

DIFFERENTIAL DIAGNOSIS OF CHEST INFILTRATES IN IMMUNOCOMPROMISED PATIENTS

	CAUSE OF PNEUMONIA	
INFILTRATE	**INFECTIOUS**	**NONINFECTIOUS**
Localized	Bacteria (including *Legionella,* mycobacteria)	Local hemorrhage or embolism, tumor
Nodular	Fungi (e.g., *Aspergillus* or *Mucor), Nocardia*	Recurrent tumor
Diffuse	Viruses (especially CMV), *Chlamydia, Pneumocystis, Toxoplasma gondii,* mycobacteria	Congestive heart failure, radiation pneumonitis, drug-induced lung injury, diffuse alveolar hemorrhage (described after BMT)

Abbreviations: BMT, bone marrow transplantation; CMV, cytomegalovirus.

In addition to causing pulmonary disease, *Aspergillus* may invade through the nose or palate, with deep sinus penetration. The appearance of a discolored area in the nasal passages or on the hard palate should prompt a search for invasive *Aspergillus*. This situation is likely to require surgical debridement. Catheter infections with *Aspergillus* usually require both removal of the catheter and antifungal therapy.

Diffuse interstitial infiltrates suggest viral, parasitic, or *Pneumocystis* pneumonia. If the patient has a diffuse interstitial pattern on chest x-ray, it may be reasonable, while considering invasive diagnostic procedures, to institute empirical treatment for *Pneumocystis* with TMP-SMX and for *Chlamydia*, *Mycoplasma*, and *Legionella* with a quinolone or an erythromycin derivative (e.g., azithromycin). Noninvasive procedures, such as staining of sputum smears for *Pneumocystis*, serum cryptococcal antigen tests, and urine testing for *Legionella* antigen, may be helpful. Serum galactomannan and β-D-glucan tests may be helpful in diagnosing *Aspergillus* infection, but their utility is limited by their lack of sensitivity. In transplant recipients who are seropositive for CMV, a determination of CMV load in the serum should be considered. Viral load studies (which allow physicians to quantitate viruses) have superseded simple measurement of serum IgG, which merely documents prior exposure to virus. Infections with viruses that cause only upper respiratory symptoms in immunocompetent hosts, such as respiratory syncytial virus (RSV), influenza viruses, and parainfluenza viruses, may be associated with fatal pneumonitis in immunocompromised hosts. Polymerase chain reaction testing now allows rapid diagnosis of viral pneumonia, which can lead to treatment in some cases (e.g., influenza).

Bleomycin is the most common cause of chemotherapy-induced lung disease. Other causes include alkylating agents (such as cyclophosphamide, chlorambucil, and melphalan), nitrosoureas [carmustine (BCNU), lomustine (CCNU), and methyl-CCNU], busulfan, procarbazine, methotrexate, and hydroxyurea. Both infectious and noninfectious (drug- and/or radiation-induced) pneumonitis can cause fever and abnormalities on chest x-ray; thus, the differential diagnosis of an infiltrate in a patient receiving chemotherapy encompasses a broad range of conditions (Table 12-7). The treatment of radiation pneumonitis (which may respond dramatically to glucocorticoids) or drug-induced pneumonitis is different from that of infectious pneumonia, and a biopsy may be important in the diagnosis. Unfortunately, no definitive diagnosis can be made in ~30% of cases, even after bronchoscopy.

Open-lung biopsy is the gold standard of diagnostic techniques. Biopsy via a visualized thoracostomy can replace an open procedure in many cases. When a biopsy cannot be performed, empirical treatment can be undertaken; a quinolone or an erythromycin derivative (azithromycin) and TMP-SMX are used in the case of diffuse infiltrates, and an antifungal agent is administered in the case of nodular infiltrates. The risks should be weighed carefully in these cases. If inappropriate drugs are administered, empirical treatment may prove toxic or ineffective; either of these outcomes may be riskier than biopsy.

CARDIOVASCULAR INFECTIONS

Patients with Hodgkin's disease are prone to persistent infections by *Salmonella*, sometimes (and particularly often in elderly patients) affecting a vascular site. The use of IV catheters deliberately lodged in the right atrium is associated with a high incidence of bacterial endocarditis, presumably related to valve damage followed by bacteremia. Nonbacterial thrombotic endocarditis has been described in association with a variety of malignancies (most often solid tumors) and may follow bone marrow transplantation as well. The presentation of an embolic event with a new cardiac murmur suggests this diagnosis. Blood cultures are negative in this disease of unknown pathogenesis.

ENDOCRINE SYNDROMES

Infections of the endocrine system have been described in immunocompromised patients. *Candida* infection of the thyroid may be difficult to diagnose during the neutropenic period. It can be defined by indium-labeled WBC scans or gallium scans after neutrophil counts increase. CMV infection can cause adrenalitis with or without resulting adrenal insufficiency. The presentation of a sudden endocrine anomaly in an immunocompromised patient may be a sign of infection in the involved end organ.

MUSCULOSKELETAL INFECTIONS

Infection that is a consequence of vascular compromise, resulting in gangrene, can occur when a tumor restricts the blood supply to muscles, bones, or joints. The process of diagnosis and treatment of such infection is similar to that in normal hosts, with the following caveats:

1. *In terms of diagnosis*, a lack of physical findings resulting from a lack of granulocytes in the granulocytopenic patient should make the clinician more aggressive in obtaining tissue rather than relying on physical signs.
2. *In terms of therapy*, aggressive debridement of infected tissues may be required, but it is usually difficult to operate on patients who have recently received chemotherapy, both because of a lack of platelets (which results in bleeding complications) and because of a lack of WBCs (which may lead to secondary infection). A blood culture positive for *Clostridium perfringens*—an organism commonly associated with gas gangrene—can have a number of meanings (Chap. 46). Bloodstream infections with intestinal organisms such as *Streptococcus bovis* and *C. perfringens* may arise spontaneously from lower gastrointestinal lesions (tumor or polyps); alternatively, these lesions may be harbingers of invasive disease. The clinical setting must be considered in order to define the appropriate treatment for each case.

RENAL AND URETERAL INFECTIONS

Infections of the urinary tract are common among patients whose ureteral excretion is compromised (Table 12-1). *Candida*, which has a predilection for the kidney, can

invade either from the bloodstream or in a retrograde manner (via the ureters or bladder) in immunocompromised patients. The presence of "fungus balls" or persistent candiduria suggests invasive disease. Persistent funguria (with *Aspergillus* as well as *Candida*) should prompt a search for a nidus of infection in the kidney.

Certain viruses are typically seen only in immunosuppressed patients. BK virus (polyomavirus hominis 1) has been documented in the urine of bone marrow transplant recipients and, like adenovirus, may be associated with hemorrhagic cystitis. BK-induced cystitis usually remits with decreasing immunosuppression. Anecdotal reports have described the treatment of infections due to adenovirus and BK virus with cidofovir.

ABNORMALITIES THAT PREDISPOSE TO INFECTION

(Table 12-1)

THE LYMPHOID SYSTEM

It is beyond the scope of this chapter to detail how all the immunologic abnormalities that result from cancer or from chemotherapy for cancer lead to infections. Disorders of the immune system are discussed in other sections of this book. As has been noted, patients with antibody deficiency are predisposed to overwhelming infection with encapsulated bacteria (including *S. pneumoniae*, *H. influenzae*, and *N. meningitidis*). Infections that result from the lack of a functional cellular immune system are described in Chap. 93. It is worth mentioning, however, that patients undergoing intensive chemotherapy for any form of cancer will have not only defects due to granulocytopenia but also lymphocyte dysfunction, which may be profound. Thus, these patients—especially those receiving glucocorticoid-containing regimens or drugs that inhibit either T cell activation (calcineurin inhibitors or drugs like fludarabine, which affect lymphocyte function) or cytokine induction—should be given prophylaxis for *Pneumocystis* pneumonia.

THE HEMATOPOIETIC SYSTEM

Initial studies in the 1960s revealed a dramatic increase in the incidence of infections (fatal and nonfatal) among cancer patients with a granulocyte count of <500/μL. The use of prophylactic antibacterial agents has reduced the number of bacterial infections, but 35–78% of febrile neutropenic patients being treated for hematologic malignancies develop infections at some time during chemotherapy. Aerobic pathogens (both gram-positive and gram-negative) predominate in all series, but the exact organisms isolated vary from center to center. Infections with anaerobic organisms are uncommon. Geographic patterns affect the types of fungi isolated. Tuberculosis and malaria are common causes of fever in the developing world and may present in this setting as well.

Neutropenic patients are unusually susceptible to infection with a wide variety of bacteria; thus, antibiotic therapy should be initiated promptly to cover likely pathogens if infection is suspected. Indeed, early initiation of antibacterial agents is mandatory to prevent deaths. Like most immunocompromised patients, neutropenic patients are threatened by their own microbial flora, including gram-positive and gram-negative organisms found commonly on the skin and in the bowel (Table 12-4). Because treatment with narrow-spectrum agents leads to infection with organisms not covered by the antibiotics used, the initial regimen should target all pathogens likely to be initial causes of bacterial infection in neutropenic hosts. As noted in the algorithm shown in **Fig. 12-2**, administration of antimicrobial agents is routinely continued until neutropenia resolves—i.e., the granulocyte count is sustained above 500/μL for at least 2 days. In some cases, patients remain febrile after resolution of neutropenia. In these instances, the risk of sudden death from overwhelming bacteremia is greatly reduced, and the following diagnoses should be seriously considered: (1) fungal infection, (2) bacterial abscesses or undrained foci of infection, and (3) drug fever (including reactions to antimicrobial agents as well as to chemotherapy or cytokines). In the proper setting, viral infection or graft-versus-host disease should be considered. In clinical practice, antibacterial therapy is usually discontinued when the patient is no longer neutropenic and all evidence of bacterial disease has been eliminated. Antifungal agents are then discontinued if there is

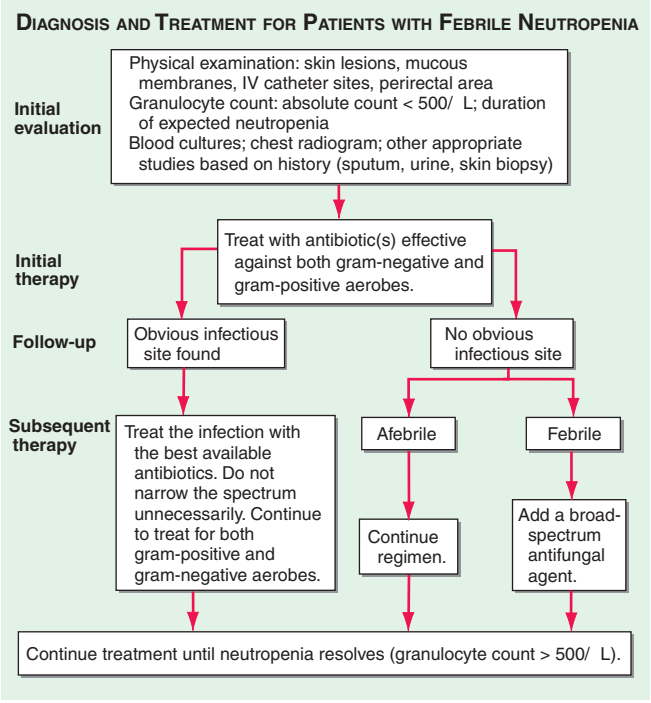


FIGURE 12-2
Algorithm for the diagnosis and treatment of febrile-neutropenic patients.

no evidence of fungal disease. If the patient remains febrile, a search for viral diseases or unusual pathogens is conducted while unnecessary cytokines and other drugs are systematically eliminated from the regimen.

TREATMENT Infections in Cancer Patients

ANTIBACTERIAL THERAPY Hundreds of antibacterial regimens have been tested for use in patients with cancer. The major risk of infection is related to the degree of neutropenia seen as a consequence of either the disease or the therapy. Many of the relevant studies have involved small populations in which the outcomes have generally been good, and most have lacked the statistical power to detect differences among the regimens studied. Each febrile neutropenic patient should be approached as a unique problem, with particular attention given to previous infections and recent antibiotic exposures. Several general guidelines are useful in the initial treatment of neutropenic patients with fever (Fig. 12-2):

1. In the initial regimen, it is necessary to use antibiotics active against both gram-negative and gram-positive bacteria (Table 12-4).
2. Monotherapy with an aminoglycoside or an antibiotic without good activity against gram-positive organisms (e.g., ciprofloxacin or aztreonam) is not adequate in this setting.
3. The agents used should reflect both the epidemiology and the antibiotic resistance pattern of the hospital.
4. If the pattern of resistance justifies its use, a single third-generation cephalosporin constitutes an appropriate initial regimen in many hospitals.
5. Most standard regimens are designed for patients who have not previously received prophylactic antibiotics. The development of fever in a patient who has received antibiotics affects the choice of subsequent therapy, which should target resistant organisms and organisms known to cause infections in patients being treated with the antibiotics already administered.
6. Randomized trials have indicated the safety of oral antibiotic regimens in the treatment of "low-risk" patients with fever and neutropenia. Outpatients who are expected to remain neutropenic for <10 days and who have no concurrent medical problems (such as hypotension, pulmonary compromise, or abdominal pain) can be classified as low risk and treated with a broad-spectrum oral regimen.
7. Several large-scale studies indicate that prophylaxis with a fluoroquinolone (ciprofloxacin or levofloxacin) decreases morbidity and mortality rates among afebrile patients who are anticipated to have neutropenia of long duration.

The initial antibacterial regimen should be refined on the basis of culture results (Fig. 12-2). Blood cultures are the most relevant on which to base therapy; surface cultures of skin and mucous membranes may be misleading. In the case of gram-positive bacteremia or another gram-positive infection, it is important that the antibiotic be optimal for the organism isolated. Although it is not desirable to leave the patient unprotected, the addition of more and more antibacterial agents to the regimen is not appropriate unless there is a clinical or microbiologic reason to do so. Planned progressive therapy (the serial, empirical addition of one drug after another without culture data) is not efficacious in most settings and may have unfortunate consequences. Simply adding another antibiotic for fear that a gram-negative infection is present is a dubious practice. The synergy exhibited by β-lactams and aminoglycosides against certain gram-negative organisms (especially *P. aeruginosa*) provides the rationale for using two antibiotics in this setting, but recent analyses suggest that efficacy is not enhanced by the addition of aminoglycosides, while toxicity may be increased. Mere "double coverage," with the addition of a quinolone or another antibiotic that is not likely to exhibit synergy, has not been shown to be of benefit and may cause additional toxicities and side effects. Cephalosporins can cause bone marrow suppression, and vancomycin is associated with neutropenia in some healthy individuals. Furthermore, the addition of multiple cephalosporins may induce β-lactamase production by some organisms; cephalosporins and double β-lactam combinations should probably be avoided altogether in *Enterobacter* infections.

ANTIFUNGAL THERAPY Fungal infections in cancer patients are most often associated with neutropenia. Neutropenic patients are predisposed to the development of invasive fungal infections, most commonly those due to *Candida* and *Aspergillus* species and occasionally those caused by *Fusarium*, *Trichosporon*, and *Bipolaris*. Cryptococcal infection, which is common among patients taking immunosuppressive agents, is uncommon among neutropenic patients receiving chemotherapy for AML. Invasive candidal disease is usually caused by *C. albicans* or *C. tropicalis*, but can be caused by *C. krusei*, *C. parapsilosis*, and *C. glabrata*.

For decades it has been common clinical practice to add amphotericin B to antibacterial regimens if a neutropenic patient remains febrile despite 4–7 days of treatment with antibacterial agents. The rationale for this empirical addition is that it is difficult to culture fungi before they cause disseminated disease and that mortality rates from disseminated fungal infections in granulocytopenic patients are high. Before the introduction of newer azoles into clinical practice, amphotericin B was the mainstay of antifungal therapy. The insolubility of amphotericin B has resulted in the marketing of several lipid formulations that are less toxic than the amphotericin B deoxycholate complex. Echinocandins (e.g., caspofungin) are useful in the treatment of infections caused by azole-resistant *Candida* as well as in therapy for aspergillosis and have been shown to be equivalent to liposomal amphotericin B for the empirical treatment of patients with prolonged fever and neutropenia.

Newer azoles have also been demonstrated to be effective in this setting. Although fluconazole is efficacious in the treatment of infections due to many *Candida* spp., its use against serious fungal infections in immunocompromised patients is limited by its narrow spectrum: it has no activity against *Aspergillus* or against several non-*albicans Candida* spp. The broad-spectrum azoles (e.g., voriconazole and posaconazole) provide another option for the treatment of *Aspergillus* infection (Chap. 111), including CNS infection, in which amphotericin B has usually failed. Clinicians should be aware that the spectrum of each azole is somewhat different and that no drug can be assumed to be efficacious against all fungi. For example, while voriconazole is active against *Pseudallescheria boydii*, amphotericin B is not; however, voriconazole has no activity against *Mucor*. Posaconazole, which is administered orally, is useful as a prophylactic agent in patients with prolonged neutropenia. Studies in progress are assessing the use of these agents in combinations. For a full discussion of antifungal therapy, see Chap. 105.

ANTIVIRAL THERAPY The availability of a variety of agents active against herpes-group viruses, including some new agents with a broader spectrum of activity, has heightened focus on the treatment of viral infections, which pose a major problem in cancer patients. Viral diseases caused by the herpes group are prominent. Serious (and sometimes fatal) infections due to HSV and CMV are well documented, and VZV infections may be fatal to patients receiving chemotherapy. The roles of human herpesvirus (HHV)-6, HHV-7, and HHV-8 (Kaposi's sarcoma–associated herpesvirus) in cancer patients are still being defined (Chap. 87). While clinical experience is most extensive with acyclovir, which can be used therapeutically or prophylactically, a number of derivative drugs offer advantages over this agent (Table 12-8).

In addition to the herpes group, several respiratory viruses (especially RSV) may cause serious disease in cancer patients. While influenza vaccination is recommended (see next), it may be ineffective in this patient population. The availability of antiviral drugs with activity against influenza viruses gives the clinician additional options for the treatment of these patients (Table 12-9).

TABLE 12-8

ANTIVIRAL AGENTS ACTIVE AGAINST HERPESVIRUSES

AGENT	DESCRIPTION	SPECTRUM	TOXICITY	OTHER ISSUES
Acyclovir	Inhibits HSV polymerase	HSV, VZV (± CMV, EBV)	Rarely has side effects; crystalluria can occur at high doses	Long history of safety; original antiviral agent
Famciclovir	Prodrug of penciclovir (a guanosine analogue)	HSV, VZV (± CMV)	Associated with cancer in rats	Longer effective half-life than acyclovir
Valacyclovir	Prodrug of acyclovir; better absorption	HSV, VZV (± CMV)	Associated with thrombotic microangiopathy in one study of immunocompromised patients	Better oral absorption and longer effective half-life than acyclovir; can be given as a single daily dose for prophylaxis
Ganciclovir	More potent polymerase inhibitor; more toxic than acyclovir	HSV, VZV, CMV, HHV-6	Bone marrow suppression	Neutropenia may respond to G-CSF or GM-CSF
Valganciclovir	Prodrug of ganciclovir; better absorption	HSV, VZV, CMV, HHV-6	Bone marrow suppression	—
Cidofovir	Nucleotide analogue of cytosine	HSV, VZV, CMV; good in vitro activity against adenovirus and others	Nephrotoxic marrow suppression	Given IV once a week
Foscarnet	Phosphonoformic acid; inhibits viral DNA polymerase	HSV, VZV, CMV, HHV-6	Nephrotoxic; electrolyte abnormalities common	IV only

Abbreviations: ±, agent has some activity but not enough for the treatment of infections; CMV, cytomegalovirus; EBV, Epstein-Barr virus; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; HHV, human herpesvirus; HSV, herpes simplex virus; VZV, varicella-zoster virus.

TABLE 12-9

OTHER ANTIVIRAL AGENTS USEFUL IN THE TREATMENT OF INFECTIONS IN CANCER PATIENTS

AGENT	DESCRIPTION	SPECTRUM	TOXICITY	OTHER ISSUES
Amantadine, rimantadine	Interfere with uncoating	Influenza A only	5–10% fewer CNS effects with rimantadine	May be given prophylactically
Zanamivir	Neuraminidase inhibitor	Influenza A and B	Usually well tolerated	Inhalation only
Oseltamivir	Neuraminidase inhibitor	Influenza A and B	Usually well tolerated	PO dosing
Pleconaril	Blocks enterovirus binding and uncoating	90% of enteroviruses, 80% of rhinoviruses	Generally well tolerated	Decreases duration of meningitis; available for compassionate use only
Interferons	Cytokines with broad spectrum of activity	Used locally for warts, systemically for hepatitis	Fever, myalgias, bone marrow suppression	Not shown to be helpful in CMV infection; use limited by toxicity
Ribavirin	Purine analogue (precise mechanism of action unknown)	Broad theoretical spectrum; documented use against RSV, Lassa fever virus, and hepatitis viruses (with interferon)	IV form causes anemia	Given by aerosol for RSV infection (efficacy in doubt); approved for use in children with heart/lung disease; given with interferon for hepatitis C

Abbreviations: CMV, cytomegalovirus; CNS, central nervous system; RSV, respiratory syncytial virus.

OTHER THERAPEUTIC MODALITIES Another way to address the problems of the febrile neutropenic patient is to replenish the neutrophil population. Although granulocyte transfusions are effective in the treatment of refractory gram-negative bacteremia, they do not have a documented role in prophylaxis. Because of the expense, the risk of leukoagglutinin reactions (which has probably been decreased by improved cell-separation procedures), and the risk of transmission of CMV from unscreened donors (which has been reduced by the use of filters), granulocyte transfusion is reserved for patients unresponsive to antibiotics. This modality is efficacious for documented gram-negative bacteremia refractory to antibiotics, particularly in situations where granulocyte numbers will be depressed for only a short period. The demonstrated usefulness of granulocyte colony-stimulating factor (G-CSF) in mobilizing neutrophils and advances in preservation techniques may make this option more useful than in the past.

A variety of cytokines, including G-CSF and granulocyte-macrophage colony-stimulating factor (GM-CSF), enhance granulocyte recovery after chemotherapy and consequently shorten the period of maximal vulnerability to fatal infections. Interferon γ has been demonstrated to be effective in some infections caused by intracellular organisms, presumably because of its ability to activate macrophages. The role of these cytokines in routine practice is still a matter of some debate. Most authorities recommend their use only when neutropenia is both severe and prolonged. The cytokines themselves may have adverse effects, including fever, hypoxemia, and pleural effusions or serositis in other areas.

Once neutropenia has resolved, the risk of infection decreases dramatically. However, depending on what drugs they receive, patients who continue on chemotherapeutic protocols remain at high risk for certain diseases. Any patient receiving more than a maintenance dose of glucocorticoids (including many treatment regimens for diffuse lymphoma) should also receive prophylactic TMP-SMX because of the risk of *Pneumocystis* infection; those with ALL should receive such prophylaxis for the duration of chemotherapy.

PREVENTION OF INFECTION IN CANCER PATIENTS

EFFECT OF THE ENVIRONMENT

Outbreaks of fatal *Aspergillus* infection have been associated with construction projects and materials in several hospitals. The association between spore counts and risk of infection suggests the need for a high-efficiency air-handling system in hospitals that care for large numbers of neutropenic patients. The use of laminar-flow rooms and prophylactic antibiotics has decreased the number of infectious episodes in severely neutropenic patients. However, because of the expense of such a program and the failure to show that it dramatically affects

mortality rates, most centers do not routinely use laminar flow to care for neutropenic patients. Some centers use "reverse isolation," in which health care providers and visitors to a patient who is neutropenic wear gowns and gloves. Since most of the infections these patients develop are due to organisms that colonize the patients' own skin and bowel, the validity of such schemes is dubious, and limited clinical data do not support their use. Hand washing by all staff caring for neutropenic patients should be required to prevent the spread of resistant organisms.

The presence of large numbers of bacteria (particularly *P. aeruginosa*) in certain foods, especially fresh vegetables, has led some authorities to recommend a special "low-bacteria" diet. A diet consisting of cooked and canned food is satisfactory to most neutropenic patients and does not involve elaborate disinfection or sterilization protocols. However, there are no studies to support even this type of dietary restriction. Counseling of patients to avoid leftovers, deli foods, and unpasteurized dairy products is recommended.

PHYSICAL MEASURES

Although few studies address this issue, patients with cancer are predisposed to infections resulting from anatomic compromise (e.g., lymphedema resulting from node dissections after radical mastectomy). Surgeons who specialize in cancer surgery can provide specific guidelines for the care of such patients, and patients benefit from commonsense advice about how to prevent infections in vulnerable areas.

IMMUNOGLOBULIN REPLACEMENT

Many patients with multiple myeloma or CLL have immunoglobulin deficiencies as a result of their disease, and all allogeneic bone marrow transplant recipients are hypogammaglobulinemic for a period after transplantation. However, current recommendations reserve intravenous immunoglobulin replacement therapy for those patients with severe (<400 mg/dL), prolonged hypogammaglobulinemia. Antibiotic prophylaxis has been shown to be cheaper and is efficacious in preventing infections in most CLL patients with hypogammaglobulinemia. Routine use of immunoglobulin replacement is not recommended.

SEXUAL PRACTICES

The use of condoms is recommended for severely immunocompromised patients. Any sexual practice that results in oral exposure to feces is not recommended. Neutropenic patients should be advised to avoid any practice that results in trauma, as even microscopic cuts may result in bacterial invasion and fatal sepsis.

ANTIBIOTIC PROPHYLAXIS

Several studies indicate that the use of oral fluoroquinolones prevents infection and decreases mortality rates among severely neutropenic patients. Fluconazole prevents *Candida* infections when given prophylactically to patients receiving bone marrow transplants. The use of broader-spectrum antifungal agents (e.g., posaconazole) appears to be more efficacious. Prophylaxis for *Pneumocystis* is mandatory for patients with ALL and for all cancer patients receiving glucocorticoid-containing chemotherapy regimens.

VACCINATION OF CANCER PATIENTS

In general, patients undergoing chemotherapy respond less well to vaccines than do normal hosts. Their greater need for vaccines thus leads to a dilemma in their management. Purified proteins and inactivated vaccines are almost never contraindicated and should be given to patients even during chemotherapy. For example, all adults should receive diphtheria–tetanus toxoid boosters at the indicated times as well as seasonal influenza vaccine. However, if possible, vaccination should not be undertaken concurrent with cytotoxic chemotherapy. If patients are expected to be receiving chemotherapy for several months and vaccination is indicated (e.g., influenza vaccination in the fall), the vaccine should be given midcycle—as far apart in time as possible from the antimetabolic agents that will prevent an immune response. The meningococcal and pneumococcal polysaccharide vaccines should be given to patients before splenectomy, if possible. The *H. influenzae* type b conjugate vaccine should be administered to all splenectomized patients.

In general, live virus (or live bacterial) vaccines should not be given to patients during intensive chemotherapy because of the risk of disseminated infection. Recommendations on vaccination are summarized in Table 12-2.

CHAPTER 13

INFECTIONS IN TRANSPLANT RECIPIENTS

Robert Finberg ■ Joyce Fingeroth

This chapter considers aspects of infection unique to patients receiving transplanted organs. The evaluation of infections in transplant recipients involves consideration of both the donor and the recipient of the transplanted organ. Two central issues are of paramount importance: (1) Infectious agents (particularly viruses, but also bacteria, fungi, and parasites) can be introduced into the recipient by the donor organ. (2) Treatment of the recipient with medicine to prevent rejection can suppress normal immune responses, greatly increasing susceptibility to infection. Thus, what might have been a latent or asymptomatic infection in an immunocompetent donor or in the recipient prior to therapy can become a life-threatening problem when the recipient becomes immunosuppressed. The pretransplantation evaluation of each patient should be guided by an analysis of both (1) what infections the recipient is currently harboring, since organisms that exist in a state of latency or dormancy before the procedure may cause fatal disease when the patient receives immunosuppressive treatment; and (2) what organisms are likely to be transmitted by the donor organ, particularly those to which the recipient may be naïve.

PRETRANSPLANTATION EVALUATION

The donor

A variety of organisms have been transmitted by organ transplantation **(Table 13-1)**. Transmission of infections that may have been latent or not clinically apparent in the donor has resulted in the development of specific donor-screening protocols. Serologic studies should be ordered to detect viruses such as herpes simplex virus types 1 and 2 (HSV-1, HSV-2), varicella-zoster virus (VZV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), and Kaposi's sarcoma–associated herpesvirus (KSHV) as well as hepatitis A, B, and C viruses and HIV. In addition, when relevant, donors should be screened for viruses such as West Nile virus, rabies virus, human T lymphotropic virus type I, and lymphocytic choriomeningitis virus as well as for parasites such as *Toxoplasma gondii*, *Strongyloides stercoralis*, *Schistosoma* species, and *Trypanosoma cruzi* (the latter particularly in Latin America). Clinicians caring for prospective organ donors should examine chest radiographs for evidence of granulomatous disease (e.g., caused by mycobacteria or fungi) and should perform skin testing or obtain blood for immune cell–based assays that detect active or latent *Mycobacterium tuberculosis* infection. Evaluation for syphilis should also be performed. An investigation of the donor's dietary habits (e.g., consumption of raw meat or fish or of unpasteurized dairy products), occupations or avocations (e.g., gardening or spelunking), and travel history (e.g., travel to areas with endemic fungi) is also indicated and may mandate additional testing (Table 13-1).

The recipient

It is expected that the recipient will have been even more comprehensively assessed than the donor. Additional studies recommended for the recipient include evaluation for acute respiratory virus and gastrointestinal pathogens in the immediate pretransplantation period. An important caveat is that, because of immune dysfunction resulting from chemotherapy or underlying chronic disease, serologic testing of the recipient may prove less reliable than usual.

The donor cells/organ

Careful attention to the sterility of the medium used to process the donor organ, combined with meticulous microbiologic evaluation, reduces rates of transmission of bacteria (or, rarely, yeasts) that may be present or grow in the organ culture medium. From 2% to >20% of donor kidneys are estimated to be contaminated with bacteria—in most cases, with the organisms that colonize the skin or grow in the tissue culture medium used to bathe the donor organ while it awaits implantation. The reported rate of bacterial contamination of transplanted stem cells (bone marrow, peripheral blood, cord blood) is as high as 17% but most commonly is ~1%. The use of enrichment columns and monoclonal antibody depletion procedures results in a higher incidence of contamination. In one

TABLE 13-1

COMMON PATHOGENS TRANSMITTED BY ORGAN TRANSPLANTATION: FREQUENT SITES OF REACTIVATION AND DISEASE[a]

	BLOOD	LUNGS	HEART	BRAIN	LIVER/SPLEEN	SKIN
Bacteria/Mycobacteria						
Mycobacterium tuberculosis	±	+			±	
Atypical mycobacteria	+	+				
Brucella spp.	+					
Viruses						
Cytomegalovirus[b]	+	+	±	±	+	
Epstein-Barr virus[c]	+	+	±	±	+	
Herpes simplex virus		±		±	±	+
Human herpesvirus type 6	+	±		±		+
Kaposi's sarcoma–associated herpesvirus	+	±			±	+
Hepatitis B and C viruses					+	
Rabies virus[d]				+		
West Nile virus	+			+		
Lymphocytic choriomeningitis virus	+			+	±	
Fungi						
Candida albicans	+	+			+	+
Histoplasma capsulatum	+	+			+	+
Cryptococcus neoformans	+	+		+	±	±
Parasites						
Toxoplasma gondii[e]		+	+	+		
Strongyloides stercoralis[f,g]		+				
Trypanosoma cruzi[g]			+			
Plasmodium falciparum[g]	+					
Schistosoma spp.					+	
Prion Diseases						
Creutzfeldt-Jakob disease (CJD)[h]				+		
Variant CJD/bovine spongiform encephalopathy[i]				+		

[a] +, well documented; ±, less common.
[b] Cytomegalovirus reactivation is prone to occur in the transplanted organ. The same may be true for Kaposi's sarcoma–associated herpesvirus.
[c] Epstein-Barr virus reactivation usually presents as an extranodal proliferation of transformed B cells and can be present either as a diffuse disease or as a mass lesion in a single organ. It can occur in the allograft.
[d] Rabies virus has been transmitted through corneal transplants.
[e] T. *gondii* usually causes disease in the brain. In hematopoietic stem cell transplant recipients, acute pulmonary disease may also occur. Heart transplant recipients develop disease in the allograft.
[f] *Strongyloides* "hyperinfection" may present with pulmonary disease—often associated with gram-negative bacterial pneumonia.
[g] While transmission with organs has been described, it is unusual.
[h] CJD (sporadic and familial) has been transmitted with corneal transplants. Whether it can be transmitted with blood is not known.
[i] Variant CJD can be transmitted with transfused non-leukodepleted blood, posing a theoretical risk to transplant recipients.

series of patients receiving contaminated stem cells, 14% had fever or bacteremia, but none died. Results of cultures performed at the time of cryopreservation and at the time of thawing were helpful in guiding therapy for the recipient.

INFECTIONS IN HEMATOPOIETIC STEM CELL TRANSPLANT RECIPIENTS

Transplantation of hematopoietic stem cells (HSCs) from bone marrow or from peripheral or cord blood for cancer, immunodeficiency, or autoimmune disease results in a transient state of complete immunologic incompetence. Immediately after myeloablative chemotherapy and transplantation, both innate immune cells (phagocytes, natural killer cells) and adaptive immune cells (T and B cells) are absent, and the host is extremely susceptible to infection. The reconstitution that follows transplantation has been likened to maturation of the immune system in neonates. The analogy does not entirely predict infections seen in HSC transplant recipients, however, because the stem cells mature in an old host who has several latent infections already. The choice among

the current variety of methods for obtaining stem cells is determined by availability and by the need to optimize the chances of cure for an individual recipient. One strategy is autologous HSC transplantation, in which the donor and the recipient are the same. After chemotherapy, stem cells are collected and are purged (ex vivo) of residual neoplastic populations. Allogeneic HSC transplantation has the advantage of providing a graft-versus-tumor effect. In this case, the recipient is matched to varying degrees for human leukocyte antigen (HLA) with a donor who may be related or unrelated. In some individuals, nonmyeloablative therapy (mini-allo transplantation) is used and permits recipient cells to persist for some time after transplantation while preserving the graft-versus-tumor effect and sparing the recipient myeloablative therapy. Cord-blood transplantation is increasingly utilized in adults; two independent cord-blood units are typically required for suitable neutrophil engraftment early after transplantation, even though only one of the units is likely to provide long-term engraftment. In each circumstance, a different balance is struck between the toxicity of conditioning therapy, the need for a maximal graft-versus-target effect, short-term and long-term infectious complications, and the risk of graft-versus-host disease (GVHD; acute versus chronic). The various approaches differ in terms of reconstitution speed, cell lineage, and likelihood of GVHD—all factors that can produce distinct effects on the risk of infection after transplantation **(Table 13-2)**. Despite these caveats, most infections occur in a predictable time frame after transplantation **(Table 13-3)**.

BACTERIAL INFECTIONS

In the first month after HSC transplantation, infectious complications are similar to those in granulocytopenic patients receiving chemotherapy for acute leukemia (Chap. 12). Because of the anticipated 1- to 4-week duration of neutropenia and the high rate of bacterial infection in this population, many centers give prophylactic antibiotics to patients upon initiation of myeloablative therapy. Quinolones decrease the incidence of gram-negative bacteremia among these patients. Bacterial infections are common in the first few days after HSC transplantation. The organisms involved are predominantly those found on the skin, mucosa, or IV catheters (*Staphylococcus aureus*, coagulase-negative staphylococci, streptococci) or aerobic

TABLE 13-2

RISK OF INFECTION, BY TYPE OF HEMATOPOIETIC STEM CELL TRANSPLANT

TYPE OF HEMATOPOIETIC STEM CELL TRANSPLANT	SOURCE OF STEM CELLS	RISK OF EARLY INFECTION: NEUTROPHIL DEPLETION	RISK OF LATE INFECTION: IMPAIRED T AND B CELL FUNCTION	RISK OF ONGOING INFECTION: GVHD[a] AND IATROGENIC IMMUNOSUPPRESSION	GRAFT VERSUS TUMOR EFFECT
Autologous	Recipient (self)	High risk; neutrophil recovery sometimes prolonged	~ 1 year	Minimal to no risk of GVHD and late-onset severe infection	None (–)
Syngeneic (genetic twin)	Identical twin	Low risk; 1–2 weeks for recovery	~ 1 year	Minimal risk of GVHD and late-onset severe infection	+/–
Allogeneic related	Sibling	Low risk; 1–2 weeks for recovery	~ 1 year	Minimal to moderate risk of GVHD and late-onset severe infection	++
Allogeneic related	Child/parent (haploidentical)	Intermediate risk; 2–3 weeks for neutrophil recovery	1–2 years	Moderate risk of GVHD and late-onset severe infection	++++
Allogeneic unrelated adult	Unrelated donor	Intermediate risk; 2–3 weeks for neutrophil recovery	1–2 years	High risk of GVHD and late-onset severe infection	++++
Allogeneic unrelated cord blood	Unrelated cord blood units (×2)	Intermediate to high risk; neutrophil recovery sometimes prolonged	Prolonged	Minimal to moderate risk of GVHD and late-onset severe infection	++++
Allogeneic mini (nonmyeloablative)	Donor (transiently coexisting with recipient cells)	Low risk; neutrophil counts close to normal	1–2+ years	Variable risk of GVHD and late-onset severe infection[b]	++++ (but develops slowly)

[a]GVHD, graft-versus-host disease.
[b]Depending on the disparity of the match (major and minor histocompatibility antigens), GVHD may be severe or mild, the requirement for immunosuppression intense or minimal, and the risk of severe late infections coordinate with the degree of immunosuppression.

TABLE 13-3

COMMON SOURCES OF INFECTIONS AFTER HEMATOPOIETIC STEM CELL TRANSPLANTATION

	PERIOD AFTER TRANSPLANTATION		
INFECTION SITE	**EARLY (<1 MONTH)**	**MIDDLE (1–4 MONTHS)**	**LATE (>6 MONTHS)**
Disseminated	Aerobic bacteria (gram-negative, gram-positive)	*Nocardia, Candida*, *Aspergillus*, EBV	Encapsulated bacteria (*Streptococcus pneumoniae, Haemophilus influenzae, Neisseria meningitidis*)
Skin and mucous membranes	HSV	HHV-6	VZV
Lungs	Aerobic bacteria (gram-negative, gram-positive), *Candida, Aspergillus*, other molds, HSV	CMV, seasonal respiratory viruses, *Pneumocystis*, *Toxoplasma*	*Pneumocystis, S. pneumoniae*
Gastrointestinal tract	*Clostridium difficile*	CMV, adenovirus	EBV, CMV
Kidney		BK virus, adenovirus	
Brain	HHV-6	HHV-6, *Toxoplasma*	*Toxoplasma*, JC virus (rare)
Bone marrow	HHV-6		

Abbreviations: CMV, cytomegalovirus; EBV, Epstein-Barr virus; HHV-6, human herpesvirus type 6; HSV, herpes simplex virus; VZV, varicella-zoster virus.

bacteria that colonize the bowel (*Escherichia coli*, *Klebsiella*, *Pseudomonas*). *Bacillus cereus*, although rare, has emerged as a pathogen early after transplantation and can cause meningitis, which is unusual in these patients. Chemotherapy, use of broad-spectrum antibiotics, and delayed reconstitution of humoral immunity place HSC transplant patients at risk for diarrhea and colitis caused by *Clostridium difficile* overgrowth and toxin production.

Beyond the first few days of neutropenia, infections with nosocomial pathogens (e.g., vancomycin-resistant enterococci, *Stenotrophomonas maltophilia*, *Acinetobacter* species, and extended-spectrum β-lactamase-producing gram-negative organisms) as well as with filamentous bacteria (e.g., *Nocardia* species) become more common. Vigilance is indicated, particularly for patients with a history of active or known latent tuberc ulosis, even when they have been appropriately pretreated. Episodes of bacteremia due to encapsulated organisms mark the late posttransplantation period (>6 months after HSC reconstitution); patients who have undergone splenectomy and those with persistent hypogammaglobulinemia are at particular risk.

FUNGAL INFECTIONS

Beyond the first week after transplantation, fungal infections become increasingly common, particularly among patients who have received broad-spectrum antibiotics. As in most granulocytopenic patients, *Candida* infections are most commonly seen in this setting. However, with increased use of prophylactic fluconazole, infections with resistant fungi—in particular, *Aspergillus* and other molds (*Fusarium*, *Scedosporium*, *Penicillium)*—have become more common, prompting some centers to replace fluconazole with agents such as micafungin, voriconazole, and even posaconazole. The role of antifungal prophylaxis with these different agents, in contrast to empirical treatment for suspected (based on positive β-D-glucan assay or galactomannan antigen test) or documented infection, remains controversial (Chap. 12). In patients with GVHD who require prolonged or indefinite courses of glucocorticoids and other immunosuppressive agents [e.g., cyclosporine, tacrolimus (FK 506, Prograf), mycophenolate mofetil (Cellcept), rapamycin (sirolimus, Rapamune), antithymocyte globulin, or anti-CD52 antibody (alemtuzumab, Campath, an antilymphocyte and antimonocyte monoclonal antibody)], there is a high risk of fungal infection (usually with *Candida* or *Aspergillus*), even after engraftment and resolution of neutropenia. These patients are also at high risk for reactivation of latent fungal infection (histoplasmosis, coccidioidomycosis, or blastomycosis) in areas where endemic fungi reside and after involvement in activities such as gardening or caving. Prolonged use of central venous catheters for parenteral nutrition (lipids) increases the risk of fungemia with *Malassezia*. Some centers administer prophylactic antifungal agents to these patients. Because of the high and prolonged risk of *Pneumocystis jiroveci* pneumonia (especially among patients being treated for hematologic malignancies), most patients receive maintenance prophylaxis with trimethoprim-sulfamethoxazole (TMP-SMX) starting 1 month after engraftment and continuing for at least 1 year.

PARASITIC INFECTIONS

The regimen just described for the fungal pathogen *Pneumocystis* may also protect patients seropositive for

the parasite *T. gondii*, which can cause pneumonia, visceral disease (occasionally), and central nervous system (CNS) lesions (more commonly). The advantages of maintaining HSC transplant recipients on daily TMP-SMX for 1 year after transplantation include some protection against *Listeria monocytogenes* and nocardial disease as well as late infections with *Streptococcus pneumoniae* and *Haemophilus influenzae*, which stem from the inability of the immature immune system to respond to polysaccharide antigens.

With increasing international travel, parasitic diseases typically restricted to particular environmental niches may pose a risk of reactivation in certain patients after HSC transplantation. Thus, in recipients with an appropriate history who were not screened and/or treated before transplantation or in patients with recent exposures, evaluation for infection with *Strongyloides*, *Leishmania*, or various parasitic causes of diarrheal illness (*Giardia*, *Cryptosporidium*, microsporidia) may be warranted.

VIRAL INFECTIONS

HSC transplant recipients are susceptible to infection with a variety of viruses, including primary and reactivation syndromes caused by most human herpesviruses **(Table 13-4)** and acute infections caused by viruses that circulate in the community.

Herpes simplex virus

Within the first 2 weeks after transplantation, most patients who are seropositive for HSV-1 excrete the virus from the oropharynx. The ability to isolate HSV declines with time. Administration of prophylactic acyclovir (or valacyclovir) to seropositive HSC transplant recipients has been shown to reduce mucositis and prevent HSV pneumonia (a rare condition reported almost exclusively in allogeneic HSC transplant recipients). Both esophagitis (usually due to HSV-1) and anogenital disease (commonly caused by HSV-2) may be prevented with acyclovir prophylaxis. For further discussion, see Chap. 84.

Varicella-zoster virus

Reactivation of VZV manifests as herpes zoster and may occur within the first month but more commonly occurs several months after transplantation. Reactivation rates are ~40% for allogeneic HSC transplant recipients and 25% for autologous recipients. Localized zoster can spread rapidly in an immunosuppressed patient. Fortunately, disseminated disease can usually be controlled with high doses of acyclovir. Because of frequent dissemination among patients with skin lesions, acyclovir is given prophylactically in some centers to prevent severe disease. Low doses of acyclovir (400 mg orally, three times daily) appear to be effective in preventing reactivation of VZV. However, acyclovir can also suppress the development of VZV-specific immunity. Thus, its administration for only 6 months after transplantation does not prevent zoster from occurring when treatment is stopped. Administration of low doses of acyclovir for an entire year after transplantation is effective and may eliminate most cases of posttransplantation zoster. For further discussion, see Chap. 85.

TABLE 13-4

HERPESVIRUS SYNDROMES OF TRANSPLANT RECIPIENTS

VIRUS	REACTIVATION DISEASE
Herpes simplex virus type 1	Oral lesions Esophageal lesions Pneumonia (only in HSC transplant recipients) Hepatitis (rare)
Herpes simplex virus type 2	Anogenital lesions Hepatitis (rare)
Varicella-zoster virus	Zoster (can disseminate)
Cytomegalovirus	Associated with graft rejection Fever and malaise Bone marrow failure Pneumonitis Gastrointestinal disease
Epstein-Barr virus	B cell lymphoproliferative disease/lymphoma Oral hairy leukoplakia (rare)
Human herpesvirus type 6	Fever Delayed monocyte/platelet engraftment Encephalitis (controversial)
Human herpesvirus type 7	Undefined
Kaposi's sarcoma–associated virus	Kaposi's sarcoma Primary effusion lymphoma (rare) Multicentric Castleman's disease (rare) Marrow aplasia (rare)

Abbreviation: HSC, hematopoietic stem cell.

Cytomegalovirus

The onset of CMV disease (interstitial pneumonia, bone marrow suppression, graft failure, hepatitis/colitis) usually begins 30–90 days after HSC transplantation, when the granulocyte count is adequate but immunologic reconstitution has not occurred. CMV disease rarely develops earlier than 14 days after transplantation and may become evident as late as 4 months after the procedure. It is of greatest concern in the second month after transplantation, particularly in allogeneic HSC transplant recipients. In cases in which the donor marrow is depleted of T cells (to prevent GVHD or eliminate a T cell tumor), the disease may be manifested earlier. The use of alemtuzumab to prevent GVHD in nonmyeloablative transplantation has been associated with an increase in CMV disease. Patients who receive ganciclovir for prophylaxis, preemptive treatment, or treatment (see later) may develop recurrent CMV

infection even later than 4 months after transplantation, as treatment appears to delay the development of the normal immune response to CMV infection. Although CMV disease may present as isolated fever, granulocytopenia, thrombocytopenia, or gastrointestinal disease, the foremost cause of death from CMV infection in the setting of HSC transplantation is pneumonia.

With the standard use of CMV-negative or filtered blood products, primary CMV infection should be a major risk in allogeneic transplantation only when the donor is CMV-seropositive and the recipient is CMV-seronegative. Reactivation disease or superinfection with another strain from the donor is also common in CMV-positive recipients, and most seropositive patients who undergo HSC transplantation excrete CMV, with or without clinical findings. Serious CMV disease is much more common among allogeneic than autologous recipients and is often associated with GVHD. In addition to pneumonia and marrow suppression (and, less often, graft failure), manifestations of CMV disease in HSC transplant recipients include fever with or without arthralgias, myalgias, hepatitis, and esophagitis. CMV ulcerations occur in both the lower and the upper gastrointestinal tract, and it may be difficult to distinguish diarrhea due to GVHD from that due to CMV infection. The finding of CMV in the liver of a patient with GVHD does not necessarily mean that CMV is responsible for hepatic enzyme abnormalities. It is interesting that the ocular and neurologic manifestations of CMV infections, which are common in patients with AIDS, are uncommon in patients who develop disease after transplantation.

Management of CMV disease in HSC transplant recipients includes strategies directed at prophylaxis, preemptive therapy (suppression of silent replication), and treatment of disease. Prophylaxis results in a lower incidence of disease at the cost of treating many patients who otherwise would not require therapy. Because of the high fatality rate associated with CMV pneumonia in these patients and the difficulty of early diagnosis of CMV infection, prophylactic IV ganciclovir (or oral valganciclovir) has been used in some centers and has been shown to abort CMV disease during the period of maximal vulnerability (from engraftment to day 120 after transplantation). Ganciclovir also prevents HSV reactivation and reduces the risk of VZV reactivation; thus acyclovir prophylaxis should be discontinued when ganciclovir is administered. The foremost problem with the administration of ganciclovir relates to adverse effects, which include dose-related bone marrow suppression (thrombocytopenia, leukopenia, anemia, and pancytopenia). Because the frequency of CMV pneumonia is lower among autologous HSC transplant recipients (2–7%) than among allogeneic HSC transplant recipients (10–40%), prophylaxis in the former group will not become the rule until a less toxic oral antiviral agent becomes available.

Preemptive treatment of CMV—that is, initiation of therapy with drugs only after CMV is detected in blood, typically by a nucleic acid amplification test—is used at most centers. The preemptive approach has supplanted prophylactic therapy, or treatment of all seropositive (recipient and/or donor) HSC transplants with an antiviral agent (typically ganciclovir), because of toxic drug side effects (e.g., neutropenia and bone marrow suppression). Quantitative viral load assays, which are not dependent on circulating leukocytes, have supplanted older antigen-based assays for CMV. A positive test (or increasing viral load) prompts the initiation of preemptive therapy with ganciclovir. Preemptive approaches that target patients who have polymerase chain reaction (PCR) evidence of CMV can still lead to unnecessary treatment of many individuals with drugs that have adverse effects on the basis of a laboratory test that is not highly predictive of disease; however, invasive disease, particularly in the form of pulmonary infection, is difficult to treat and is associated with high mortality rates. When prophylaxis or preemptive therapy is stopped, late manifestations of CMV replication may occur, although by then the HSC transplant patient is often equipped with improved graft function and is better able to combat disease.

CMV pneumonia in HSC transplant recipients (unlike that in other clinical settings) is often treated with both IV immunoglobulin (IVIg) and ganciclovir. In patients who cannot tolerate ganciclovir, foscarnet is a useful alternative, although it may produce nephrotoxicity and electrolyte imbalance. When neither ganciclovir nor foscarnet is clinically tolerated, cidofovir can be used; however, its efficacy is less well established, and its side effects include nephrotoxicity. Case reports have suggested that the immunosuppressive agent leflunomide may be active in this setting, but controlled studies are lacking. Transfusion of CMV-specific T cells from the donor has decreased viral load in a small series of patients; this result suggests that immunotherapy may play a role in the treatment of this disease in the future. For further discussion, see Chap. 87.

Human herpesviruses 6 and 7

Human herpesvirus type 6 (HHV-6), the cause of roseola in children, is a ubiquitous herpesvirus that reactivates (as determined by quantitative plasma PCR) in ~50% of HSC transplant recipients 2–4 weeks after transplantation. Reactivation is more common among patients requiring glucocorticoids for GVHD and among those receiving second transplants. Reactivation of HHV-6, primarily type B, may be associated with delayed monocyte and platelet engraftment. Limbic encephalitis developing after transplantation has been associated with HHV-6 in cerebrospinal fluid (CSF). The causality of the association is not well defined: in several cases, plasma viremia was detected long before the onset of encephalitis. Nevertheless, most patients with encephalitis had very high viral loads in plasma at the time of CNS illness, and viral antigen has been detected in hippocampal astrocytes. HHV-6 DNA is sometimes found in lung samples after transplantation. However, its role in pneumonitis is unclear, as co-pathogens are frequently present. While HHV-6 is

susceptible to foscarnet or cidofovir (and possibly to ganciclovir) in vitro, the efficacy of antiviral treatment has not been well studied. Little is known about the related herpesvirus HHV-7 or its role in posttransplantation infection. For further discussion, see Chap. 87.

Epstein-Barr virus

Primary EBV infection can be fatal to HSC transplant recipients; EBV reactivation can cause EBV–B cell lymphoproliferative disease (EBV-LPD), which may also be fatal to patients taking immunosuppressive drugs. Latent EBV infection of B cells leads to several interesting phenomena in HSC transplant recipients. The marrow ablation that occurs as part of the HSC transplantation procedure may sometimes eliminate latent EBV from the host. Infection can then be reacquired immediately after transplantation by transfer of infected donor B cells. Rarely, transplantation from a seronegative donor may result in cure. The recipient is then at risk for a second primary infection.

EBV-LPD can develop in the recipient's B cells (if any survive marrow ablation), but is more likely to be a consequence of outgrowth of infected donor cells. Both lytic replication and latent replication of EBV are more likely during immunosuppression (e.g., they are associated with GVHD and the use of antibodies to T cells). Although less likely in autologous transplantation, reactivation can occur in T cell–depleted autologous recipients (e.g., patients being given antibodies to T cells for the treatment of a T cell lymphoma with marrow depletion). EBV-LPD, which can become apparent as early as 1–3 months after engraftment, can cause high fevers and cervical adenopathy resembling the symptoms of infectious mononucleosis but more commonly presents as an extranodal mass. The incidence of EBV-LPD among allogeneic HSC transplant recipients is 0.6–1%, which contrasts with figures of ~5% for renal transplant recipients and up to 20% for cardiac transplant patients. In all cases, EBV-LPD is more likely to occur with high-dose, prolonged immunosuppression, especially that caused by the use of antibodies to T cells, glucocorticoids, and calcineurin inhibitors (e.g., cyclosporine, tacrolimus). Ganciclovir, administered to preempt CMV disease, may reduce EBV lytic replication and thereby diminish the pool of B cells that can become newly infected and give rise to LPD. Increasing evidence indicates that replacement of calcineurin inhibitors with mTor inhibitors (e.g., rapamycin) exerts an antiproliferative effect on EBV-infected B cells that decreases the likelihood of developing LPD or unrelated proliferative disorders associated with transplant-related immunosuppression.

PCR can be used to monitor EBV production after HSC transplantation. High or increasing viral loads predict an enhanced likelihood of developing EBV-LPD and should prompt rapid reduction of immunosuppression and search for nodal or extra nodal disease. If reduction of immunosuppression does not have the desired effect, administration of a monoclonal antibody to CD20 (rituximab or others) for the treatment of B cell lymphomas that express this surface protein has elicited dramatic responses and currently constitutes first-line therapy for CD20-positive EBV-LPD. However, long-term suppression of new antibody responses accompanies therapy, and recurrences are not infrequent. Additional B cell–directed antibodies, including anti-CD22, are under study. The role of antiviral drugs is uncertain because no available agents have been documented to have activity against the different forms of latent EBV infection. Diminishing lytic replication and virion production in these patients would theoretically produce a statistical decrease in the frequency of latent disease by decreasing the number of virions available to cause additional infection. In case reports and small animal studies, ganciclovir and/or high-dose zidovudine (AZT), together with other agents, has been used to eradicate EBV-LPD and CNS lymphomas, another EBV-associated complication of transplantation. Both interferon and retinoic acid have been employed in the treatment of EBV-LPD, as has IVIg, but no large prospective studies have assessed the efficacy of any of these agents. Several additional drugs are undergoing preclinical evaluation. Standard chemotherapeutic regimens are used if disease persists after reduction of immunosuppressive agents and administration of antibodies. EBV-specific T cells generated from the donor have been used experimentally to prevent and to treat EBV-LPD in allogeneic recipients, and efforts are under way to increase the activity and specificity of ex vivo–generated T cells. For further discussion, see Chap. 86.

Human herpesvirus 8 (KSHV)

The EBV-related gammaherpesvirus KSHV, which is causally associated with Kaposi's sarcoma, primary effusion lymphoma, and multicentric Castleman's disease, has rarely resulted in disease in HSC transplant recipients, although some cases of virus-associated marrow aplasia have been reported in the peritransplantation period. The relatively low seroprevalence of KSHV in the population and the limited duration of profound T cell suppression after HSC transplantation provide a plausible explanation for the currently low incidence of KSHV disease compared with that in recipients of solid organ transplants and patients with HIV infection. For further discussion, see Chap. 87.

Other (nonherpes) viruses

The diagnosis of pneumonia in HSC transplant recipients poses special problems. Because patients have undergone treatment with multiple chemotherapeutic agents and sometimes irradiation, their differential diagnosis should include—in addition to bacterial and fungal pneumonia—CMV pneumonitis, pneumonia of other viral etiologies, parasitic pneumonia, diffuse alveolar

hemorrhage, and chemical- or radiation-associated pneumonitis. Since fungi and viruses [e.g., influenza A and B viruses, respiratory syncytial virus (RSV), parainfluenza virus (types 1–4), adenovirus, enterovirus, bocavirus, human metapneumovirus, coronavirus, and rhinovirus (increasingly detected by multiplex PCR)] can also cause pneumonia in this setting, it is important to diagnose CMV specifically (see "Cytomegalovirus," earlier in chapter). *M. tuberculosis* has been an uncommon cause of pneumonia among HSC transplant recipients in Western countries (accounting for <0.1–0.2% of cases), but is common in Hong Kong (5.5%) and in countries where the prevalence of tuberculosis is high. The recipient's exposure history is clearly critical in an assessment of post-transplantation infections.

Both RSV and parainfluenza viruses, particularly type 3, can cause severe or even fatal pneumonia in HSC transplant recipients. Infections with both of these agents sometimes occur as disastrous nosocomial epidemics. Therapy with palivizumab or ribavirin for RSV infection remains controversial. Influenza also occurs in HSC transplant recipients and generally mirrors the presence of infection in the community. Progression to pneumonia is more common when infection occurs early after transplantation and when the recipient is lymphopenic. Several drugs are available for the treatment of influenza. Amantadine and rimantadine have limited effects, primarily reducing symptoms and shortening the duration of illness caused by sensitive strains of influenza A virus. The neuraminidase inhibitors oseltamivir (oral) and zanamivir (aerosolized) are active against both influenza A virus and influenza B virus and are a reasonable treatment option. Parenteral forms of neuraminidase inhibitors such as peramivir (intravenous) are undergoing clinical trials. Peramivir is currently available through the Centers for Disease Control and Prevention (CDC) for the treatment of severe H1N1 influenza. An important preventive measure is immunization of household members, hospital staff members, and other frequent contacts. Adenoviruses can be isolated from HSC transplant recipients at rates varying from 5% to ≤18%. Like CMV infection, adenovirus infection usually occurs in the first to third month after transplantation and is often asymptomatic, although pneumonia, hemorrhagic cystitis/nephritis, severe gastroenteritis with hemorrhage, and fatal disseminated infection have been reported. A role for cidofovir therapy has been suggested, but the efficacy of this agent is unproven in adenovirus infection.

Although diverse respiratory viruses can sometimes cause severe pneumonia and respiratory failure in HSC transplant recipients, mild or even asymptomatic infection may be more common. For example, rhinoviruses and coronaviruses are frequent co-pathogens in HSC transplant recipients; however, whether they independently contribute to significant pulmonary infection is not known. At present, the overall contribution to the burden of lower respiratory tract disease in HSC transplant recipients for the secondary group of viral respiratory pathogens listed earlier is unknown.

Infections with parvovirus B19 (presenting as anemia or occasionally as pancytopenia) and disseminated enteroviruses (sometimes fatal) can occur. Parvovirus B19 infection can be treated with IVIg (Chap. 89). Intranasal pleconaril, a capsid-binding agent, is being studied for the treatment of enterovirus (and rhinovirus) infection.

Rotaviruses are a common cause of gastroenteritis in HSC transplant recipients. The polyomavirus BK virus is found at high titers in the urine of patients who are profoundly immunosuppressed. BK viruria may be associated with hemorrhagic cystitis in these patients. Compared with the incidence among patients with impaired T cell function due to HIV infection, progressive multifocal leukoencephalopathy caused by the related JC virus is relatively rare among HSC transplant recipients (Chap. 31). When transmitted by mosquitoes or by blood transfusion, West Nile virus can cause encephalitis and death after HSC transplantation.

INFECTIONS IN SOLID ORGAN TRANSPLANT RECIPIENTS

Rates of morbidity and mortality among recipients of solid organ transplants (SOTs) are reduced by the use of effective antibiotics. The organisms that cause acute infections in recipients of SOTs are different from those that infect HSC transplant recipients because SOT recipients do not go through a period of neutropenia. As the transplantation procedure involves major surgery, however, SOT recipients are subject to infections at anastomotic sites and to wound infections. Compared with HSC transplant recipients, SOT patients are immunosuppressed for longer periods (often permanently). Thus they are susceptible to many of the same organisms as patients with chronically impaired T cell immunity (Chap. 12, especially Table 12-1). Moreover, the persistent HLA mismatch between recipient immune cells (e.g., effector T cells) and the donor organ (allograft) places the organ at permanently increased risk of infection.

During the early period (<1 month after transplantation; **Table 13-5**), infections are most commonly caused by extracellular bacteria (staphylococci, streptococci, enterococci, *E. coli*, other gram-negative organisms), which often originate in surgical wound or anastomotic sites. The type of transplant largely determines the spectrum of infection. In subsequent weeks, the consequences of the administration of agents that suppress cell-mediated immunity become apparent, and acquisition—or, more commonly, reactivation—of viruses, mycobacteria, endemic fungi, and parasites (from the recipient or from the transplanted organ) can occur. CMV infection is often a problem, particularly in the first 6 months after transplantation, and may present as severe systemic disease or as infection of the transplanted organ. HHV-6 reactivation (assessed by plasma PCR) occurs within the first 2–4 weeks after transplantation and may be associated with fever, leukopenia, and very rare cases of encephalitis. Data suggest that replication of HHV-6 and HHV-7 may exacerbate CMV-induced disease. CMV is associated not only with generalized immunosuppression but also with

organ-specific, rejection-related syndromes: glomerulopathy in kidney transplant recipients, bronchiolitis obliterans in lung transplant recipients, vasculopathy in heart transplant recipients, and the vanishing bile duct syndrome in liver transplant recipients. A complex interplay between increased CMV replication and enhanced graft rejection is well established: elevated immunosuppression leads to increased CMV replication, which is associated with graft rejection. For this reason, considerable attention has been focused on the diagnosis, prophylaxis, and treatment of CMV infection in SOT recipients. Early transmission of West Nile virus to transplant recipients from a donated organ or transfused blood has been reported; however, the risk of West Nile acquisition (at least in transfused blood) has been reduced by implementation of screening procedures. In rare instances, rabies virus and lymphocytic choriomeningitis virus have also been transmitted in this setting; although accompanied by distinct clinical syndromes, both viral infections have resulted in fatal encephalitis. As screening for unusual viruses is not routine, only vigilant assessment of the prospective donor is likely to prevent the use of an infected organ.

Beyond 6 months after transplantation, infections characteristic of patients with defects in cell-mediated immunity—e.g., infections with *Listeria*, *Nocardia*, *Rhodococcus*, mycobacteria, various fungi, and other intracellular pathogens—may be a problem. International patients and global travelers may experience reactivation of dormant infections with trypanosomes, *Leishmania*, *Plasmodium*, *Strongyloides*, and other parasites. Reactivation of latent *M. tuberculosis* infection, while rare in Western nations, is far more common among persons from developing countries. The recipient is typically the source, although reactivation and spread from the donor organ can occur. While pulmonary disease remains most common,

TABLE 13-5

COMMON INFECTIONS AFTER SOLID ORGAN TRANSPLANTATION, BY SITE OF INFECTION

	PERIOD AFTER TRANSPLANTATION		
INFECTED SITE	**EARLY (<1 MONTH)**	**MIDDLE (1–4 MONTHS)**	**LATE (>6 MONTHS)**
Donor organ	Bacterial and fungal infections of the graft, anastomotic site, and surgical wound	CMV infection	EBV infection (may present in allograft organ)
Systemic	Bacteremia and candidemia (often resulting from central venous catheter colonization)	CMV infection (fever, bone marrow suppression)	CMV infection, especially in patients given early post-transplantation prophylaxis; EBV proliferative syndromes (may occur in donor organs)
Lung	Bacterial aspiration pneumonia with prevalent nosocomial organisms associated with intubation and sedation (highest risk in lung transplantation)	*Pneumocystis* infection; CMV pneumonia (highest risk in lung transplantation); *Aspergillus* infection (highest risk in lung transplantation)	*Pneumocystis* infection; granulomatous lung diseases (nocardiae, reactivated fungal and mycobacterial diseases)
Kidney	Bacterial and fungal (*Candida*) infections (cystitis, pyelonephritis) associated with urinary tract catheters (highest risk in kidney transplantation)	Renal transplantation: BK virus infection (associated with nephropathy); JC virus infection	Renal transplantation: bacteria (late urinary tract infections, usually not associated with bacteremia); BK virus (nephropathy, graft failure, generalized vasculopathy)
Liver and biliary tract	Cholangitis	CMV hepatitis	CMV hepatitis
Heart		*Toxoplasma gondii* infection (highest risk in heart transplantation)	*T. gondii* (highest risk in heart transplantation)
Gastrointestinal tract	Peritonitis, especially after liver transplantation	Colitis secondary to *Clostridium difficile* infection (risk can persist)	Colitis secondary to *C. difficile* infection (risk can persist)
Central nervous system		*Listeria* (meningitis); *T. gondii* infection	*Listeria* meningitis; *Cryptococcus* meningitis; *Nocardia* abscess; JC virus–associated PML

Abbreviations: CMV, cytomegalovirus, EBV, Epstein-Barr virus, PML, progressive multifocal leukoencephalopathy.

atypical sites may be involved and mortality rates can be high (up to 30%). Elimination of these late infections will not be possible until the patient develops specific tolerance to the transplanted organ in the absence of drugs that lead to generalized immunosuppression. Meanwhile, vigilance, prophylaxis/preemptive therapy (when indicated), and rapid diagnosis and treatment of infections can be lifesaving in SOT recipients, who, unlike most HSC transplant recipients, continue to be immunosuppressed.

SOT recipients are susceptible to EBV-LPD from as early as 2 months to many years after transplantation. The prevalence of this complication is increased by potent and prolonged use of T cell–suppressive drugs. Decreasing the degree of immunosuppression may in some cases reverse the condition. Among SOT patients, those with heart and lung transplants—who receive the most intensive immunosuppressive regimens—are most likely to develop EBV-LPD, particularly in the lungs. Although the disease usually originates in recipient B cells, several cases of donor origin, particularly in the transplanted organ, have been noted. High organ-specific content of B lymphoid tissues (e.g., bronchial-associated lymphoid tissue in the lung), anatomic factors (e.g., lack of access of host T cells to the transplanted organ because of disturbed lymphatics), and differences in major histocompatibility loci between the host T cells and the organ (e.g., lack of cell migration or lack of effective T cell/macrophage cooperation) may result in defective elimination of EBV-infected B cells. SOT recipients are also highly susceptible to the development of Kaposi's sarcoma and, less frequently, to the B cell–proliferative disorders associated with KSHV, such as primary effusion lymphoma and multicentric Castleman's disease. Kaposi's sarcoma is 550–1000 times more common in SOT recipients than in the general population, can develop very rapidly after transplantation, and can also occur in the allograft. However, because the seroprevalence of KSHV is very low in Western countries, Kaposi's sarcoma is not often observed. Data suggest that a switch of immunosuppressive agents—from calcineurin inhibitors (cyclosporine, tacrolimus) to mTor pathway active agents (sirolimus, everolimus)—after adequate wound healing may significantly reduce the likelihood of developing Kaposi's sarcoma and perhaps of EBV-LPD and certain other posttransplantation malignancies.

KIDNEY TRANSPLANTATION

(See Table 13-5)

Early infections

Bacteria often cause infections that develop in the period immediately after kidney transplantation. There is a role for perioperative antibiotic prophylaxis, and many centers give cephalosporins to decrease the risk of postoperative complications. Urinary tract infections developing soon after transplantation are usually related to anatomic alterations resulting from surgery. Such early infections may require prolonged treatment (e.g., 6 weeks of antibiotic administration for pyelonephritis). Urinary tract infections that occur >6 months after transplantation may be treated for shorter periods because they do not seem to be associated with the high rate of pyelonephritis or relapse seen with infections that occur in the first 3 months.

Daily prophylaxis with one double-strength tablet of TMP-SMX (800 mg of sulfamethoxazole; 160 mg of trimethoprim) for the first 4–6 months after transplantation decreases the incidence of early and middle-period infections (see next, Table 13-5, and **Table 13-6**).

Middle-period infections

Because of continuing immunosuppression, kidney transplant recipients are predisposed to lung infections characteristic of those in patients with T cell deficiency (i.e., infections with intracellular bacteria, mycobacteria, nocardiae, fungi, viruses, and parasites). A high mortality rate associated with *Legionella pneumophila* infection (Chap. 52) led to the closing of renal transplant units in hospitals with endemic legionellosis.

About 50% of all renal transplant recipients presenting with fever 1–4 months after transplantation have evidence of CMV disease; CMV itself accounts for the fever in more than two-thirds of cases and thus is the predominant pathogen during this period. CMV infection (Chap. 87) may also present as arthralgias, myalgias, or organ-specific symptoms. During this period, this infection may represent primary disease (in the case of a seronegative recipient of a kidney from a seropositive donor) or may represent reactivation disease or superinfection. Patients may have atypical lymphocytosis. Unlike immunocompetent patients, however, they rarely have lymphadenopathy or splenomegaly. Therefore, clinical suspicion and laboratory confirmation are necessary for diagnosis. The clinical syndrome may be accompanied by bone marrow suppression (particularly leukopenia). CMV also causes glomerulopathy and is associated with an increased incidence of other opportunistic infections. Because of the frequency and severity of disease, a considerable effort has been made to prevent and treat CMV infection in renal transplant recipients. An immune globulin preparation enriched with antibodies to CMV was used by many centers in the past in an effort to protect the group at highest risk for severe infection (seronegative recipients of seropositive kidneys). However, with the development of effective oral antiviral agents, CMV immune globulin is no longer used. Ganciclovir (valganciclovir) is beneficial when prophylaxis is indicated and for the treatment of serious CMV disease. The availability of valganciclovir has allowed most centers to move to oral prophylaxis for transplant recipients. Infection with the other herpesviruses may become evident within 6 months after transplantation or later. Early after transplantation, HSV may cause either oral or anogenital lesions that are usually responsive to acyclovir. Large ulcerating lesions in the anogenital area may lead to bladder

TABLE 13-6

PROPHYLACTIC REGIMENS COMMONLY USED TO DECREASE RISK OF INFECTION IN TRANSPLANT RECIPIENTS

RISK FACTOR	ORGANISM	PROPHYLACTIC DRUG	EXAMINATION(S)[a]
Travel to or residence in area with known risk of endemic fungal infection	*Histoplasma, Blastomyces, Coccidioides*	Consider imidazoles based on clinical and laboratory assessment	Chest radiography, antigen testing, serology
Latent herpesviruses	HSV, VZV, CMV, EBV	Acyclovir after HSC transplantation to prevent HSV and VZV infection; ganciclovir for CMV (?EBV/?KSHV) in some settings	Serologic tests for HSV, VZV, CMV, HHV-6, EBV, KSHV; PCR
Latent fungi and parasites	*Pneumocystis jiroveci, Toxoplasma gondii*	Trimethoprim-sulfamethoxazole (dapsone or atovaquone)	Serologic test for *Toxoplasma*
History of exposure to active or latent tuberculosis	*Mycobacterium tuberculosis*	Isoniazid if recent conversion or positive chest imaging and/or no previous treatment	Chest imaging; TST and/or cell-based assay

[a]Serologic examination, TST (tuberculin skin test), and interferon assays may be less reliable after transplantation.
Abbreviations: CMV, cytomegalovirus; EBV, Epstein-Barr virus; HHV-6, human herpesvirus type 6; HSC, hematopoietic stem cell; HSV, herpes simplex virus; KSHV, Kaposi's sarcoma–associated herpesvirus; PCR, polymerase chain reaction; VZV, varicella-zoster virus.

and rectal dysfunction as well as predisposing to bacterial infection. VZV may cause fatal disseminated infection in nonimmune kidney transplant recipients, but in immune patients reactivation zoster usually does not disseminate outside the dermatome; thus disseminated VZV infection is a less fearsome complication in kidney transplantation than in HSC transplantation. HHV-6 reactivation may take place and (although usually asymptomatic) may be associated with fever, rash, marrow suppression, or rarely encephalitis.

EBV disease is more serious; it may present as an extranodal proliferation of B cells that invade the CNS, nasopharynx, liver, small bowel, heart, and other organs, including the transplanted kidney. The disease is diagnosed by the finding of a mass of proliferating EBV-positive B cells. The incidence of EBV-LPD is higher among patients who acquire EBV infection from the donor and among patients given high doses of cyclosporine, tacrolimus, glucocorticoids, and anti–T cell antibodies. Disease may regress once immunocompetence is restored. KSHV infection can be transmitted with the donor kidney and result in development of Kaposi's sarcoma, although it more often represents reactivation of latent infection of the recipient. Kaposi's sarcoma often appears within 1 year after transplantation, although the range of onset is wide (1 month to ~20 years). Avoidance of immunosuppressive agents that inhibit calcineurin has been associated with less Kaposi's sarcoma, less EBV disease, and even less CMV replication. The use of rapamycin (sirolimus) has independently led to regression of Kaposi's sarcoma.

The papovaviruses BK virus and JC virus (polyomavirus hominis types 1 and 2) have been cultured from the urine of kidney transplant recipients (as they have from that of HSC transplant recipients) in the setting of profound immunosuppression. High levels of BK virus replication detected by PCR in urine and blood are predictive of pathology, especially in the setting of renal transplantation. JC virus may rarely cause similar disease in kidney transplantation. Urinary excretion of BK virus and BK viremia are associated with the development of ureteral strictures, polyomavirus-associated nephropathy (1–10% of renal transplant recipients), and (less commonly) generalized vasculopathy. Timely detection and early reduction of immunosuppression are critical and can reduce rates of graft loss related to polyomavirus-associated nephropathy from 90% to 10–30%. Therapeutic responses to IVIg, quinolones, leflunomide, and cidofovir have been reported, but the efficacy of these agents has not been substantiated through adequate clinical study. Most centers approach the problem by reducing immunosuppression in an effort to enhance host immunity and decrease viral titers. JC virus is associated with rare cases of progressive multifocal leukoencephalopathy. Adenoviruses may persist and cause hemorrhagic nephritis/cystitis with continued immunosuppression in these patients, but disseminated disease as seen in HSC transplant recipients is much less common.

Kidney transplant recipients are also subject to infections with other intracellular organisms. These patients may develop pulmonary infections with *Mycobacterium*, *Aspergillus*, and *Mucor* species as well as infections with other pathogens in which the T cell/macrophage axis plays an important role. *Listeria monocytogenes* is a common cause of bacteremia ≥1 month after renal transplantation and should be seriously considered in renal transplant recipients presenting with fever and headache.

Kidney transplant recipients may develop *Salmonella* bacteremia, which can lead to endovascular infections and require prolonged therapy. Pulmonary infections with *Pneumocystis* are common unless the patient is maintained on TMP-SMX prophylaxis. *Nocardia* infection (Chap. 67) may present in the skin, bones, and lungs or in the CNS, where it usually takes the form of single or multiple brain abscesses. Nocardiosis generally occurs ≥1 month after transplantation and may follow immunosuppressive treatment for an episode of rejection. Pulmonary manifestations most commonly consist of localized disease with or without cavities, but the disease may be disseminated. The diagnosis is made by culture of the organism from sputum or from the involved nodule. As with *Pneumocystis*, prophylaxis with TMP-SMX is often efficacious in the prevention of disease.

Toxoplasmosis can occur in seropositive patients but is less common than in other transplant settings, usually developing in the first few months after kidney transplantation. Again, TMP-SMX is helpful in prevention. In endemic areas, histoplasmosis, coccidioidomycosis, and blastomycosis may cause pulmonary infiltrates or disseminated disease.

Late infections

Late infections (>6 months after kidney transplantation) may involve the CNS and include CMV retinitis as well as other CNS manifestations of CMV disease. Patients (particularly those whose immunosuppression has been increased) are at risk for subacute meningitis due to *Cryptococcus neoformans*. Cryptococcal disease may present in an insidious manner (sometimes as a skin infection before the development of clear CNS findings). *Listeria* meningitis may have an acute presentation and requires prompt therapy to avoid a fatal outcome. TMP-SMX prophylaxis may reduce the frequency of Listeria infections.

Patients who continue to take glucocorticoids are predisposed to ongoing infection. "Transplant elbow," a recurrent bacterial infection in and around the elbow that is thought to result from a combination of poor tensile strength of the skin of steroid-treated patients and steroid-induced proximal myopathy, requires patients to push themselves up with their elbows to get out of chairs. Bouts of cellulitis (usually caused by *S. aureus*) recur until patients are provided with elbow protection.

Kidney transplant recipients are susceptible to invasive fungal infections, including those due to *Aspergillus* and *Rhizopus*, which may present as superficial lesions before dissemination. Mycobacterial infection (particularly that with *Mycobacterium marinum*) can be diagnosed by skin examination. Infection with *Prototheca wickerhamii* (an achlorophyllic alga) has been diagnosed by skin biopsy. Warts caused by human papillomaviruses (HPVs) are a late consequence of persistent immunosuppression; imiquimod or other forms of local therapy are usually satisfactory. Merkel cell carcinoma, a rare and aggressive neuroendocrine skin tumor the frequency of which is increased fivefold in elderly SOT (especially kidney) recipients, has been linked to a novel polyoma virus (Merkel cell polyomavirus).

Notably, although BK virus replication and virus-associated disease can be detected far earlier, the median time to clinical diagnosis of polyomavirus-associated nephropathy is ~300 days, qualifying it as a late-onset disease. With establishment of better screening procedures (e.g., blood PCR), it is likely that this disease will be detected earlier (see "Middle-Period Infections," earlier in the chapter).

HEART TRANSPLANTATION

Early infections

Sternal wound infection and mediastinitis are early complications of heart transplantation. An indolent course is common, with fever or a mildly elevated white blood cell count preceding the development of site tenderness or drainage. Clinical suspicion based on evidence of sternal instability and failure to heal may lead to the diagnosis. Common microbial residents of the skin (e.g., *S. aureus*, including methicillin-resistant strains, and *Staphylococcus epidermidis*) as well as gram-negative organisms (e.g., *Pseudomonas aeruginosa*) and fungi (e.g., *Candida*) are often involved. In rare cases, mediastinitis in heart transplant recipients can also be due to *Mycoplasma hominis* (Chap. 80). Since this organism requires an anaerobic environment for growth and may be difficult to see on conventional medium, the laboratory should be alerted that *M. hominis* infection is suspected. *M. hominis* mediastinitis has been cured with a combination of surgical debridement (sometimes requiring muscle-flap placement) and the administration of clindamycin and tetracycline. Organisms associated with mediastinitis may sometimes be cultured from pericardial fluid.

Middle-period infections

T. gondii (Chap. 124) residing in the heart of a seropositive donor may be transmitted to a seronegative recipient. Thus serologic screening for *T. gondii* infection is important before and in the months after cardiac transplantation. Rarely, active disease can be introduced at the time of transplantation. The overall incidence of toxoplasmosis is so high in the setting of heart transplantation that some prophylaxis is always warranted. Although alternatives are available, the most frequently used agent is TMP-SMX, which prevents infection with *Pneumocystis* as well as with *Nocardia* and several other bacterial pathogens. CMV also has been transmitted by heart transplantation. *Toxoplasma*, *Nocardia*, and *Aspergillus* can cause CNS infections. *L. monocytogenes* meningitis should be considered in heart transplant recipients with fever and headache.

CMV infection is associated with poor outcomes after heart transplantation. The virus is usually detected 1–2 months after transplantation, causes early signs and laboratory abnormalities (usually fever and atypical lymphocytosis or leukopenia and thrombocytopenia) at 2–3 months, and can produce severe disease (e.g., pneumonia) at 3–4 months. An interesting observation is that seropositive recipients usually develop viremia faster than patients whose primary CMV infection

is a consequence of transplantation. Between 40% and 70% of patients develop symptomatic CMV disease in the form of (1) CMV pneumonia, the most likely form to be fatal; (2) CMV esophagitis and gastritis, sometimes accompanied by abdominal pain with or without ulcerations and bleeding; and (3) the CMV syndrome, consisting of CMV in the blood along with fever, leukopenia, thrombocytopenia, and hepatic enzyme abnormalities. Ganciclovir is efficacious in the treatment of CMV infection; prophylaxis with ganciclovir or possibly with other antiviral agents, as described for renal transplantation, may reduce the overall incidence of CMV-related disease.

Late infections

EBV infection usually presents as a lymphoma-like proliferation of B cells late after heart transplantation, particularly in patients maintained on intense immunosuppressive therapy. A subset of heart and heart-lung transplant recipients may develop early fulminant EBV-LPD (within 2 months). Treatment includes the reduction of immunosuppression (if possible), the use of glucocorticoid and calcineurin inhibitor–sparing regimens, and the consideration of therapy with anti–B cell antibodies (rituximab and possibly others). Immunomodulatory and antiviral agents continue to be studied. Ganciclovir prophylaxis for CMV disease may indirectly reduce the risk of EBV-LPD through reduced spread of replicating EBV to naïve B cells. Aggressive chemotherapy is a last resort, as discussed earlier for HSC transplant recipients. KSHV-associated disease, including Kaposi's sarcoma and primary effusion lymphoma, has been reported in heart transplant recipients. GVHD prophylaxis with sirolimus may decrease the risk of both rejection and outgrowth of KSHV-infected cells. Prophylaxis for *Pneumocystis* infection is required for these patients (see "Lung Transplantation, Late Infections," next).

LUNG TRANSPLANTATION

Early infections

It is not surprising that lung transplant recipients are predisposed to the development of pneumonia. The combination of ischemia and the resulting mucosal damage, together with accompanying denervation and lack of lymphatic drainage, probably contributes to the high rate of pneumonia (66% in one series). The prophylactic use of high doses of broad-spectrum antibiotics for the first 3–4 days after surgery may decrease the incidence of pneumonia. Gram-negative pathogens (Enterobacteriaceae and *Pseudomonas* species) are troublesome in the first 2 weeks after surgery (the period of maximal vulnerability). Pneumonia can also be caused by *Candida* (possibly as a result of colonization of the donor lung), *Aspergillus*, and *Cryptococcus*.

Mediastinitis may occur at an even higher rate among lung transplant recipients than among heart transplant recipients and most commonly develops within 2 weeks of surgery. In the absence of prophylaxis, pneumonitis due to CMV (which may be transmitted as a consequence of transplantation) usually presents between 2 weeks and 3 months after surgery, with primary disease occurring later than reactivation disease.

Middle-period infections

The incidence of CMV infection, either reactivated or primary, is 75–100% if either the donor or the recipient is seropositive for CMV. CMV-induced disease after solid organ transplantation appears to be most severe in recipients of lung and heart-lung transplants. Whether this severity relates to the mismatch in lung antigen presentation and host immune cells or is attributable to nonimmunologic factors is not known. More than half of lung transplant recipients with symptomatic CMV disease have pneumonia. Difficulty in distinguishing the radiographic picture of CMV infection from that of other infections or from organ rejection further complicates therapy. CMV can also cause bronchiolitis obliterans in lung transplants. The development of pneumonitis related to HSV has led to the prophylactic use of acyclovir. Such prophylaxis may also decrease rates of CMV disease, but ganciclovir is more active against CMV and is also active against HSV. The prophylaxis of CMV infection with IV ganciclovir—or increasingly with valganciclovir, the oral alternative—is recommended for lung transplant recipients. Antiviral alternatives are discussed in the earlier section on HSC transplantation. Although the overall incidence of serious disease is decreased during prophylaxis, late disease may occur when prophylaxis is stopped—a pattern observed increasingly in recent years. With recovery from peritransplantation complications and, in many cases, a decrease in immunosuppression, the recipient is often better equipped to combat late infection.

Late infections

The incidence of *Pneumocystis* infection (which may present with a paucity of findings) is high among lung and heart-lung transplant recipients. Some form of prophylaxis for *Pneumocystis* pneumonia is indicated in all organ transplant situations (Table 13-6). Prophylaxis with TMP-SMX for 12 months after transplantation may be sufficient to prevent *Pneumocystis* disease in patients whose immunosuppression is not increased.

As in other transplant recipients, infection with EBV may cause either a mononucleosis-like syndrome or EBV-LPD. The tendency of the B cell blasts to present in the lung appears to be greater after lung transplantation than after the transplantation of other organs, possibly because of a rich source of B cells in bronchial-associated lymphoid tissue. Reduction of immunosuppression and switching of regimens, as discussed in earlier sections, cause remission in some cases, but airway compression can be fatal and more rapid intervention may therefore become necessary. The approach to EBV-LPD is similar to that described in other sections.

LIVER TRANSPLANTATION

Early infections

As in other transplantation settings, early bacterial infections are a major problem after liver transplantation. Many centers administer systemic broad-spectrum antibiotics for the first 24 h or sometimes longer after surgery, even in the absence of documented infection. However, despite prophylaxis, infectious complications are common and correlate with the duration of the surgical procedure and the type of biliary drainage. An operation lasting >12 h is associated with an increased likelihood of infection. Patients who have a choledochojejunostomy with drainage of the biliary duct to a Roux-en-Y jejunal bowel loop have more fungal infections than those whose bile is drained via a choledochocholedochostomy with anastomosis of the donor common bile duct to the recipient common bile duct.

Peritonitis and intraabdominal abscesses are common complications of liver transplantation. Bacterial peritonitis or localized abscesses may result from biliary leaks. Early leaks are even more common with live-donor liver transplants. Peritonitis in liver transplant recipients is often polymicrobial, commonly involving enterococci, aerobic gram-negative bacteria, staphylococci, anaerobes, *Candida*, or sometimes other invasive fungi. Only one-third of patients with intraabdominal abscesses have bacteremia. Abscesses within the first month after surgery may occur not only in and around the liver but also in the spleen, pericolic area, and pelvis. Treatment includes antibiotic administration and drainage as necessary.

Liver transplant patients have a high incidence of fungal infections, and the occurrence of fungal (often candidal) infection correlates with preoperative use of glucocorticoids, long duration of treatment with antibacterial agents, and posttransplantation use of immunosuppressive agents. Many centers give fluconazole prophylactically in this setting.

Middle-period infections

The development of postsurgical biliary stricture predisposes patients to cholangitis. The incidence of strictures is increased in live-donor liver transplantation. Transplant recipients who develop cholangitis may have high spiking fevers and rigors but often lack the characteristic signs and symptoms of classic cholangitis, including abdominal pain and jaundice. Although these findings may suggest graft rejection, rejection is typically accompanied by marked elevation of liver function enzymes. In contrast, in cholangitis in transplant recipients, results of liver function tests (with the possible exception of alkaline phosphatase levels) are often within the normal range. Definitive diagnosis of cholangitis in liver transplant recipients requires demonstration of aggregated neutrophils in bile duct biopsy specimens. Unfortunately, invasive studies of the biliary tract (either T-tube cholangiography or endoscopic retrograde cholangiopancreatography) may themselves lead to cholangitis. For this reason, many clinicians recommend an empirical trial of therapy with antibiotics covering gram-negative organisms and anaerobes before these procedures are undertaken as well as antibiotic coverage if procedures are eventually performed.

Reactivation of viral hepatitis is a common complication of liver transplantation (Chap. 95). Recurrent hepatitis B and C infections, for which transplantation may be performed, are problematic. To prevent hepatitis B virus reinfection, prophylaxis with an optimal antiviral agent or combination of agents (lamivudine, adefovir, entecavir) and hepatitis B immune globulin is currently recommended, although the optimal dose, route, and duration of therapy remain controversial. Success in preventing reinfection with hepatitis B virus has increased in recent years; in contrast, reinfection of the graft with hepatitis C virus occurs in all patients, with a variable time frame. Studies of aggressive pretransplantation treatment of selected recipients with antiviral agents and prophylactic/preemptive regimens are ongoing. However, early initiation of treatment for histologically documented disease with a combination of ribavirin and pegylated interferon has produced sustained responses at rates in the range of 25–40%. Several protease and polymerase inhibitors that block production of hepatitis C virus as well as a monoclonal antibody to the virus are undergoing preclinical and clinical trials.

As in other transplantation settings, reactivation disease with herpesviruses is common (Table 13-4). Herpesviruses can be transmitted in donor organs. Although CMV hepatitis occurs in ~4% of liver transplant recipients, it is usually not so severe as to require retransplantation. Without prophylaxis, CMV disease develops in the majority of seronegative recipients of organs from CMV-positive donors, but fatality rates are lower among liver transplant recipients than among lung or heart-lung transplant recipients. Disease due to CMV can also be associated with the vanishing bile duct syndrome after liver transplantation. Patients respond to treatment with ganciclovir; prophylaxis with oral forms of ganciclovir or high-dose acyclovir may decrease the frequency of disease. A role for HHV-6 reactivation in early posttransplantation fever and leukopenia has been proposed, although the more severe sequelae described in HSC transplantation are unusual. HHV-6 and HHV-7 appear to exacerbate CMV disease in this setting. EBV-LPD after liver transplantation shows a propensity for involvement of the liver, and such disease may be of donor origin. See previous sections for discussion of EBV infections in solid organ transplantation.

PANCREAS TRANSPLANTATION

Pancreas transplantation is most frequently performed together with or after kidney transplantation, although it may be performed alone. Transplantation of the pancreas can be complicated by early bacterial and yeast infections. Most pancreatic transplants are drained into the bowel, with the remaining transplants drained into the bladder. A cuff of duodenum is used in the anastomosis between the pancreatic graft and either the gut or the

bladder. Bowel drainage poses a risk of early intraabdominal and allograft infections with enteric bacteria and yeasts. These infections can result in loss of the graft. Bladder drainage causes a high rate of urinary tract infection and sterile cystitis; however, infection can usually be cured with appropriate antimicrobial agents. In both procedures, prophylactic antimicrobial agents are commonly used at the time of surgery. Aggressive immunosuppression is associated with late-onset systemic viral and fungal infections; thus many centers administer an antifungal drug and an antiviral agent (ganciclovir or a congener) for prophylaxis.

Issues related to the development of CMV infection, EBV-LPD, and infections with opportunistic pathogens in patients receiving a pancreatic transplant are similar to those in other SOT recipients.

MISCELLANEOUS INFECTIONS IN SOLID ORGAN TRANSPLANTATION

Indwelling IV catheter infections

The prolonged use of indwelling IV catheters for administration of medications, blood products, and nutrition is common in diverse transplantation settings and poses a risk of local and bloodstream infections. Significant insertion-site infection is most commonly caused by *S. aureus*. Bloodstream infection most frequently develops within a week of catheter placement or in patients who become neutropenic. Coagulase-negative staphylococci are the most common isolates from the blood.

For further discussion of differential diagnosis and therapeutic options, see Chap. 12.

Tuberculosis

The incidence of tuberculosis within the first 12 months after solid organ transplantation is greater than that observed after HSC transplantation (0.23–0.79%) and ranges broadly worldwide (1.2–15%), reflecting the prevalence of tuberculosis in local populations. Lesions suggesting prior tuberculosis on chest radiograph, older age, diabetes, chronic liver disease, GVHD, and intense immunosuppression are predictive of tuberculosis reactivation and development of disseminated disease in a host with latent disease. Tuberculosis has rarely been transmitted from the donor organ. In contrast to the low mortality rate among HSC transplant recipients, mortality rates among SOT patients are reported to be as high as 30%. Vigilance is indicated, as the presentation of disease is often extrapulmonary (gastrointestinal, genitourinary, central nervous, endocrine, musculoskeletal, laryngeal) and atypical, sometimes manifesting as a fever of unknown origin. A careful history and a direct evaluation of both the recipient and the donor prior to transplantation are optimal. Skin testing of the recipient with purified protein derivative may be unreliable because of chronic disease and/or immunosuppression, but newer cell-based assays that measure interferon and/or cytokine production may prove more sensitive in the future. Isoniazid toxicity has not been a significant problem except in the setting of liver transplantation. Therefore, appropriate prophylaxis should proceed. An assessment of the need to treat latent disease should include careful consideration of the possibility of a false-negative test result. Pending final confirmation of suspected tuberculosis, aggressive multidrug treatment in accordance with the guidelines of the CDC, the Infectious Diseases Society of America, and the American Thoracic Society is indicated because of the high mortality rates among these patients. Altered drug metabolism (e.g., upon co-administration of rifampin and certain immunosuppressive agents) can be managed with careful monitoring of drug levels and appropriate dose adjustment. Close follow-up of hepatic enzymes is warranted, particularly during treatment with isoniazid, pyrazinamide, and/or rifampin. Drug-resistant tuberculosis is especially problematic in these individuals (Chap. 70).

Virus-associated malignancies

In addition to malignancy associated with gammaherpesvirus infection (EBV, KSHV) and simple warts (HPV), other tumors that are virus-associated or suspected of being virus-associated are more likely to develop in transplant recipients, particularly those who require long-term immunosuppression, than in the general population. The interval to tumor development is usually >1 year. Transplant recipients develop nonmelanoma skin or lip cancers that, in contrast to de novo skin cancers, have a high ratio of squamous cells to basal cells. HPV may play a major role in these lesions. Cervical and vulvar carcinomas, quite clearly associated with HPV, develop with increased frequency in female transplant recipients. Among renal transplant recipients, rates of melanoma are modestly increased and rates of cancers of the kidney and bladder are increased.

VACCINATION OF TRANSPLANT RECIPIENTS

In addition to receiving antibiotic prophylaxis, transplant recipients should be vaccinated against likely pathogens **(Table 13-7)**. In the case of HSC transplant recipients, optimal responses cannot be achieved until after immune reconstitution, despite previous immunization of both donor and recipient. Recipients of an allogeneic HSC transplant must be reimmunized if they are to be protected against pathogens. The situation is less clear-cut in the case of autologous transplantation. T and B cells in the peripheral blood may reconstitute the immune response if they are transferred in adequate numbers. However, cancer patients (particularly those with Hodgkin's disease, in whom vaccination has been extensively studied) who are undergoing chemotherapy do not respond normally to immunization, and titers of antibodies to infectious agents fall more rapidly than in healthy individuals. Therefore, even immunosuppressed patients who have not undergone HSC transplantation may need booster vaccine injections. If memory cells are specifically eliminated as part of a stem cell "cleanup" procedure, it will be necessary to reimmunize the recipient with a new

TABLE 13-7

VACCINATION OF HEMATOPOIETIC STEM CELL (HSC) TRANSPLANT OR SOLID ORGAN TRANSPLANT (SOT) RECIPIENTS

	TYPE OF TRANSPLANTATION	
VACCINE	**HSC**	**SOT***
Streptococcus pneumoniae, Haemophilus influenzae, Neisseria meningitidis	Immunize after transplantation. See CDC recommendations. (For pneumococcus, a new primary series may be indicated.)	Immunize before transplantation. See CDC recommendations. (For pneumococcus, a booster with polysaccharide vaccine every 5 years may be recommended.)
Influenza	Vaccinate in the fall. Vaccinate close contacts.	Vaccinate in the fall. Vaccinate close contacts.
Polio	Administer inactivated vaccine.	Administer inactivated vaccine.
Measles/mumps/rubella	Immunize 24 months after transplantation if GVHD is absent.	Immunize before transplantation with attenuated vaccine.
Diphtheria, pertussis, tetanus	Reimmunize after transplantation with primary series, DTaP. See CDC recommendations.	Immunize or boost before transplantation with Tdap; give boosters at 10 years or as required.
Hepatitis B and A	Reimmunize after transplantation. See CDC recommendations.	Immunize before transplantation.
Human papillomavirus	Recommendations are pending.	Recommendations are pending.

*Immunizations should be given before solid organ transplantation whenever possible.

Abbreviations: CDC, Centers for Disease Control and Prevention; DTaP, full-level diphtheria and tetanus toxoids and acellular pertussis, adsorbed; GVHD, graft-versus-host disease; Tdap, tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis.

Note: Recommendations from the CDC should be checked regularly as they frequently change upon receipt of new clinical information and new formulations of specific vaccines.

primary series. Optimal times for immunizations of different transplant populations are being evaluated. Yearly immunization of household and other contacts (including health care personnel) against influenza benefits the patient by preventing local spread.

In the absence of compelling data as to optimal timing, it is reasonable to administer the pneumococcal and *H. influenzae* type b conjugate vaccines to both autologous and allogeneic HSC transplant recipients beginning 12 months after transplantation. A series that includes both the 13-valent pneumococcal conjugate vaccine and the 23-valent Pneumovax is now recommended (following CDC guidelines). The pneumococcal and *H. influenzae* type b vaccines are particularly important for patients who have undergone splenectomy. The *Neisseria meningitidis* polysaccharide conjugate vaccine (Menactra or Menveo) is also recommended. In addition, diphtheria, tetanus, acellular pertussis, and inactivated polio vaccines can all be given at these same intervals (12 months and, as required, 24 months after transplantation). Some authorities recommend a new primary series for tetanus/diphtheria/pertussis and inactivated polio vaccine beginning 12 months after transplantation. Vaccination to prevent hepatitis B and hepatitis A (both killed vaccines) also seems advisable. Live-virus measles/mumps/rubella (MMR) vaccine can be given to autologous HSC transplant recipients 24 months after transplantation and to most allogeneic HSC transplant recipients at the same point if they are not receiving maintenance therapy with immunosuppressive drugs and do not have ongoing GVHD. The risk of spread from a household contact is lower for MMR vaccine than for polio vaccine. Neither patients nor their household contacts should be vaccinated with vaccinia unless they have been exposed to the smallpox virus. Among patients who have active GVHD and/or are taking high maintenance doses of glucocorticoids, it may be prudent to avoid all live-virus vaccines.

In the case of SOT recipients, administration of all the usual vaccines and of the indicated booster doses should be completed before immunosuppression, if possible, to maximize responses. For patients taking immunosuppressive agents, the administration of pneumococcal vaccine should be repeated every 5 years. No data are available for the meningococcal vaccine, but it is probably reasonable to administer it along with the pneumococcal vaccine. *H. influenzae* conjugate vaccine is safe and should be efficacious in this population; therefore, its administration before transplantation is recommended. Booster doses of this vaccine are not recommended for adults. SOT recipients who continue to receive immunosuppressive drugs should not receive live-virus vaccines. A person in this group who is exposed to measles should be given measles immune globulin. Similarly, an immunocompromised patient who is seronegative for varicella and who comes into contact with a person who has chickenpox should be given varicella-zoster immune globulin as soon as possible, certainly within 96 h; if this is not possible, the patient should be started immediately on a 10- to 14-day course of acyclovir therapy. Upon the discontinuation of treatment, clinical disease may still occur in a small number of patients; thus vigilance is indicated. Rapid re-treatment with acyclovir should limit the symptoms of disease. Household contacts of transplant recipients can receive live attenuated VZV vaccine, but vaccinees should avoid direct contact with the patient if a rash develops. Virus-like particle (VLP) vaccines have been licensed for the prevention of infection with several HPV serotypes most commonly implicated in

cervical and anal carcinomas and in anogenital and laryngeal warts. VLP vaccines are not live; however, no information is yet available about their immunogenicity or efficacy in transplant recipients.

Immunocompromised patients who travel may benefit from some but not all vaccines (Chaps. 4 and 5). In general, these patients should receive any killed or inactivated vaccine preparation appropriate to the area they are visiting; this recommendation includes the vaccines for Japanese encephalitis, hepatitis A and B, poliomyelitis, meningococcal infection, and typhoid. The live typhoid vaccines are not recommended for use in most immunocompromised patients, but inactivated or purified polysaccharide typhoid vaccine can be used. Live yellow fever vaccine should not be administered. On the other hand, primary immunization or boosting with the purified-protein hepatitis B vaccine is indicated if patients are likely to be exposed. Patients who will reside for >6 months in areas where hepatitis B is common (Africa, Southeast Asia, the Middle East, Eastern Europe, parts of South America, and the Caribbean) should receive hepatitis B vaccine. Inactivated hepatitis A vaccine should also be used in the appropriate setting (Chap. 4). A combined vaccine is now available that provides dual protection against hepatitis A and hepatitis B. If hepatitis A vaccine is not administered, travelers should consider receiving passive protection with immune globulin (the dose depending on the duration of travel in the high-risk area).

CHAPTER 14

HEALTH CARE–ASSOCIATED INFECTIONS

Robert A. Weinstein

The costs of hospital-acquired (nosocomial) and other health care–associated infections are great. It is estimated that these infections affect 1.7 million patients, cost ~$28–33 billion, and contribute to 99,000 deaths in U.S. hospitals annually. Although efforts to lower infection risks have been challenged by the growing numbers of immunocompromised patients, antibiotic-resistant bacteria, fungal and viral superinfections, and invasive devices and procedures, the viewpoint of consumer advocates—often termed "zero tolerance"—is that almost all health care–associated infections should be avoidable with strict application of evidence-based guidelines for prevention and control **(Table 14-1)**. This chapter reviews health care–acquired and device-related infections as well as basic surveillance, prevention, control, and treatment activities.

ORGANIZATION, RESPONSIBILITIES, AND INCREASING SCRUTINY OF HEALTH CARE–ASSOCIATED INFECTIONS

The standards of the Joint Commission require all accredited hospitals to have an active program for surveillance, prevention, and control of nosocomial infections. Education of physicians in infection control and health care epidemiology is required in infectious disease fellowship programs and is available by online courses. Concerns over "patient safety" have led to federal legislation that prevents U.S. hospitals from upgrading Medicare charges to pay for hospital costs resulting from at least 10 specific nosocomial events **(Table 14-2)** and have prompted national efforts to improve, measure, and publicly report on processes of patient care (e.g., timely administration and appropriateness of perioperative antibiotic prophylaxis) and patient outcomes (e.g., surgical wound infection rates). In 2009, the U.S. Department of Health and Human Services released a major interagency Action Plan to Prevent Healthcare-Associated Infections that includes a list of 5-year national prevention targets, such as a 50% reduction in central-line bloodstream infections (see *www.hhs.gov/ophs/initiatives/hai/*).

SURVEILLANCE

Traditionally, infection preventionists have surveyed inpatients for infections acquired in hospitals (defined as those neither present nor incubating at the time of admission). Surveillance most often requires review of microbiology laboratory results, "shoe-leather" epidemiology

TABLE 14-1

SOURCES OF INFECTION CONTROL GUIDELINES AND OVERSIGHT

ORGANIZATION	ROLE	MAJOR CONSTITUENTS	WEBSITE
Joint Commission	Regulatory	Hospitals, long-term-care facilities, laboratories	*www.jointcommission.org*
CAP	Regulatory	Laboratories	*www.cap.org*
OSHA	Regulatory	Workers	*www.osha.gov*
CMS	Regulatory	Medicare/Medicaid providers	*www.cms.hhs.gov*
PQRI	Regulatory and advisory	Eligible professionals	*www.cms.hhs.gov/pqri/*
HHS Action Plan	Regulatory and advisory	Health care and infection prevention personnel	*www.hhs.gov/ophs/initiatives/hai/*
CDC			
DHQP	Advisory	Health care facilities and personnel	*www.cdc.gov/ncidod/dhqp*
HICPAC	Advisory	Health care facilities and personnel	*www.cdc.gov/ncidod/dhqp/hicpac.html*
NIOSH	Advisory	Workers	*www.cdc.gov/niosh*
AHRQ	Advisory	Broad (e.g., health care personnel)	*www.ahrq.gov*
NQF	Advisory	Broad (e.g., health care personnel)	*www.qualityforum.org*
IOM	Advisory	Broad (e.g., health care personnel)	*www.iom.edu*
Federal Influenza Planning	Advisory	Health care and public health personnel	*pandemicflu.gov/professional/hospital/*
Trust for America's Health	Advisory	Broad (e.g., the public)	healthyamericans.org
CSTE	Advisory and professional society	Public health personnel	*www.cste.org*
IDSA	Professional society	Infectious disease physicians/researchers	*www.idsociety.org*
SHEA	Professional society	Health care epidemiologists	*www.shea-online.org*
HIS	Professional society	Health care epidemiologists	*www.his.org.uk/resource_library.cfm*
APIC	Professional society	Infection preventionists	*www.apic.org*
MedQIC	Quality improvement	Broad (e.g., health care personnel)	*www.qualitynet.org*
IHI	Quality improvement	Broad (e.g., health care personnel)	*www.ihi.org*
Leapfrog Group	Quality improvement	Broad (payers, consumers, employers, and health care personnel)	*www.leapfroggroup.org/for_hospitals*
NSQIP	Quality improvement	Surgery services	*www.acsnsqip.org*

Note: CAP, College of American Pathologists; OSHA, Occupational Safety & Health Administration; CMS, Centers for Medicare & Medicaid Services; PQRI, Physician Quality Reporting Initiative; HHS, Health and Human Services; CDC, Centers for Disease Control and Prevention; DHQP, Division of Healthcare Quality Promotion; HICPAC, Healthcare Infection Control Practices Advisory Committee; NIOSH, National Institute for Occupational Safety and Health; AHRQ, Agency for Healthcare Research and Quality; NQF, National Quality Forum; IOM, Institute of Medicine; CSTE, Council of State and Territorial Epidemiologists; IDSA, Infectious Diseases Society of America; SHEA, Society for Healthcare Epidemiology of America; HIS, Hospital Infection Society; APIC, Association for Professionals in Infection Control and Epidemiology; MedQIC, Medicare Quality Improvement Community; IHI, Institute for Healthcare Improvement; NSQIP, National Surgical Quality Improvement Program.

on nursing wards, and application of standardized definitions of infection. More "high-tech" infection-control programs may use computerized hospital databases for algorithm-driven electronic surveillance (e.g., of vascular catheter and surgical wound infections). Commercial health care information systems that facilitate these functions are considered "value-added" products. Although infection surveillance in nursing homes and long-term acute-care hospitals (LTACHs) is still in its formative stage, the role of some facilities in the transmission of antimicrobial-resistant pathogens will require their increased attention to infection surveillance and control.

Most hospitals aim surveillance at infections associated with high-level morbidity or expense. Quality-improvement activities in infection control have led to increased surveillance of personnel compliance with

TABLE 14-2

HEALTH CARE–ACQUIRED CONDITIONS NOT ELIGIBLE FOR ADDITIONAL FEDERAL PAYMENT[a]
Vascular catheter–associated infections
Specific surgical-site infections (i.e., after coronary artery bypass graft surgery, certain orthopedic procedures, and certain bariatric surgeries)
Catheter-associated urinary tract infections
Decubitus ulcers (stages III and IV)
Fractures/other injuries from falls or trauma
Foreign objects retained after surgery
Air embolism
Blood incompatibilities
Venous thromboembolism (after hip or knee replacement)
Manifestations of poor glycemic control

[a]Based on the U.S. Federal Deficit Reduction Act of 2005. As of October 1, 2008, Medicare stopped paying additional money to hospitals for these 10 health care–acquired conditions. See *www.cms.hhs.gov/HospitalAcqCond/06_Hospital-Acquired_Conditions.asp* (last accessed November 16, 2009).

infection control policies (e.g., adherence to influenza vaccination recommendations). In the spirit of "what is measured improves," the majority of states now require public reporting of processes for prevention of health care–associated infection and/or patient outcomes **(Fig. 14-1)**. These state laws have added new complexity to what hospitals measure and how they measure it. For example, in some locales, the surveillance pendulum is swinging back to use of "house-wide" surveillance, and many states now require that hospitals use the Centers for Disease Control and Prevention (CDC) National Healthcare Safety Network (NHSN) reporting system to provide uniform definitions and to facilitate transmission of data. (The NHSN is the successor to the National Nosocomial Infections Surveillance System, a program of the CDC that collected data from ~350 hospitals using standardized definitions of nosocomial infections. Increasing reliance on the NHSN by states to facilitate public reporting has led to participation by almost half of the ~5200 acute-care hospitals in the United States. This increased participation may represent a watershed in providing a more robust nationwide view of health care–associated infections.)

Results of surveillance are expressed as rates. In general, 5–10% of patients develop nosocomial infections. However, such broad statistics have little value unless qualified by duration of risk, by site of infection, by patient population, and by exposure to risk factors. Meaningful denominators for infection rates include the number of patients exposed to a specific risk (e.g., patients using mechanical ventilators) or the number of intervention days (e.g., 1000 patient-days on a ventilator). Temporal trends in rates should be reviewed, and rates should be compared with regional and national benchmarks. However, interhospital comparisons may be misleading because of the wide range in risk factors

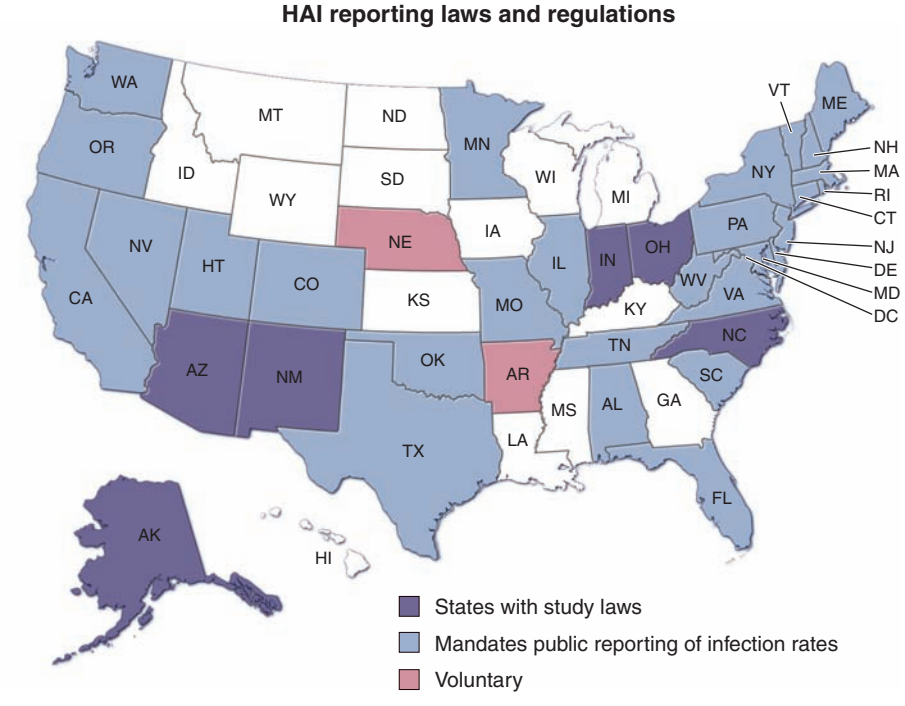


FIGURE 14-1
Map indicating states with mandatory public reporting of health care–associated infections (HAIs), states with public-reporting study laws, and states with voluntary reporting laws. See *www.apic.org/am/images/maps/mandrpt_map.gif* (last accessed November 16, 2009).

and severity of underlying illnesses. Although systems for making adjustments for these factors either are rudimentary or have not been well validated, process measures (e.g., adherence to hand hygiene) do not usually require risk adjustment, and outcome measures (e.g., cardiac surgery wound infection rates) can identify hospitals with outlier infection rates (e.g., in the top deciles) for further evaluation. Moreover, temporal analysis of a hospital's infection rates can help to determine whether control measures are succeeding and where increased efforts should be focused.

EPIDEMIOLOGIC BASIS AND GENERAL MEASURES FOR PREVENTION AND CONTROL

Nosocomial infections follow basic epidemiologic patterns that can help to direct prevention and control measures. Nosocomial pathogens have reservoirs, are transmitted by largely predictable routes, and require susceptible hosts. Reservoirs and sources exist in the inanimate environment (e.g., tap water contaminated with *Legionella*) and in the animate environment (e.g., infected or colonized health care workers, patients, and hospital visitors). The mode of transmission usually is either cross-infection (e.g., indirect spread of pathogens from one patient to another on the inadequately cleaned hands of hospital personnel) or autoinoculation (e.g., aspiration of oropharyngeal flora into the lungs along an endotracheal tube). Occasionally, pathogens (e.g., group A streptococci and many respiratory viruses) are spread from person to person via large infectious droplets released by coughing or sneezing. Much less common—but often devastating in terms of epidemic risk—is true airborne spread of small or droplet nuclei (as in nosocomial chickenpox) or common-source spread by contaminated materials (e.g., contaminated intravenous fluids). Factors that increase host susceptibility include underlying conditions, abnormalities of innate defense (e.g., due to genetic polymorphisms), and the many medical-surgical interventions and procedures that bypass or compromise normal host defenses.

Hospitals' infection-control programs must determine general and specific control measures. Given the prominence of cross-infection, hand hygiene is the single most important preventive measure in hospitals. Health care workers' rates of adherence to hand-hygiene recommendations are abysmally low (<50%). Reasons cited include inconvenience, time pressures, and skin damage from frequent washing. Sinkless alcohol rubs are quick and highly effective and actually improve hand condition since they contain emollients and allow the retention of natural protective oils that would be removed with repeated rinsing. Use of alcohol hand rubs between patient contacts is now recommended for all health care workers except when hands are visibly soiled or after care of a patient who is part of a health-care facility outbreak of infection with *Clostridium difficile*, whose spores resist killing by alcohol and require mechanical removal. In these cases, washing with soap and running water is recommended.

NOSOCOMIAL AND DEVICE-RELATED INFECTIONS

The fact that at least 25–50% of nosocomial infections are due to the combined effect of the patient's own flora and invasive devices highlights the importance of improvements in the use and design of such devices. Intensive education, "bundling" of evidence-based interventions **(Table 14-3)**, and use of checklists to facilitate adherence can reduce infection rates through improved asepsis in handling and earlier removal of invasive devices, but the maintenance of such gains requires ongoing efforts. It is especially noteworthy that turnover or shortages of trained personnel jeopardize safe and effective patient care and have been associated with increased infection rates.

Urinary tract infections

Urinary tract infections (UTIs) account for ~34% of nosocomial infections; up to 3% of bacteriuric patients develop bacteremia. Although UTIs contribute at most 15% to prolongation of hospital stay and may have an attributable cost in the range of only $1300, these infections are important reservoirs and sources for spread of antibiotic-resistant bacteria in hospitals. Almost all nosocomial UTIs are associated with preceding instrumentation or indwelling bladder catheters, which create a 3–10% risk of infection each day. UTIs generally are caused by pathogens that spread up the periurethral space from the patient's perineum or gastrointestinal tract—the most common pathogenesis in women—or via intraluminal contamination of urinary catheters, usually due to cross-infection by caregivers who are irrigating catheters or emptying drainage bags. Pathogens come occasionally from inadequately disinfected urologic equipment and rarely from contaminated supplies.

Hospitals should closely monitor essential performance measures for preventing nosocomial UTIs (Table 14-3). Sealed catheter–drainage tube junctions can help to prevent breaks in the system. Prompts to clinicians to assess a patient's need for continued use of an indwelling bladder catheter can improve removal rates and may lessen the risk of UTI but also may be met with resistance by direct caregivers. Guidelines for managing postoperative urinary retention (e.g., with bladder scanners) also may limit the use or duration of catheterization. Other approaches to the prevention of UTIs have included use of topical meatal antimicrobial agents, drainage bag disinfectants, and anti-infective catheters. None of the latter three measures is considered routine.

Administration of systemic antimicrobial agents for other purposes decreases the risk of UTI during the first 4 days of catheterization, after which resistant bacteria or yeasts emerge as pathogens. Selective decontamination of the gut is also associated with a reduced risk. Again, however, neither approach is routine.

Irrigation of catheters, with or without antimicrobial agents, may actually increase the risk of infection. A condom catheter for men without bladder obstruction

TABLE 14-3

EXAMPLES OF "BUNDLED INTERVENTIONS" TO PREVENT COMMON HEALTH CARE–ASSOCIATED INFECTIONS AND OTHER ADVERSE EVENTS

Prevention of Central Venous Catheter Infections
Educate personnel about catheter insertion and care.
Use chlorhexidine to prepare the insertion site.
Use maximal barrier precautions during catheter insertion.
Consolidate insertion supplies (e.g., in an insertion kit or cart).
Use a checklist to enhance adherence to the bundle.
Empower nurses to halt insertion if asepsis is breached.
Cleanse patients daily with chlorhexidine.
Ask daily: Is the catheter needed? Remove catheter if not needed or used.
Prevention of Ventilator-Associated Pneumonia and Complications
Elevate head of bed to 30–45 degrees.
Decontaminate oropharynx regularly with chlorhexidine.
Give "sedation vacation" and assess readiness to extubate daily.
Use peptic ulcer disease prophylaxis.
Use deep-vein thrombosis prophylaxis (unless contraindicated).
Prevention of Surgical-Site Infections
Choose a surgeon wisely.
Administer prophylactic antibiotics within 1 h before surgery; discontinue within 24 h.
Limit any hair removal to the time of surgery; use clippers or do not remove hair at all.
Prepare surgical site with chlorhexidine-alcohol.
Maintain normal perioperative glucose levels (cardiac surgery patients).[a]
Maintain perioperative normothermia (colorectal surgery patients).[a]
Prevention of Urinary Tract Infections
Place bladder catheters only when absolutely needed (e.g., to relieve obstruction), not solely for the provider's convenience.
Use aseptic technique for catheter insertion and urinary tract instrumentation.
Minimize manipulation or opening of drainage systems.
Ask daily: Is the bladder catheter needed? Remove catheter if not needed.
Prevention of Pathogen Cross-Transmission
Cleanse hands with alcohol hand rub before and after all contacts with patients or their environments.

[a]These components of care are supported by clinical trials and experimental evidence in the specified populations; they may prove valuable for other surgical patients as well.

Source: Adapted from information presented at the following websites: *www.cdc.gov/ncidod/dhqp/gl_intravascular.html; www.cdc.gov/ncidod/dhqp/gl_hcpneumonia.html; www.cdc.gov/ncidod/dhqp/gl_surgicalsite.html; www.cdc.gov/ncidod/dhqp/dpac_uti_pc.html; www.ihi.org; www.qualitynet.org/medqic*.

may be more acceptable than an indwelling catheter and may lessen the risk of UTI if maintained carefully. The role of suprapubic catheters in preventing infection is not well defined.

Treatment of UTIs is based on the results of quantitative urine cultures (Chap. 28). The most common pathogens are *Escherichia coli*, nosocomial gram-negative bacilli, enterococci, and *Candida*. Several caveats apply in the treatment of institutionally acquired infection. First, in patients with chronic indwelling bladder catheters, especially those in long-term-care facilities, "catheter flora"—microorganisms living on encrustations within the catheter lumen—may differ from actual urinary tract pathogens. Therefore, for suspected infection in the setting of chronic catheterization (especially in women), it is useful to replace the bladder catheter and to obtain a freshly voided urine specimen. Second, as in all nosocomial infections, at the time treatment is initiated on the basis of a positive culture, it is useful to repeat the culture to verify the persistence of infection. Third, the frequency with which UTIs occur may lead to the erroneous assumption that this site alone is the source of infection in a febrile hospitalized patient. Fourth, recovery of *Staphylococcus aureus* from urine cultures may result from hematogenous seeding and may indicate an occult systemic infection. Finally, although *Candida* is now the most common pathogen in nosocomial UTIs in patients on intensive care units (ICUs), treatment of candiduria is often unsuccessful and is recommended only when there is upper-pole or bladder-wall invasion, obstruction, neutropenia, or immunosuppression.

Pneumonia

Pneumonia accounts for ~13% of nosocomial infections. Ventilator-associated pneumonia, which occurs in 1 to >4 patients per 1000 ventilator-days, is responsible for a mean of 10 extra hospital days and $23,000 in extra costs per episode. Almost all cases of bacterial nosocomial pneumonia are caused by aspiration of endogenous or hospital-acquired oropharyngeal (and occasionally gastric) flora. Nosocomial pneumonias are associated with more deaths than are infections at any other body site. However, attributable mortality for ventilator-associated pneumonia—the most common and lethal form of nosocomial pneumonia—is in the 6–14% range; this figure suggests that the risk of dying from nosocomial pneumonia is affected greatly by other factors, including comorbidities, inadequate antibiotic treatment, and the involvement of specific pathogens (particularly *Pseudomonas aeruginosa* or *Acinetobacter*). Surveillance and accurate diagnosis of pneumonia are often problematic in hospitals because many patients, especially those in the ICU, have abnormal chest roentgenographs, fever, and leukocytosis potentially attributable to multiple causes. Viral pneumonias, which are particularly important in pediatric and immunocompromised patients, are discussed in the virology section and in Chap. 18.

Risk factors for nosocomial pneumonia, particularly ventilator-associated pneumonia, include those events

that increase colonization by potential pathogens (e.g., prior antimicrobial therapy, contaminated ventilator circuits or equipment, or decreased gastric acidity); those that facilitate aspiration of oropharyngeal contents into the lower respiratory tract (e.g., intubation, decreased levels of consciousness, or presence of a nasogastric tube); and those that reduce host defense mechanisms in the lung and permit overgrowth of aspirated pathogens (e.g., chronic obstructive pulmonary disease, extremes of age, or upper abdominal surgery).

Control measures for pneumonia (Table 14-3) are aimed at the remediation of risk factors in general patient care (e.g., minimizing aspiration-prone supine positioning) and at meticulous aseptic care of respirator equipment (e.g., disinfecting or sterilizing all inline reusable components such as nebulizers, replacing tubing/breathing circuits only if required because of malfunction or visible soiling—rather than on the basis of duration of use—to lessen the number of breaks in the system, and teaching aseptic technique for suctioning). Although the benefits of selective decontamination of the oropharynx and gut with nonabsorbable antimicrobial agents and/or use of short-course postintubation systemic antibiotics have been controversial, a randomized multicenter trial demonstrated lowered ICU mortality rates among patients on mechanical ventilation who underwent oropharyngeal decontamination.

Among the logical preventive measures that require further investigation are endotracheal intubation providing channels for subglottic drainage of secretions, which has been associated with reduced infection risks during short-term postoperative use, and noninvasive mechanical ventilation whenever feasible. Use of silver-coated endotracheal tubes may lessen risk of ventilator-associated pneumonia, but is not considered routine. It is noteworthy that reducing the rate of ventilator-associated pneumonia often has not reduced overall ICU mortality; this fact suggests that this infection is a marker for patients with an otherwise-heightened risk of death.

The most likely pathogens for nosocomial pneumonia and treatment options are discussed in Chap. 18. Several considerations regarding diagnosis and treatment are worth emphasizing. First, clinical criteria for diagnosis (e.g., fever, leukocytosis, development of purulent secretions, new or changing radiographic infiltrates, changes in oxygen requirement or ventilator settings) have high sensitivity but relatively low specificity. These criteria are most useful for selecting patients for bronchoscopic or nonbronchoscopic procedures that yield lower respiratory tract samples protected from upper-tract contamination; quantitative cultures of such specimens have diagnostic sensitivities in the range of 80%. Second, early-onset nosocomial pneumonia, which manifests within the first 4 days of hospitalization, is most often caused by community-acquired pathogens such as *Streptococcus pneumoniae* and *Haemophilus* species, although some recent studies have challenged this view. Late-onset pneumonias most commonly are due to *S. aureus*, *P. aeruginosa*, *Enterobacter* species, *Klebsiella pneumoniae*, or *Acinetobacter*—a pathogen that is common in tropical countries and of increasing concern in ICUs in the United States. When invasive techniques are used to diagnose ventilator-associated pneumonia, the proportion of isolates accounted for by gram-negative bacilli decreases from 50–70% to 35–45%. Infection is polymicrobial in as many as 20–40% of cases. The role of anaerobic bacteria in ventilator-associated pneumonia is not well defined. Third, one multicenter study suggested that 8 days is an appropriate duration of therapy for nosocomial pneumonia, with a longer duration (15 days in that study) when the pathogen is *Acinetobacter* or *P. aeruginosa*. Finally, in febrile patients (particularly those who have endotracheal or gastric tubes inserted through the nares), more occult sources of respiratory tract infection, especially bacterial sinusitis and otitis media, should be considered.

Surgical wound infections

Wound infections account for ~17% of nosocomial infections but contribute up to 7–10 extra postoperative hospital days and from $3000 to $29,000 in extra costs, depending on the operative procedure and pathogen(s). The average wound infection has an incubation period of 5–7 days—longer than many postoperative stays. For this reason and because many procedures are now performed on an outpatient basis, the incidence of wound infections has become more difficult to assess. These infections usually are caused by the patient's endogenous or hospital-acquired skin and mucosal flora and occasionally are due to airborne spread of skin squames that may be shed into the wound from members of the operating-room team. True airborne spread of infection through droplet nuclei is rare in operating rooms unless there is a "disseminator" (e.g., of group A streptococci or staphylococci) among the staff. In general, the most common risks for postoperative wound infection are related to the surgeon's technical skill, the patient's underlying diseases (e.g., diabetes mellitus, obesity) or advanced age, and inappropriate timing of antibiotic prophylaxis. Additional risk factors include the presence of drains, prolonged preoperative hospital stays, shaving of the operative site by razor the day before surgery, a long duration of surgery, and infection at remote sites (e.g., untreated UTI).

The substantial literature related to risk factors for surgical-site infections and the recognized morbidity and cost of these infections have led to national prevention efforts—e.g., the Surgical Care Improvement Project (SCIP)—and to recommendations for "bundling" of evidence-based preventive measures (Table 14-3). Additional measures include attention to technical surgical issues and operating-room asepsis (e.g., avoiding open or prophylactic drains) as well as preoperative therapy for active infection. Reporting of surveillance results to surgeons has been associated with reductions in infection rates. Preoperative administration of intranasal mupirocin to patients colonized with *S. aureus*, preoperative antiseptic bathing, and supplemental intra- and postoperative oxygen remain controversial because of conflicting study results, but evidence seems to be mounting in favor of these interventions.

The process of diagnosing and treating wound infections begins with a careful assessment of the surgical site in the febrile postoperative patient. Clinical findings range

from obvious cellulitis or abscess formation to subtler clues such as a sternal "click" following open-heart surgery. Diagnosis of deeper organ-space infections or subphrenic abscesses requires a high index of suspicion and the use of CT or MRI. Diagnosis of infections of prosthetic devices, such as orthopedic implants, may be particularly difficult and often requires the use of interventional radiographic techniques to obtain periprosthetic specimens for culture. Because cultures of periprosthetic joint tissue obtained at surgery may miss pathogens that are cloistered in prosthesis-adherent biofilms, cultures of sonicates from explanted prosthetic joints have been more sensitive, particularly for patients who have received antimicrobial agents within 2 weeks of surgery.

The most common pathogens in postoperative wound infections are *S. aureus*, coagulase-negative staphylococci, and enteric and anaerobic bacteria. In rapidly progressing postoperative infections, which manifest within 24–48 h of a surgical procedure, the level of suspicion regarding group A streptococcal or clostridial infection (Chaps. 39 and 46) should be high. Treatment of postoperative wound infections requires source control—drainage or surgical excision of infected or necrotic material—and antibiotic therapy aimed at the most likely or laboratory-confirmed pathogens.

Infections related to vascular access and monitoring

Intravascular device–related bacteremias cause ~14% of nosocomial infections; central vascular catheters (CVCs) account for most of these bloodstream infections. National estimates indicate that as many as 200,000 bloodstream infections associated with CVCs occur each year in the United States, with an attributable mortality of 12–25%, an excess mean length of hospital stay of 12 days, and an estimated cost of $3700 to $29,000 per episode; one-third to one-half of these episodes occur in ICUs. With increasing care of seriously ill patients in the community, vascular catheter–associated bloodstream infections acquired in outpatient settings are becoming more frequent. Broader surveillance for infections—outside ICUs and even outside hospitals—will be needed.

Catheter-related bloodstream infections derive largely from the cutaneous microflora of the insertion site, with pathogens migrating extraluminally to the catheter tip, usually during the first week after insertion. In addition, contamination of hubs of CVCs or of the ports of "needle-less" systems may lead to intraluminal infection over longer periods, particularly with surgically implanted or cuffed catheters. Intrinsic (during the manufacturing process) or extrinsic (on-site in a health care facility) contamination of infusate, although rare, is the most common cause of epidemic device-related bloodstream infection; extrinsic contamination may cause up to half of endemic bacteremias related to arterial infusions used for hemodynamic monitoring. The most common pathogens isolated from vascular device–associated bacteremias include coagulase-negative staphylococci, *S. aureus* (with ≥50% of isolates in the United States resistant to methicillin), enterococci, nosocomial gram-negative bacilli, and *Candida*. Many pathogens, especially staphylococci, produce extracellular polysaccharide biofilms that facilitate attachment to catheters and provide sanctuary from antimicrobial agents. "Quorum-sensing" proteins help bacterial cells communicate during biofilm development.

Infections related to vascular catheters and monitoring devices may be the most preventable of nosocomial infections. Evidence-based bundles of control measures (Table 14-3) have been strikingly effective, eliminating almost all infections in one ICU study. Hospitals should periodically monitor adherence to these performance indicators. Use of antimicrobial- or antiseptic-impregnated CVCs does not appear necessary if the prevention bundle is fully implemented.

Additional control measures for infections associated with vascular access include using a chlorhexidine-impregnated patch at the skin-catheter junction; bathing medical ICU patients daily with chlorhexidine; applying semitransparent access-site dressings (for ease of bathing and site inspection and protection of the site from secretions); avoiding the femoral site for catheterization because of an especially high risk of infection (most likely related to the density of the skin flora); moving peripheral catheters to a new site at specified intervals (e.g., every 72–96 h), which may be facilitated by use of an IV therapy team; and applying disposable transducers for pressure monitoring and aseptic technique for accessing transducers or other vascular ports.

Unresolved issues include the best frequency for rotation of CVC sites (given that guidewire-assisted catheter changes at the same site do not lessen and can even increase infection risk); the appropriate role of mupirocin ointment, a topical antibiotic with excellent antistaphylococcal activity, in site care; the relative degrees of risk posed by peripherally inserted central catheters (PICC lines); and the risk-benefit of prophylactic use of heparin (to avoid catheter thrombi, which may be associated with increased risk of infection) or of vancomycin or alcohol (as catheter flushes or "locks"—i.e., concentrated anti-infective solutions instilled into the catheter lumen) for high-risk patients.

Vascular device–related infection is suspected on the basis of the appearance of the catheter site or the presence of fever or bacteremia without another source in patients with vascular catheters. The diagnosis is confirmed by the recovery of the same species of microorganism from peripheral-blood cultures (preferably two cultures drawn from peripheral veins by separate venipunctures) and from semiquantitative or quantitative cultures of the vascular catheter tip. Less commonly used diagnostic measures include (1) differential faster time to positivity (>2 h) for blood drawn through the vascular access device compared with a sample from a peripheral vein and (2) differences in quantitative cultures (a threefold or greater "step-up") for blood samples drawn simultaneously from a peripheral vein and from a CVC. When infusion-related sepsis is considered (e.g., because of the abrupt onset of fever or shock temporally related to infusion therapy), a sample of the infusate or blood product should be retained for culture.

Therapy for vascular access–related infection is directed at the pathogen recovered from the blood and/or infected site. Important considerations in treatment are the need for an echocardiogram (to evaluate the patient for endocarditis), the duration of therapy, and the need to remove potentially infected catheters. In one report, approximately one-fourth of patients with intravascular catheter–associated *S. aureus* bacteremia who were studied by transesophageal echocardiography had evidence of endocarditis; this test may be useful in determining the appropriate duration of treatment.

Detailed consensus guidelines for the management of intravascular catheter–related infections have been published and recommend catheter removal in most cases of bacteremia or fungemia due to nontunneled CVCs. When attempting to salvage a potentially infected catheter, some clinicians use the "antibiotic lock" technique, which may facilitate penetration of infected biofilms, in addition to systemic antimicrobial therapy. In a single-center study of hemodialysis catheters, only about one-third of salvage attempts were successful, although delayed removal did not appear to increase the risk of complications.

Often, a potentially infected CVC may be exchanged over a guidewire. If cultures of the removed catheter tip are positive, the replacement catheter will be moved to a new site; if the tip cultures are negative, the replacement catheter may remain in the original site, but may be at increased risk of subsequent infection due to this manipulation.

The authors of the consensus treatment guidelines advise that the decision to remove a tunneled catheter or implanted device suspected of being the source of bacteremia or fungemia should be based on the severity of the patient's illness, the strength of the evidence that the device is infected, the presence of local or systemic complications, an assessment of the specific pathogens, and the patient's response to antimicrobial therapy if the catheter or device is initially retained. For patients with track-site infection, successful therapy without catheter removal is unusual. For patients with suppurative venous thrombophlebitis, excision of the affected vein is usually required.

ISOLATION TECHNIQUES

Written policies for the isolation of infectious patients are a standard component of infection control programs. To replace its prior pathogen-specific guidelines, the CDC published recommendations in 2006 for the control of multidrug-resistant organisms in health care settings; in 2007, the CDC published a revised edition of its basic isolation guidelines to provide updated recommendations for all components of health care, including acute-care hospitals and long-term, ambulatory, and home-care settings.

Standard precautions are designed for the care of all patients in hospitals and aim to reduce the risk of transmission of microorganisms from both recognized and unrecognized sources. These precautions include gloving as well as hand cleansing for potential contact with (1) blood; (2) all other body fluids, secretions, and excretions, whether or not they contain visible blood; (3) nonintact skin; and (4) mucous membranes. Depending on exposure risks, standard precautions also include use of masks, eye protection, and gowns.

Precautions for the care of patients with potentially contagious clinical syndromes (e.g., acute diarrhea) or with suspected or diagnosed colonization or infection with transmissible pathogens are based on probable routes of transmission: *airborne*, *droplet*, or *contact*, for which personnel don at a minimum N95 respirators, surgical face masks, or glove and gown, respectively. Sets of precautions may be combined for diseases that have more than one route of transmission (e.g., contact and airborne isolation for varicella).

Because some prevalent antibiotic-resistant pathogens, particularly vancomycin-resistant enterococci (VRE), may be present on *intact* skin of patients in hospitals, some experts recommend gloving for all contact with patients who are acutely ill and/or from high-risk units, such as ICUs. Wearing gloves does not replace the need for hand hygiene because hands sometimes (in up to 20% of interactions) become contaminated during wearing or removal of gloves.

EPIDEMIC AND EMERGING PROBLEMS

Outbreaks and emerging pathogens are always big news but probably account for <5% of nosocomial infections. The investigation and control of nosocomial epidemics require that infection control personnel develop a case definition, confirm that an outbreak really exists (since apparent epidemics may be pseudo-outbreaks due to surveillance or laboratory artifacts), review aseptic practices and disinfectant use, determine the extent of the outbreak, perform an epidemiologic investigation to determine modes of transmission, work closely with microbiology personnel to culture for common sources or personnel carriers as appropriate and to type epidemiologically important isolates, and heighten surveillance to judge the effect of control measures. Control measures generally include reinforcing routine aseptic practices and hand hygiene during a search for compliance problems that may have fostered the outbreak, ensuring appropriate isolation of cases (and instituting cohort isolation and nursing if needed), and implementing further controls on the basis of the investigation's findings. Examples of some emerging and potential epidemic problems follow.

Viral respiratory infections: Pandemic influenza

Infections caused by the severe acute respiratory syndrome (SARS)–associated coronavirus challenged health care systems globally in 2003 (Chap. 91). Basic infection-control measures helped to keep the worldwide case and death counts at ~8000 and ~800, respectively, although SARS was unforgiving of lapses in protocol adherence or laboratory biosafety.

The epidemiology of SARS—spread largely in households once patients were ill or in hospitals—contrasts markedly with that of influenza (Chap. 92), which is often contagious a day before symptom onset; can spread rapidly in the community among nonimmune persons; and even in its seasonal variety kills as many as 35,000 persons each year in the United States. Control of seasonal influenza has depended on (1) the use of effective vaccines, with increasingly broad evidence-based recommendations for vaccination of children, the general public, and health care workers; (2) the use of antiviral medications for early treatment and for prophylaxis as part of outbreak control, especially for high-risk patients and in high-risk settings like nursing homes or hospitals; and (3) infection control (surveillance and droplet precautions) for symptomatic patients.

With occurrence of localized outbreaks of avian (H5N1) influenza in Asia over the past few years, concerns about potential pandemic influenza led to recommendations for universal "respiratory hygiene and cough etiquette" (basically, "cover your cough"), as described and promoted in the CDC's 2007 *Guideline for Isolation Precautions*, and for "source containment" (e.g., use of face masks and spatial separation) for outpatients with potentially infectious respiratory illnesses; to re-examinations of the value in the 1918–1919 influenza pandemic of nonpharmacologic interventions, such as "social distancing" (e.g., closing schools and community venues); and to debate about the level of respiratory protection required for health care workers (i.e., whether to use the higher-efficiency N95 respirators recommended for airborne isolation rather than the surgical masks used for droplet precautions).

In the spring of 2009, a novel strain of influenza virus—H1N1 or "swine flu" virus—caused the first influenza pandemic in four decades. Interventions based on experience with seasonal influenza and prior pandemics included (1) aggressive use of infection control measures (e.g., droplet and contact precautions for suspected influenza cases); (2) hierarchical use of limited supplies of H1N1 monovalent influenza vaccine for pregnant woman, children, and adults with comorbidities (because of greater risk or worse H1N1 outcomes) and for health care and public safety workers (because of the perceived need to maintain a cohort of well essential-infrastructure workers); (3) prompt therapeutic use of neuraminidase inhibitors and emergency authorization for clinical use of experimental parenteral preparations from this class; and (4) prophylactic use of neuraminidase inhibitors in select settings (e.g., for exposed health care workers). Prominent among controversial infection-control issues were optimal respiratory protection (N95 respirators versus surgical masks) for health care workers entering influenza isolation rooms and the need to mandate influenza vaccination of health care workers because of the embarrassingly low rates of vaccination in this high-risk group.

Nosocomial diarrhea

A new, more virulent strain of *C. difficile*—BI/NAP1/027—has emerged in North America, and overall rates of *C. difficile*–associated diarrhea (Chap. 47) have increased, especially among older patients, in U.S. hospitals during the past few years. The potential role of exposure to newer fluoroquinolone antibiotics in driving these changes is being investigated. *C. difficile* control measures include judicious use of all antibiotics; heightened suspicion for "atypical" presentations (e.g., toxic megacolon or leukemoid reaction without diarrhea); and early diagnosis, treatment, and contact precautions.

Outbreaks of norovirus infection (Chap. 94) in U.S. and European health care facilities appear to be increasing in frequency, with the virus often introduced by ill visitors or staff. This pathogen should be suspected when nausea and vomiting are prominent aspects of bacterial culture–negative diarrheal syndromes. Contact precautions may need to be augmented by aggressive environmental cleaning (given the persistence of norovirus on inanimate objects), prevention of secondary cases in cleaning staff by an emphasis on the use of personal protective equipment and hand hygiene, and active exclusion of ill staff and visitors.

Chickenpox

Infection control practitioners institute a varicella exposure investigation and control plan whenever health care workers have been exposed to chickenpox (Chap. 85) or have worked while having or during the 24 h before developing chickenpox. The names of exposed workers and patients are obtained; medical histories are reviewed, and (if necessary) serologic tests for immunity are conducted; physicians are notified of susceptible exposed patients; postexposure prophylaxis with varicella-zoster immune globulin (VZIG) is considered for immunocompromised or pregnant contacts (see Table 85-1); varicella vaccine is recommended or preemptive use of acyclovir is considered as an alternative strategy in other susceptible persons; and susceptible exposed employees are furloughed during the at-risk period for disease (8–21 days or, if VZIG has been administered, 28 days). Routine varicella vaccination of children and susceptible employees has made nosocomial spread less common and problematic.

Tuberculosis

Important measures for the control of tuberculosis (Chap. 70) include prompt recognition, isolation, and treatment of cases; recognition of atypical presentations (e.g., lower-lobe infiltrates without cavitation); use of negative-pressure, 100% exhaust, private isolation rooms with closed doors and at least 6–12 air changes per hour; use of N95 respirators by caregivers entering isolation rooms; possible use of high-efficiency particulate air filter units and/or ultraviolet lights for disinfecting air when other engineering controls are not feasible or reliable; and follow-up skin-testing of susceptible personnel who have been exposed to infectious patients before isolation. The use of serologic tests, rather than skin tests, in the diagnosis of latent tuberculosis for infection control purposes remains controversial.

Group A streptococcal infections

The potential for an outbreak of group A streptococcal infection (Chap. 39) should be considered when even a single nosocomial case occurs. Most outbreaks involve surgical wounds and are due to the presence of an asymptomatic carrier in the operating room. Investigation can be confounded by carriage at extrapharyngeal sites such as the rectum and vagina. Health care workers in whom carriage has been linked to nosocomial transmission of group A streptococci are removed from the patient-care setting and are not permitted to return until carriage has been eliminated by antimicrobial therapy.

Fungal infections

Fungal spores are common in the environment, particularly on dusty surfaces. When dusty areas are disturbed during hospital repairs or renovation, the spores become airborne. Inhalation of spores by immunosuppressed (especially neutropenic) patients creates a risk of pulmonary and/or paranasal sinus infection and disseminated aspergillosis (Chap. 111). Routine surveillance among neutropenic patients for infections with filamentous fungi, such as *Aspergillus* and *Fusarium*, helps hospitals to determine whether they are facing unduly extensive environmental risks. As a matter of routine, hospitals should inspect and clean air-handling equipment, review all planned renovations with infection control personnel and subsequently construct appropriate barriers, remove immunosuppressed patients from renovation sites, and consider the use of high-efficiency particulate air intake filters for rooms housing immunosuppressed patients.

Legionellosis

Nosocomial *Legionella* pneumonia (Chap. 52) is most often due to contamination of potable water and predominantly affects immunosuppressed patients, particularly those receiving glucocorticoid medications. The risk varies greatly within and among geographic regions, depending on the extent of hospital hot-water contamination and on specific hospital practices (e.g., inappropriate use of nonsterile water in respiratory therapy equipment). Laboratory-based surveillance for nosocomial *Legionella* should be performed, and a diagnosis of legionellosis should probably be considered more often than it is. If nosocomial cases are detected, environmental samples (e.g., tap water) should be cultured. If cultures yield *Legionella* and if typing of clinical and environmental isolates reveals a correlation, eradication measures should be pursued. An alternative approach is to periodically culture tap water in wards housing high-risk patients. If *Legionella* is found, a concerted effort should be made to culture samples from all patients with nosocomial pneumonia for *Legionella*.

Antibiotic-resistant bacteria

Control of antibiotic resistance depends on close laboratory surveillance, with early detection of problems; on aggressive reinforcement of routine asepsis; on implementation of barrier precautions for all colonized and/or infected patients; on use of patient-surveillance cultures to more fully ascertain the extent of patient colonization; and on timely initiation of an epidemiologic investigation when rates increase. Molecular typing (e.g., pulsed-field gel electrophoresis) can help differentiate an outbreak due to a single strain (which necessitates an emphasis on hand hygiene and an evaluation of potential common-source exposures) from one that is polyclonal (which requires an emphasis on antibiotic prudence and device bundles; Table 14-3).

Currently, several antibiotic resistance problems are of particular concern. First, the emergence of community-associated methicillin-resistant *S. aureus* (CA-MRSA) has been dramatic in many countries, with as many as 50% of community-acquired "staph infections" in some U.S. cities now caused by strains resistant to β-lactam antibiotics (Chap. 38). The potential incursion of CA-MRSA into hospitals and the resulting impact on surveillance and control of nosocomial MRSA infections are of enormous concern. Second, in the ongoing global reemergence of nosocomial multidrug-resistant gram-negative bacilli, new problems include plasmid-mediated resistance to fluoroquinolones, metallo-β-lactamase-mediated resistance to carbapenems, strains of *K. pneumoniae* that contain carbapenemases (KPCs), and panresistant strains of *Acinetobacter*. Many multidrug-resistant gram-negative bacilli are susceptible only to colistin, a drug that is consequently being "rediscovered."

Third, there has been renewed recognition of the role of nursing homes, and now LTACHs, in the spread of resistant gram-negative bacilli such as KPCs. Fourth, there has been increasing community-based spread of *E. coli* strains harboring an enzyme, CTX-M, that renders them broadly resistant to β-lactam antibiotics; given the community focus of spread, these strains may be seen as a gramnegative version of CA-MRSA. Finally, clinical infections with MRSA strains exhibiting high-level vancomycin resistance due to VRE-derived plasmids have been reported in a few patients—almost all in the United States and most in Michigan—in the setting of prolonged or repeated treatment with vancomycin and/or VRE colonization. Much more common is vancomycin "MIC creep": increasing prevalence of MRSA strains that exhibit upper-limit susceptibility to vancomycin.

Colonized personnel who are implicated in nosocomial transmission of multidrug-resistant pathogens and patients who pose a threat can be decontaminated, depending on the pathogen. In a few ICUs, gastrointestinal decontamination of patients has been used successfully as a temporary emergency control measure for outbreaks of infection due to gram-negative bacilli. Other promising ICU control measures include daily bathing of patients with chlorhexidine and enforcement of environmental cleaning; in recent trials, the bathing intervention led to reduced risk of bacteremia in medical ICU patients, and both of these measures reduced cross-transmission of VRE. "Search-and-destroy" methods—i.e., active surveillance cultures to detect and isolate the "resistance iceberg" of patients colonized with MRSA—in non-outbreak settings are credited

with elimination of nosocomial MRSA in the Netherlands and Denmark.

Because the excessive use of broad-spectrum antibiotics underlies many resistance problems, "antibiotic stewardship" has been promulgated actively. The main tenets are to restrict the use of particular agents to narrowly defined indications in order to limit selective pressure on the nosocomial flora and, when broad-spectrum therapy is begun empirically in critically ill patients, to "de-escalate" treatment as soon as possible on the basis of the results of culture and susceptibility tests.

Bioterrorism and other "surge-event" preparedness

The horrific attack on the World Trade Center in New York City on September 11, 2001; the subsequent mailings of anthrax spores in the United States; and ongoing revelations of terrorist plans and activities in many countries, including the United States, have made bioterrorism a prominent source of concern to hospital infection-control programs (Chap. 7). The essentials for hospital preparedness entail education, internal and external communication, and risk assessment. Up-to-date information is available from the CDC (see *www.bt.cdc.gov*).

EMPLOYEE HEALTH SERVICE ISSUES

An institution's employee health service is a critical component of its infection control efforts. New employees should be processed through the service, where a contagious-disease history can be taken; evidence of immunity to a variety of diseases, such as hepatitis B, chickenpox, measles, mumps, and rubella, can be sought; immunizations for hepatitis B, measles, mumps, rubella, and varicella can be given as needed and a reminder about the essential need for yearly influenza immunization can be imparted; baseline and "booster" PPD (purified protein derivative of tuberculin) skin-testing for tuberculosis can be performed; and education about personal responsibility for infection control can be initiated. Evaluations of employees should be codified to meet the requirements of accrediting and regulatory agencies.

The employee health service must have protocols for dealing with workers exposed to contagious diseases (e.g., influenza) and those percutaneously or mucosally exposed to the blood of patients infected with HIV or hepatitis B or C virus. For example, postexposure HIV prophylaxis with a combination of two or three antiretroviral agents is recommended; free consultation is available from the CDC PEPLine (1-888-HIV-4911). Protocols are also needed for dealing with caregivers who have common contagious diseases (such as chickenpox, group A streptococcal infection, influenza or another respiratory infection, or infectious diarrhea) and for those who have less common but high-visibility public health problems (such as chronic hepatitis B or C or HIV infection) for which exposure control guidelines have been published by the CDC and by the Society for Healthcare Epidemiology of America.

CHAPTER 15

APPROACH TO THE ACUTELY ILL INFECTED FEBRILE PATIENT

Tamar F. Barlam ■ Dennis L. Kasper

The physician treating the acutely ill febrile patient must be able to recognize infections that require emergent attention. If such infections are not adequately evaluated and treated at initial presentation, the opportunity to alter an adverse outcome may be lost. In this chapter, the clinical presentations of and approach to patients with relatively common infectious disease emergencies are discussed. These infectious processes and their treatments are discussed in detail in other chapters.

APPROACH TO THE PATIENT Acute Febrile Illness

Before the history is elicited and a physical examination performed, an immediate assessment of the patient's general appearance can yield valuable information. The perceptive physician's subjective sense that a patient is septic or toxic often proves accurate. Visible agitation or anxiety in a febrile patient can be a harbinger of critical illness.

HISTORY Presenting symptoms are frequently nonspecific. Detailed questions should be asked about the onset and duration of symptoms and about changes in severity or rate of progression over time. Host factors and comorbid conditions may enhance the risk of infection with certain organisms or of a more fulminant course than is usually seen. Lack of splenic function, alcoholism with significant liver disease, IV drug use, HIV infection, diabetes, malignancy, organ transplantation, and chemotherapy all predispose to specific infections and frequently to increased severity. The patient should be questioned about factors that might help identify a nidus for invasive infection, such as recent upper respiratory tract infections, influenza, or varicella; prior trauma; disruption of cutaneous barriers due to lacerations, burns, surgery, body piercing, or decubiti; and the presence of foreign bodies, such as nasal packing after rhinoplasty, tampons, or prosthetic joints. Travel, contact with pets or other animals, or activities that might result in tick or mosquito exposure can lead to diagnoses that would not otherwise be considered. Recent dietary intake, medication use, social or occupational contact with ill individuals, vaccination history, recent sexual contacts, and menstrual history may be relevant. A review of systems should focus on any neurologic signs or sensorium alterations, rashes or skin lesions, and focal pain or tenderness and should also include a general review of respiratory, gastrointestinal, or genitourinary symptoms.

PHYSICAL EXAMINATION A complete physical examination should be performed, with special attention to several areas that are sometimes given short shrift in routine examinations. Assessment of the patient's general appearance and vital signs, skin and soft tissue examination, and the neurologic evaluation are of particular importance.

The patient may appear either anxious and agitated or lethargic and apathetic. Fever is usually present, although elderly patients and compromised hosts [e.g., patients who are uremic or cirrhotic and those who are taking glucocorticoids or nonsteroidal anti-inflammatory drugs (NSAIDs)] may be afebrile despite serious underlying infection. Measurement of blood pressure, heart rate, and respiratory rate helps determine the degree of hemodynamic and metabolic compromise. The patient's airway must be evaluated to rule out the risk of obstruction from an invasive oropharyngeal infection.

The etiologic diagnosis may become evident in the context of a thorough skin examination (Chap. 9). Petechial rashes are typically seen with meningococcemia or Rocky Mountain spotted fever (RMSF; see Fig. 11-16); erythroderma is associated with toxic shock syndrome (TSS) and drug fever. The soft tissue and muscle examination is critical. Areas of erythema or duskiness, edema, and tenderness may indicate underlying necrotizing fasciitis, myositis, or myonecrosis. The neurologic examination must include a careful assessment of mental status for signs of early encephalopathy. Evidence of nuchal rigidity or focal neurologic findings should be sought.

DIAGNOSTIC WORKUP After a quick clinical assessment, diagnostic material should be obtained rapidly and antibiotic and supportive treatment begun. Blood (for cultures; baseline complete blood count with differential; measurement of serum electrolytes, blood urea nitrogen, serum creatinine, and serum glucose; and liver function tests) can be obtained at the time an IV line is placed and before antibiotics are administered. Three sets of blood cultures should be performed for patients with possible acute endocarditis. Asplenic patients should have a blood smear examined to confirm the presence of Howell-Jolly bodies (indicating the absence of splenic function) and a buffy coat examined for bacteria; these patients can have $>10^6$ organisms per milliliter of blood (compared with 10^4/mL in patients with an intact spleen). Blood smears from patients at risk for severe parasitic disease, such as malaria or babesiosis (see Chap. 121), must be examined for the diagnosis and quantitation of parasitemia. Blood smears may also be diagnostic in ehrlichiosis and anaplasmosis.

Patients with possible meningitis should have cerebrospinal fluid (CSF) obtained before the initiation of antibiotic therapy. Focal findings, depressed mental status, or papilledema should be evaluated by brain imaging prior to lumbar puncture, which, in this setting, could initiate herniation. *Antibiotics should be administered before imaging but after blood for cultures has been drawn.* If CSF cultures are negative, blood cultures will provide the diagnosis in 50–70% of cases.

Focal abscesses necessitate immediate CT or MRI as part of an evaluation for surgical intervention. Other diagnostic procedures, such as wound cultures, should not delay the initiation of treatment for more than minutes. Once emergent evaluation, diagnostic procedures, and (if appropriate) surgical consultation (see next) have been completed, other laboratory tests can be conducted. Appropriate radiography, computed axial tomography, MRI, urinalysis, erythrocyte sedimentation rate (ESR) determination, and transthoracic or transesophageal echocardiography may all prove important.

TREATMENT The Acutely Ill Patient

In the acutely ill patient, empirical antibiotic therapy is critical and should be administered without undue delay. Increased prevalence of antibiotic resistance in

community-acquired bacteria must be considered when antibiotics are selected. **Table 15-1** lists first-line treatments for infections considered in this chapter. In addition to the rapid initiation of antibiotic therapy, several of these infections require urgent surgical attention. Neurosurgical evaluation for subdural empyema, otolaryngologic surgery for possible mucormycosis, and cardiothoracic surgery for critically ill patients with acute endocarditis are as important as antibiotic therapy. For infections such as necrotizing fasciitis and clostridial myonecrosis, rapid surgical intervention supersedes other diagnostic or therapeutic maneuvers.

Adjunctive treatments may reduce morbidity and mortality rates and include dexamethasone for bacterial meningitis; IV immunoglobulin for TSS and necrotizing fasciitis caused by group A *Streptococcus*; low-dose hydrocortisone and fludrocortisone for septic shock; and drotrecogin alfa (activated), also known as recombinant human activated protein C, for meningococcemia and severe sepsis. Adjunctive therapies should usually be initiated within the first hours of treatment; however, dexamethasone for bacterial meningitis must be given before or at the time of the first dose of antibiotic.

SPECIFIC PRESENTATIONS

The infections considered as follows according to common clinical presentation can have rapidly catastrophic outcomes, and their immediate recognition and treatment can be life-saving. Recommended empirical therapeutic regimens are presented in Table 15-1.

SEPSIS WITHOUT AN OBVIOUS FOCUS OF PRIMARY INFECTION

These patients initially have a brief prodrome of nonspecific symptoms and signs that progresses quickly to hemodynamic instability with hypotension, tachycardia, tachypnea, respiratory distress, and altered mental status. Disseminated intravascular coagulation (DIC) with clinical evidence of a hemorrhagic diathesis is a poor prognostic sign.

Septic shock

(See also Chap. 16) Patients with bacteremia leading to septic shock may have a primary site of infection (e.g., pneumonia, pyelonephritis, or cholangitis) that is not evident initially. Elderly patients with comorbid conditions, hosts compromised by malignancy and neutropenia, and patients who have recently undergone a surgical procedure or hospitalization are at increased risk for an adverse outcome. Gram-negative bacteremia with organisms such as *Pseudomonas aeruginosa* or *Escherichia coli* and gram-positive infection with organisms such as *Staphylococcus aureus,* including methicillin-resistant *S. aureus* (MRSA), or group A streptococci can present as intractable hypotension and multiorgan failure. Treatment can usually be initiated empirically on the basis of the presentation, host factors (Table 16-3), and local patterns of bacterial resistance. Worse outcomes are evident when antimicrobial treatment is delayed or the pathogenic etiology ultimately proves to be nonsusceptible to the initial regimen. Broad-spectrum antimicrobial agents are therefore recommended. Adjunctive therapy with either drotrecogin alfa (activated) or glucocorticoids should be considered for patients with severe sepsis.

Overwhelming infection in asplenic patients

(See also Chap. 16) Patients without splenic function are at risk for overwhelming bacterial sepsis. Asplenic adult patients succumb to sepsis at 58 times the rate of the general population. Most infections are thought to occur within the first 2 years after splenectomy, with a mortality rate of ~50%, but the increased risk persists throughout life. In asplenia, encapsulated bacteria cause the majority of infections. Adults, who are more likely to have antibody to these organisms, are at lower risk than children. *Streptococcus pneumoniae* is the most common isolate, causing 50–70% of cases, but the risk of infection with *Haemophilus influenzae* or *Neisseria meningitidis* is also high. Severe clinical manifestations of infections due to *E. coli*, *S. aureus*, group B streptococci, *P. aeruginosa*, *Capnocytophaga*, *Bordetella holmesii*, *Babesia*, and *Plasmodium* have been described.

Babesiosis

(See also Chap. 120) A history of recent travel to endemic areas raises the possibility of infection with *Babesia*. Between 1 and 4 weeks after a tick bite, the patient experiences chills, fatigue, anorexia, myalgia, arthralgia, shortness of breath, nausea, and headache; ecchymosis and/or petechiae are occasionally seen. The tick that most commonly transmits *Babesia*, *Ixodes scapularis*, also transmits *Borrelia burgdorferi* (the agent of Lyme disease) and *Anaplasma*; co-infection can occur, resulting in more severe disease. Infection with the European species *Babesia divergens* is more frequently fulminant than that due to the U.S. species *Babesia microti*. *B. divergens* causes a febrile syndrome with hemolysis, jaundice, hemoglobinemia, and renal failure and is associated with a mortality rate of >50%. Severe babesiosis is especially common in asplenic hosts but does occur in hosts with normal splenic function, particularly those who are >60 years of age and those with underlying immunosuppressive conditions such as HIV infection or malignancy. Complications include renal failure, acute respiratory failure, and DIC.

Other sepsis syndromes

Tularemia (Chap. 63) is seen throughout the United States but occurs primarily in Arkansas, Missouri, South

TABLE 15-1

EMPIRICAL TREATMENT FOR COMMON INFECTIOUS DISEASE EMERGENCIES

CLINICAL SYNDROME	POSSIBLE ETIOLOGIES	TREATMENT	COMMENTS	SEE CHAP.
Sepsis Without a Clear Focus				
Septic shock	*Pseudomonas* spp., gram-negative enteric bacilli, *Staphylococcus* spp., *Streptococcus* spp.	Vancomycin (1 g q12h) ***plus*** Gentamicin (5 mg/kg per day) ***plus either*** Piperacillin/tazobactam (3.375 g q4h) ***or*** Cefepime (2 g q12h)	Adjust treatment when culture data become available. Drotrecogin alfa (activated)[a] or low-dose hydrocortisone and fludrocortisone[b] may improve outcome in patients with septic shock.	38, 39, 54, 57, 16
Overwhelming sepsis after splenectomy	*Streptococcus pneumoniae, Haemophilus influenzae, Neisseria meningitidis*	Ceftriaxone (2 g q12h) ***plus*** Vancomycin (1 g q12h)	If a β-lactam-sensitive strain is identified, vancomycin can be discontinued.	16
Babesiosis	*Babesia microti* (U.S.), *B. divergens* (Europe)	*Either:* Clindamycin (600 mg tid) ***plus*** Quinine (650 mg tid) ***or*:** Atovaquone (750 mg q12h) ***plus*** Azithromycin (500-mg loading dose, then 250 mg/d)	Atovaquone and azithromycin are as effective as clindamycin and quinine and are associated with fewer side effects.Treatment with doxycycline (100 mg bid[c]) for potential co-infection with *Borrelia burgdorferi* or *Anaplasma* spp. may be prudent.	116, 120
Sepsis with Skin Findings				
Meningococcemia	*N. meningitidis*	Penicillin (4 mU q4h) ***or*** Ceftriaxone (2 g q12h)	Consider protein C replacement in fulminant meningococcemia.	48
Rocky Mountain spotted fever (RMSF)	*Rickettsia rickettsii*	Doxycycline (100 mg bid)	If both meningococcemia and RMSF are being considered, use ceftriaxone (2 g q12h) *plus* doxycycline (100 mg bid[c]) *or* chloramphenicol alone (50–75 mg/kg per day in four divided doses). If RMSF is diagnosed, doxycycline is the proven superior agent.	79
Purpura fulminans	*S. pneumoniae, H. influenzae, N. meningitidis*	Ceftriaxone (2 g q12h) ***plus*** Vancomycin (1 g q12h)	If a β-lactam–sensitive strain is identified, vancomycin can be discontinued.	37, 48, 50, 16
Erythroderma: toxic shock syndrome	Group A *Streptococcus, Staphylococcus aureus*	Vancomycin (1 g q12h) ***plus*** Clindamycin (600 mg q8h)	If a penicillin- or oxacillin-sensitive strain is isolated, these agents are superior to vancomycin (penicillin, 2 mU q4h; or oxacillin, 2 g q4h). The site of toxigenic bacteria should be debrided; IV immunoglobulin can be used in severe cases.[d]	38, 39
Sepsis with Soft Tissue Findings				
Necrotizing fasciitis	Group A *Streptococcus*, mixed aerobic/anaerobic flora, CA-MRSA[e]	Vancomycin (1 g q12h) ***plus*** Clindamycin (600 mg q8h) ***plus*** gentamicin (5 mg/kg per day)	Urgent surgical evaluation is critical. If a penicillin- or oxacillin-sensitive strain is isolated, these agents are superior to vancomycin (penicillin, 2 mU q4h; or oxacillin, 2 g q4h).	22, 38, 39
Clostridial myonecrosis	*Clostridium perfringens*	Penicillin (2 mU q4h) ***plus*** Clindamycin (600 mg q8h)	Urgent surgical evaluation is critical.	46

(*continued*)

TABLE 15-1

EMPIRICAL TREATMENT FOR COMMON INFECTIOUS DISEASE EMERGENCIES (*CONTINUED*)

CLINICAL SYNDROME	POSSIBLE ETIOLOGIES	TREATMENT	COMMENTS	SEE CHAP.
Neurologic Infections				
Bacterial meningitis	*S. pneumoniae, N. meningitidis*	Ceftriaxone (2 g q12h) ***plus*** Vancomycin (1 g q12h)	If a β-lactam–sensitive strain is identified, vancomycin can be discontinued. If the patient is >50 years old or has comorbid disease, add ampicillin (2 g q4h) for *Listeria* coverage. Dexamethasone (10 mg q6h × 4 days) improves outcome in adult patients with meningitis (especially pneumococcal) and cloudy CSF, positive CSF Gram's stain, or a CSF leukocyte count >1000/mL.	31
Brain abscess, suppurative intracranial infections	*Streptococcus* spp., *Staphylococcus* spp., anaerobes, gram-negative bacilli	Vancomycin (1 g q12h) ***plus*** Metronidazole (500 mg q8h) ***plus*** Ceftriaxone (2 g q12h)	Urgent surgical evaluation is critical. If a penicillin- or oxacillin-sensitive strain is isolated, these agents are superior to vancomycin (penicillin, 4 mU q4h; or oxacillin, 2 g q4h).	31
Cerebral malaria	*Plasmodium falciparum*	Artesunate (2.4 mg/kg IV at 0, 12, and 24 h; then once daily)[f] ***or*** Quinine (IV loading dose of 20 mg salt/kg; then 10 mg/kg q8h) ***plus*** Doxycycline (100 mg IV q12h)	Do not use glucocorticoids. Use IV quinidine if IV quinine is not available. During IV quinidine treatment, blood pressure and cardiac function should be monitored continuously and blood glucose monitored periodically.	116, 119
Spinal epidural abscess	*Staphylococcus* spp., gram-negative bacilli	Vancomycin (1 g q12h) ***plus*** Ceftriaxone (2 g q24h)	Surgical evaluation is essential. If a penicillin- or oxacillin-sensitive strain is isolated, these agents are superior to vancomycin (penicillin, 4 mU q4h; or oxacillin, 2 g q4h).	
Focal Infections				
Acute bacterial endocarditis	*S. aureus*, β-hemolytic streptococci, HACEK group,[g] *Neisseria* spp., *S. pneumoniae*	Ceftriaxone (2 g q12h) ***plus*** Vancomycin (1 g q12h)	Adjust treatment when culture data become available. Surgical evaluation is essential.	20

[a]Drotrecogin alfa (activated) is administered at a dose of 24 μg/kg per hour for 96 h. It has been approved for use in patients with severe sepsis and a high risk of death as defined by an Acute Physiology and Chronic Health Evaluation II (APACHE II) score of ≥25 and/or multiorgan failure.
[b]Hydrocortisone (50-mg IV bolus q6h) with fludrocortisone (50-μg tablet daily for 7 days) may improve outcomes of severe sepsis, particularly in the setting of relative adrenal insufficiency.
[c]Tetracyclines can be antagonistic in action to β-lactam agents. Adjust treatment as soon as the diagnosis is confirmed.
[d]The optimal dose of IV immunoglobulin has not been determined, but the median dose in observational studies is 2 g/kg (total dose administered over 1–5 days).
[e]Community-acquired methicillin-resistant *S. aureus.*
[f]In the United States, artesunate must be obtained through the Centers for Disease Control and Prevention. For patients diagnosed with severe malaria, full doses of parenteral antimalarial treatment should be started with whichever recommended antimalarial agent is first available.
[g]*Haemophilus aphrophilus, H. paraphrophilus, H. parainfluenzae, Aggregatibacter* (formerly *Actinobacillus*) *actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella kingae.*

Dakota, and Oklahoma. This disease is associated with wild rabbit, tick, and tabanid fly contact. The typhoidal form can be associated with gram-negative septic shock and a mortality rate of >30%, especially in patients with underlying comorbid or immunosuppressive conditions. Plague occurs infrequently in the United States (Chap. 64), primarily after contact with ground squirrels, prairie dogs, or chipmunks, but is endemic in other parts of the world, with >90% of all cases occurring in Africa. The septic form is particularly rare and is associated with shock, multiorgan failure, and a 30% mortality rate. These infections should be considered in the appropriate epidemiologic setting. The Centers for Disease Control and Prevention lists *Francisella tularensis* and *Yersinia pestis* (the agents of tularemia and plague, respectively) along with *Bacillus anthracis* (the agent of anthrax) as important organisms that might be used for bioterrorism (Chap. 7).

SEPSIS WITH SKIN MANIFESTATIONS

(See also Chap. 9) Maculopapular rashes may reflect early meningococcal or rickettsial disease but are usually associated with nonemergent infections. Exanthems are usually viral. Primary HIV infection commonly presents with a rash that is typically maculopapular and involves the upper part of the body but can spread to the palms and soles. The patient is usually febrile and can have lymphadenopathy, severe headache, dysphagia, diarrhea, myalgias, and arthralgias. Recognition of this syndrome provides an opportunity to prevent transmission and to institute treatment and monitoring early on.

Petechial rashes caused by viruses are seldom associated with hypotension or a toxic appearance, although there can be exceptions (e.g., severe measles or arboviral infection). In other settings, petechial rashes require more urgent attention.

Meningococcemia

(See also Chap. 48) Almost three-quarters of patients with bacteremic *N. meningitidis* infection have a rash. Meningococcemia most often affects young children (i.e., those 6 months to 5 years old). In sub-Saharan Africa, the high prevalence of serogroup A meningococcal disease has been a threat to public health for more than a century. Thousands of deaths occur annually in this area, which is known as the "meningitis belt," and large epidemic waves occur approximately every 8–12 years. In the United States, sporadic cases and outbreaks occur in day-care centers, schools (grade school through college), and army barracks. Household contacts of index cases are at 400–800 times greater risk of disease than the general population. Patients may exhibit fever, headache, nausea, vomiting, myalgias, changes in mental status, and meningismus. However, the rapidly progressive form of disease is not usually associated with meningitis. The rash is initially pink, blanching, and maculopapular, appearing on the trunk and extremities, but then becomes hemorrhagic, forming petechiae. Petechiae are first seen at the ankles, wrists, axillae, mucosal surfaces, and palpebral and bulbar conjunctiva, with subsequent spread to the lower extremities and trunk. A cluster of petechiae may be seen at pressure points—e.g., where a blood pressure cuff has been inflated. In rapidly progressive meningococcemia (10–20% of cases), the petechial rash quickly becomes purpuric, and patients develop DIC, multiorgan failure, and shock. Of these patients, 50–60% die, and survivors often require extensive debridement or amputation of gangrenous extremities. Hypotension with petechiae for <12 h is associated with significant mortality. Cyanosis, coma, oliguria, metabolic acidosis, and elevated partial thromboplastin time are also associated with a fatal outcome. Correction of protein C deficiency may improve outcome. Antibiotics given in the office by the primary care provider before hospital evaluation and admission may improve prognosis; this observation suggests that early initiation of treatment may be life-saving.

Rocky Mountain spotted fever

(See also Chap. 79) RMSF is a tickborne disease caused by *Rickettsia rickettsii* that occurs throughout North and South America. Up to 40% of patients do not report a history of a tick bite, but a history of travel or outdoor activity (e.g., camping in tick-infested areas) can often be ascertained. For the first 3 days, headache, fever, malaise, myalgias, nausea, vomiting, and anorexia are documented. By day 3, half of patients have skin findings. Blanching macules develop initially on the wrists and ankles and then spread over the legs and trunk. The lesions become hemorrhagic and are frequently petechial. The rash spreads to palms and soles later in the course. The centripetal spread is a classic feature of RMSF, but occurs in a minority of patients. Moreover, 10–15% of patients with RMSF never develop a rash. The patient can be hypotensive and develop noncardiogenic pulmonary edema, confusion, lethargy, and encephalitis progressing to coma. The CSF contains 10–100 cells/μL, usually with a predominance of mononuclear cells. The CSF glucose level is often normal; the protein concentration may be slightly elevated. Renal and hepatic injury and bleeding secondary to vascular damage are noted. Untreated infection has a mortality rate of 20–30%.

Other rickettsial diseases cause significant morbidity and mortality worldwide. *Mediterranean spotted fever* caused by *Rickettsia conorii* is found in Africa, southwestern and south-central Asia, and southern Europe. Patients have fever, flu-like symptoms, and an inoculation eschar at the site of the tick bite. A maculopapular rash develops within 1–7 days, involving the palms and soles but sparing the face. Elderly patients or those with diabetes, alcoholism, uremia, or congestive heart failure are at risk for severe disease characterized by neurologic involvement, respiratory distress, and gangrene of the digits. Mortality rates associated with this severe form of disease approach 50%. *Epidemic typhus*, caused by *Rickettsia prowazekii*, is transmitted in louse-infested environments and emerges in conditions

of extreme poverty, war, and natural disaster. Patients experience a sudden onset of high fevers, severe headache, cough, myalgias, and abdominal pain. A maculopapular rash develops (primarily on the trunk) in more than half of patients and can progress to petechiae and purpura. Serious signs include delirium, coma, seizures, noncardiogenic pulmonary edema, skin necrosis, and peripheral gangrene. Mortality rates approached 60% in the preantibiotic era and continue to exceed 10–15% in contemporary outbreaks. *Scrub typhus*, caused by *Orientia tsutsugamushi*—a separate genus in the family Rickettsiaceae—is transmitted by larval mites or chiggers and is one of the most common infections in southeastern Asia and the western Pacific. The organism is found in areas of heavy scrub vegetation (e.g., along riverbanks). Patients may have an inoculation eschar and may develop a maculopapular rash. Severe cases progress to pneumonia, meningoencephalitis, DIC, and renal failure. Mortality rates range from 1% to 35%.

If recognized in a timely fashion, rickettsial disease is very responsive to treatment. Doxycycline (100 mg twice daily for 3–14 days) is the treatment of choice for both adults and children. The newer macrolides and chloramphenicol may be suitable alternatives.

Purpura fulminans

(See also Chaps. 16 and 48) Purpura fulminans is the cutaneous manifestation of DIC and presents as large ecchymotic areas and hemorrhagic bullae. Progression of petechiae to purpura, ecchymoses, and gangrene is associated with congestive heart failure, septic shock, acute renal failure, acidosis, hypoxia, hypotension, and death. Purpura fulminans has been associated primarily with *N. meningitidis* but, in splenectomized patients, may be associated with *S. pneumoniae* and *H. influenzae*. Several small studies have suggested that correction of the protein C deficiency evident in meningococcal purpura fulminans with drotrecogin alfa (activated) may dramatically improve outcome.

Ecthyma gangrenosum

Septic shock caused by *P. aeruginosa* or *Aeromonas hydrophila* can be associated with ecthyma gangrenosum (see Figs. 57-1 and 11-35): hemorrhagic vesicles surrounded by a rim of erythema with central necrosis and ulceration. These gram-negative bacteremias are most common among patients with neutropenia, extensive burns, and hypogammaglobulinemia.

Other emergent infections associated with rash

Vibrio vulnificus and other noncholera *Vibrio* bacteremic infections (Chap. 61) can cause focal skin lesions and overwhelming sepsis in hosts with liver disease, diabetes, renal insufficiency, or other immunocompromising conditions. After ingestion of contaminated raw shellfish, there is a sudden onset of malaise, chills, fever, and hypotension. The patient develops bullous or hemorrhagic skin lesions, usually on the lower extremities, and 75% of patients have leg pain. The mortality rate can be as high as 50–60%, particularly when the patient presents with hypotension. Other infections, caused by agents such as *Aeromonas, Klebsiella*, and *E. coli*, can cause hemorrhagic bullae and death due to overwhelming sepsis in cirrhotic patients. *Capnocytophaga canimorsus* can cause septic shock in asplenic patients. Infection typically follows a dog bite. Patients present with fever, chills, myalgia, vomiting, diarrhea, dyspnea, confusion, and headache. Findings can include an exanthem or erythema multiforme (see Fig. 11-25), cyanotic mottling or peripheral cyanosis, petechiae, and ecchymosis. About 30% of patients with this fulminant form die of overwhelming sepsis and DIC, and survivors may require amputation because of gangrene.

Erythroderma

TSS (Chaps. 38 and 39) is usually associated with erythroderma. The patient presents with fever, malaise, myalgias, nausea, vomiting, diarrhea, and confusion. There is a sunburn-type rash that may be subtle and patchy but is usually diffuse and is found on the face, trunk, and extremities. Erythroderma, which desquamates after 1–2 weeks, is more common in *Staphylococcus*-associated than in *Streptococcus*-associated TSS. Hypotension develops rapidly—often within hours—after the onset of symptoms. Multiorgan failure is seen. Early renal failure may precede hypotension and distinguishes this syndrome from other septic shock syndromes. There may be no indication of a primary focal infection, although possible cutaneous or mucosal portals of entry for the organism can be ascertained when a careful history is taken. Colonization rather than overt infection of the vagina or a postoperative wound, for example, is typical with staphylococcal TSS, and the mucosal areas appear hyperemic but not infected. Streptococcal TSS is more often associated with skin or soft tissue infection (including necrotizing fasciitis), and patients are more likely to be bacteremic. The diagnosis of TSS is defined by the clinical criteria of fever, rash, hypotension, and multiorgan involvement. The mortality rate is 5% for menstruation-associated TSS, 10–15% for nonmenstrual TSS, and 30–70% for streptococcal TSS.

Viral hemorrhagic fevers

Viral hemorrhagic fevers (Chaps. 102 and 103) are zoonotic illnesses caused by viruses that reside in either animal reservoirs or arthropod vectors. These diseases occur worldwide and are restricted to areas where the host species live. They are caused by four major groups of viruses: Arenaviridae (e.g., Lassa fever in Africa), Bunyaviridae (e.g., Rift Valley fever in Africa or hantavirus hemorrhagic fever with renal syndrome in Asia), Filoviridae (e.g., Ebola and Marburg virus infections in Africa), and Flaviviridae (e.g., yellow fever in Africa and South America and dengue in Asia, Africa, and the Americas). Lassa fever and Ebola and Marburg virus infections are also

transmitted from person to person. The vectors for most viral fevers are found in rural areas; dengue and yellow fever are important exceptions. After a prodrome of fever, myalgias, and malaise, patients develop evidence of vascular damage, petechiae, and local hemorrhage. Shock, multifocal hemorrhaging, and neurologic signs (e.g., seizures or coma) predict a poor prognosis. Dengue (Chap. 102) is the most common arboviral disease worldwide. More than half a million cases of dengue hemorrhagic fever occur each year, with at least 12,000 deaths. Patients have a triad of symptoms: hemorrhagic manifestations, evidence of plasma leakage, and platelet counts <100,000/μL. Mortality rates are 10–20%. If dengue shock syndrome develops, mortality can reach 40%. Although supportive care to maintain blood pressure and intravascular volume with careful volume-replacement therapy is key, ribavirin also may be useful against Arenaviridae and Bunyaviridae.

SEPSIS WITH A SOFT TISSUE/MUSCLE PRIMARY FOCUS

See also Chap. 22.

Necrotizing fasciitis

This infection is characterized by extensive necrosis of the subcutaneous tissue and fascia. It may arise at a site of minimal trauma or postoperative incision and may also be associated with recent varicella, childbirth, or muscle strain. The most common causes of necrotizing fasciitis are group A streptococci alone (Chap. 39) and a mixed facultative and anaerobic flora (Chap. 22). Diabetes mellitus, peripheral vascular disease, and IV drug use are associated risk factors. Physical findings are minimal compared with the severity of pain and the degree of fever. The examination is often unremarkable except for soft tissue edema and erythema. The infected area is red, hot, shiny, swollen, and exquisitely tender. In untreated infection, the overlying skin develops blue-gray patches after 36 h, and cutaneous bullae and necrosis develop after 3–5 days. Necrotizing fasciitis due to a mixed flora, but not that due to group A streptococci, can be associated with gas production. Without treatment, pain decreases because of thrombosis of the small blood vessels and destruction of the peripheral nerves—an ominous sign. The mortality rate is 15–34% overall, >70% in association with TSS, and nearly 100% without surgical intervention. Necrotizing fasciitis may also be due to *Clostridium perfringens* (Chap. 46); in this condition, the patient is extremely toxic and the mortality rate is high. Within 48 h, rapid tissue invasion and systemic toxicity associated with hemolysis and death ensue. The distinction between this entity and clostridial myonecrosis is made by muscle biopsy. Necrotizing fasciitis caused by community-acquired MRSA has been reported. The MRSA-infected patients in one series required extensive surgical debridement, but there were no deaths.

Clostridial myonecrosis

(See also Chap. 46) Myonecrosis is often associated with trauma or surgery but can be spontaneous. The incubation period is usually 12–24 h long, and massive necrotizing gangrene develops within hours of onset. Systemic toxicity, shock, and death can occur within 12 h. The patient's pain and toxic appearance are out of proportion to physical findings. On examination, the patient is febrile, apathetic, tachycardic, and tachypneic and may express a feeling of impending doom. Hypotension and renal failure develop later, and hyperalertness is evident preterminally. The skin over the affected area is bronze-brown, mottled, and edematous. Bullous lesions with serosanguineous drainage and a mousy or sweet odor can develop. Crepitus can occur secondary to gas production in muscle tissue. The mortality rate is >65% with spontaneous myonecrosis, which is often associated with *Clostridium septicum* and underlying malignancy. The mortality rates associated with trunk and limb infection are 63% and 12%, respectively, and any delay in surgical treatment increases the risk of death.

NEUROLOGIC INFECTIONS WITH OR WITHOUT SEPTIC SHOCK

Bacterial meningitis

(See also Chap. 31) Bacterial meningitis is one of the most common infectious disease emergencies involving the central nervous system. Although hosts with cell-mediated immune deficiency (including transplant recipients, diabetic patients, elderly patients, and cancer patients receiving certain chemotherapeutic agents) are at particular risk for *Listeria monocytogenes* meningitis, most cases in adults are due to *S. pneumoniae* (30–50%) and *N. meningitidis* (10–35%). The classic presentation of fever, meningismus, and altered mental status is seen in only one-half to two-thirds of patients. The elderly can present without fever or meningeal signs despite lethargy and confusion. Cerebral dysfunction is evidenced by confusion, delirium, and lethargy that can progress to coma. A fulminant presentation with sepsis and brain edema occurs in some cases; papilledema at presentation is unusual and suggests another diagnosis (e.g., an intracranial lesion). Focal signs, including cranial nerve palsies (IV, VI, VII), can be seen in 10–20% of cases; 50–70% of patients have bacteremia. A poor outcome is associated with coma, hypotension, meningitis due to *S. pneumoniae*, respiratory distress, a CSF glucose level of <0.6 mmol/L (<10 mg/dL), a CSF protein level of >2.5 g/L, a peripheral white blood cell count of <5000/μL, and a serum sodium level of <135 mmol/L. Rapid initiation of treatment is essential; the odds of an unfavorable outcome may increase by 30% for each hour that treatment is delayed.

Suppurative intracranial infections

(See also Chap. 31) In suppurative intracranial infections, rare intracranial lesions present along with sepsis and hemodynamic instability. Rapid recognition of the toxic patient with central neurologic signs is crucial to improvement of the dismal prognosis of these entities. *Subdural empyema* arises from the paranasal sinus in 60–70% of cases. Microaerophilic streptococci and staphylococci are the predominant etiologic organisms. The patient is toxic, with fever, headache, and nuchal rigidity. Of all patients, 75% have focal signs and 6–20% die. Despite improved survival rates, 15–44% of patients are left with permanent neurologic deficits. *Septic cavernous sinus thrombosis* follows a facial or sphenoid sinus infection; 70% of cases are due to staphylococci (including MRSA), and the remainder are due primarily to aerobic or anaerobic streptococci. A unilateral or retroorbital headache progresses to a toxic appearance and fever within days. Three-quarters of patients have unilateral periorbital edema that becomes bilateral and then progresses to ptosis, proptosis, ophthalmoplegia, and papilledema. The mortality rate is as high as 30%. *Septic thrombosis of the superior sagittal sinus* spreads from the ethmoid or maxillary sinuses and is caused by *S. pneumoniae*, other streptococci, and staphylococci. The fulminant course is characterized by headache, nausea, vomiting, rapid progression to confusion and coma, nuchal rigidity, and brainstem signs. If the sinus is totally thrombosed, the mortality rate exceeds 80%.

Brain abscess

(See also Chap. 31) Brain abscess often occurs without systemic signs. Almost half of patients are afebrile, and presentations are more consistent with a space-occupying lesion in the brain; 70% of patients have headache and/or altered mental status, 50% have focal neurologic signs, and 25% have papilledema. Abscesses can present as single or multiple lesions resulting from contiguous foci or hematogenous infection, such as endocarditis. The infection progresses over several days from cerebritis to an abscess with a mature capsule. More than half of infections are polymicrobial, with an etiology consisting of aerobic bacteria (primarily streptococcal species) and anaerobes. Abscesses arising hematogenously are especially apt to rupture into the ventricular space, causing a sudden and severe deterioration in clinical status and high mortality. Otherwise, mortality is low but morbidity is high (30–55%). Patients presenting with stroke and a parameningeal infectious focus, such as sinusitis or otitis, may have a brain abscess, and physicians must maintain a high level of suspicion. Prognosis worsens in patients with a fulminant course, delayed diagnosis, abscess rupture into the ventricles, multiple abscesses, or abnormal neurologic status at presentation.

Intracranial and spinal epidural abscesses

Spinal and intracranial epidural abscesses (SEAs and ICEAs) can result in permanent neurologic deficits, sepsis, and death. At-risk patients include those with diabetes mellitus; IV drug use; chronic alcohol abuse; recent spinal trauma, surgery, or epidural anesthesia; and other comorbid conditions, such as HIV infection. In the United States and Canada, where early treatment of otitis and sinusitis is typical, ICEA is rare but the number of cases of SEA is on the rise. In Africa and areas with limited access to health care, SEAs and ICEAs cause significant morbidity and mortality. ICEAs typically present as fever, mental status changes, and neck pain, while SEAs often present as fever, localized spinal tenderness, and back pain. ICEAs are typically polymicrobial, whereas SEAs are most often due to hematogenous seeding, with staphylococci the most common etiologic agent. Early diagnosis and treatment, which may include surgical drainage, minimize rates of mortality and permanent neurologic sequelae.

Cerebral malaria

(See also Chap. 119) This entity should be urgently considered if patients who have recently traveled to areas endemic for malaria present with a febrile illness and lethargy or other neurologic signs. Fulminant malaria is caused by *Plasmodium falciparum* and is associated with temperatures of >40°C (>104°F), hypotension, jaundice, adult respiratory distress syndrome, and bleeding. By definition, any patient with a change in mental status or repeated seizure in the setting of fulminant malaria has cerebral malaria. In adults, this nonspecific febrile illness progresses to coma over several days; occasionally, coma occurs within hours and death within 24 h. Nuchal rigidity and photophobia are rare. On physical examination, symmetric encephalopathy is typical, and upper motor neuron dysfunction with decorticate and decerebrate posturing can be seen in advanced disease. Unrecognized infection results in a 20–30% mortality rate.

Other focal syndromes with a fulminant course

Infection at virtually any primary focus (e.g., osteomyelitis, pneumonia, pyelonephritis, or cholangitis) can result in bacteremia and sepsis. TSS has been associated with focal infections such as septic arthritis, peritonitis, sinusitis, and wound infection. Rapid clinical deterioration and death can be associated with destruction of the primary site of infection, as is seen in endocarditis and in necrotizing infections of the oropharynx (in which edema suddenly compromises the airway).

Rhinocerebral mucormycosis

(See also Chap. 112) Patients with diabetes or immunocompromising conditions are at risk for invasive rhinocerebral mucormycosis. Patients present with low-grade fever, dull sinus pain, diplopia, decreased mental status, decreased ocular motion, chemosis, proptosis, dusky or necrotic nasal turbinates, and necrotic hard-palate lesions that respect the midline. Without rapid

recognition and intervention, the process continues on an inexorable invasive course, with high mortality.

Acute bacterial endocarditis

(See also Chap. 20) This entity presents with a much more aggressive course than subacute endocarditis. Bacteria such as *S. aureus*,*S. pneumoniae*, *L. monocytogenes*, *Haemophilus* spp., and streptococci of groups A, B, and G attack native valves. Native-valve endocarditis caused by *S. aureus*, including MRSA, is increasing, particularly in health care settings. Mortality rates range from 10% to 40%. The host may have comorbid conditions such as underlying malignancy, diabetes mellitus, IV drug use, or alcoholism. The patient presents with fever, fatigue, and malaise <2 weeks after onset of infection. On physical examination, a changing murmur and congestive heart failure may be noted. Hemorrhagic macules on palms or soles (*Janeway lesions*) sometimes develop. Petechiae, Roth's spots, splinter hemorrhages, and splenomegaly are unusual. Rapid valvular destruction, particularly of the aortic valve, results in pulmonary edema and hypotension. Myocardial abscesses can form, eroding through the septum or into the conduction system and causing life-threatening arrhythmias or high-degree conduction block. Large friable vegetations can result in major arterial emboli, metastatic infection, or tissue infarction. Older patients with *S. aureus* endocarditis are especially likely to present with nonspecific symptoms—a circumstance that delays diagnosis and worsens prognosis. Rapid intervention is crucial for a successful outcome.

Inhalational anthrax

(See also Chap. 7) Inhalational anthrax, the most severe form of disease caused by *B. anthracis*, had not been reported in the United States for more than 25 years until the use of this organism as an agent of bioterrorism in 2001. Patients presented with malaise, fever, cough, nausea, drenching sweats, shortness of breath, and headache. Rhinorrhea was unusual. All patients had abnormal chest roentgenograms at presentation. Pulmonary infiltrates, mediastinal widening, and pleural effusions were the most common findings. Hemorrhagic meningitis was seen in 38% of these patients. Survival was more likely when antibiotics were given during the prodromal period and when multidrug regimens were used. In the absence of urgent intervention with antimicrobial agents and supportive care, inhalational anthrax progresses rapidly to hypotension, cyanosis, and death.

Avian influenza (H5N1) infection

(See also Chap. 92) Human cases of avian influenza have occurred primarily in Southeast Asia, particularly Vietnam. Avian influenza should be considered in patients with severe respiratory tract illness, particularly if they have been exposed to poultry. Patients present with high fever, an influenza-like illness, and lower respiratory tract symptoms; this illness can progress rapidly to bilateral pneumonia, acute respiratory distress syndrome, multiorgan failure, and death. Early antiviral treatment with neuraminidase inhibitors should be initiated along with aggressive supportive measures. Unlike avian influenza, for which human-to-human transmission has been rare so far, a novel swine-associated influenza A/H1N1 virus has spread rapidly throughout the world. Early in the pandemic, there has been a sudden increase in severe pneumonia affecting a younger population. Patients most at risk of severe disease are children <5 years of age, elderly persons, patients with underlying chronic conditions, and pregnant women.

Hantavirus pulmonary syndrome

(See also Chap. 102) Hantavirus pulmonary syndrome has been documented in the United States (primarily the southwestern states), Canada, and South America. Most cases occur in rural areas and are associated with exposure to rodents. Patients present with a nonspecific viral prodrome of fever, malaise, myalgias, nausea, vomiting, and dizziness that may progress to pulmonary edema and respiratory failure. Hantavirus pulmonary syndrome causes myocardial depression and increased pulmonary vascular permeability; therefore, careful fluid resuscitation and use of pressor agents are crucial. Aggressive cardiopulmonary support during the first few hours of illness can be life-saving. The early onset of thrombocytopenia may help distinguish this syndrome from other febrile illnesses in an appropriate epidemiologic setting.

CONCLUSION

Acutely ill febrile patients with the syndromes discussed in this chapter require close observation, aggressive supportive measures, and—in most cases—admission to intensive care units. The most important task of the physician is to distinguish these patients from other infected febrile patients whose illness will not progress to fulminant disease. The alert physician must recognize the acute infectious disease emergency and then proceed with appropriate urgency.

CHAPTER 16

SEVERE SEPSIS AND SEPTIC SHOCK

Robert S. Munford

DEFINITIONS

(See Table 16-1) Animals mount both local and systemic responses to microbes that traverse their epithelial barriers and enter underlying tissues. Fever or hypothermia, leukocytosis or leukopenia, tachypnea, and tachycardia are the cardinal signs of the systemic response, that is often called the *systemic inflammatory response syndrome* (SIRS). SIRS may have an infectious or a noninfectious etiology. If infection is suspected or proven, a patient with SIRS is said to have *sepsis*. When sepsis is associated with dysfunction of organs distant from the site of infection, the patient has *severe sepsis*. Severe sepsis may be accompanied by hypotension or evidence of hypoperfusion. When hypotension cannot be corrected by infusing fluids, the diagnosis is *septic shock*. These definitions were developed by consensus conference committees in 1992 and 2001 and have been widely used; there is evidence that the different stages may form a continuum.

ETIOLOGY

Sepsis can be a response to any class of microorganism. Microbial invasion of the bloodstream is not essential, since local inflammation can also elicit distant organ dysfunction and hypotension. In fact, blood cultures yield bacteria or fungi in only ~20–40% of cases of severe sepsis and 40–70% of cases of septic shock. Individual gram-negative or gram-positive bacteria account for ~70% of these isolates; the remainder are fungi or a mixture of microorganisms (Table 16-2). In patients whose blood cultures are negative, the etiologic agent is often established by culture or microscopic examination of infected material from a local site; specific identification of microbial DNA or RNA in blood or tissue samples is also used. In some case series, a majority of patients with a clinical picture of severe sepsis or septic shock have had negative microbiologic data.

EPIDEMIOLOGY

Severe sepsis is a contributing factor in >200,000 deaths per year in the United States. The incidence of severe sepsis and septic shock has increased over the past 30 years, and the annual number of cases is now >700,000 (~3 per 1000 population). Approximately two-thirds of the cases occur in patients with significant underlying illness. Sepsis-related incidence and mortality rates increase with age and preexisting comorbidity. The rising incidence of severe sepsis in the United States is attributable to the aging of the population, the increasing longevity of patients with chronic diseases, and the relatively high frequency with which sepsis develops in patients with AIDS. The widespread use of immunosuppressive drugs, indwelling catheters, and mechanical devices also plays a role.

Invasive bacterial infections are prominent causes of death around the world, particularly among young children. In sub-Saharan Africa, for example, careful screening for positive blood cultures found that community-acquired bacteremia accounted for at least one-fourth of deaths of children >1 year of age. Nontyphoidal *Salmonella* species, *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Escherichia coli* were the most commonly isolated bacteria. Bacteremic children often had HIV infection or were severely malnourished.

PATHOPHYSIOLOGY

Most cases of severe sepsis are triggered by bacteria or fungi that do not ordinarily cause systemic disease in immunocompetent hosts (Table 16-2). To survive within the human body, these microbes often exploit deficiencies in host defenses, indwelling catheters or other foreign matter, or obstructed fluid drainage conduits. Microbial pathogens, in contrast, can circumvent innate defenses because they (1) lack molecules that can be recognized by host receptors (see next) or (2) elaborate toxins or other virulence factors. In both cases, the body can mount a vigorous inflammatory reaction that results in severe sepsis yet fails to kill the invaders. The septic response may also be induced by microbial exotoxins that act as superantigens (e.g., toxic shock syndrome toxin 1; Chap. 38) as well as by many pathogenic viruses.

TABLE 16-1

DEFINITIONS USED TO DESCRIBE THE CONDITION OF SEPTIC PATIENTS	
Bacteremia	Presence of bacteria in blood, as evidenced by positive blood cultures
Septicemia	Presence of microbes or their toxins in blood
Systemic inflammatory response syndrome (SIRS)	Two or more of the following conditions: (1) fever (oral temperature >38°C) or hypothermia (<36°C); (2) tachypnea (>24 breaths/min); (3) tachycardia (heart rate >90 beats/min); (4) leukocytosis (>12,000/μL), leucopenia (<4,000/μL), or >10% bands; may have a noninfectious etiology
Sepsis	SIRS that has a proven or suspected microbial etiology
Severe sepsis (similar to "sepsis syndrome")	Sepsis with one or more signs of organ dysfunction—for example: 1. *Cardiovascular:* Arterial systolic blood pressure ≤90 mmHg or mean arterial pressure ≤70 mmHg that responds to administration of intravenous fluid 2. *Renal:* Urine output <0.5 mL/kg per hour for 1 h despite adequate fluid resuscitation 3. *Respiratory:* Pa_{O_2}/FI_{O_2} ≤250 or, if the lung is the only dysfunctional organ, ≤200 4. *Hematologic:* Platelet count <80,000/μL or 50% decrease in platelet count from highest value recorded over previous 3 days 5. *Unexplained metabolic acidosis:* A pH ≤7.30 or a base deficit ≥5.0 mEq/L and a plasma lactate level >1.5 times upper limit of normal for reporting lab 6. *Adequate fluid resuscitation:* Pulmonary artery wedge pressure ≥12 mmHg or central venous pressure ≥8 mmHg
Septic shock	Sepsis with hypotension (arterial blood pressure <90 mmHg systolic, or 40 mmHg less than patient's normal blood pressure) for at least 1 h despite adequate fluid resuscitation; *or* Need for vasopressors to maintain systolic blood pressure ≥90 mmHg *or* mean arterial pressure ≥70 mmHg
Refractory septic shock	Septic shock that lasts for >1 h and does not respond to fluid or pressor administration
Multiple-organ dysfunction syndrome (MODS)	Dysfunction of more than one organ, requiring intervention to maintain homeostasis
Predisposition–infection–response–organ dysfunction (PIRO)	A grading system that stratifies patients according to four key aspects of illness; attempts to define subgroups of patients, reducing heterogeneity in clinical trials
Critical illness–related corticosteroid insufficiency (CIRCI)	Inadequate corticosteroid activity for the patient's severity of illness; should be suspected when hypotension is not relieved by fluid administration

Source: Adapted from the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference Committee.

Host mechanisms for sensing microbes

Animals have exquisitely sensitive mechanisms for recognizing and responding to certain highly conserved microbial molecules. Recognition of the lipid A moiety of lipopolysaccharide (LPS, also called *endotoxin*; Chap. 2) is the best-studied example. A host protein (LPS-binding protein) binds lipid A and transfers the LPS to CD14 on the surfaces of monocytes, macrophages, and neutrophils. LPS then is passed to MD-2, which is bound to Toll-like receptor (TLR) 4 to form a molecular complex that transduces the LPS recognition signal to the interior of the cell. This signal rapidly triggers the production and release of mediators, such as tumor necrosis factor (TNF; see next), that amplify the LPS signal and transmit it to other cells and tissues. Bacterial peptidoglycan and lipopeptides elicit responses in animals that are generally similar to those induced by LPS; whereas these molecules also may be transferred by CD14, they interact with different TLRs. Having numerous TLR-based receptor complexes (11 different TLRs have been identified so far in humans) allows animals to recognize many conserved microbial molecules; others include lipopeptides (TLR2/1, TLR2/6), flagellin (TLR5), undermethylated DNA sequences (TLR9), and double-stranded RNA (TLR3, TLR7). The ability of some TLRs to serve as receptors for host ligands (e.g., hyaluronans, heparan sulfate, saturated fatty acids) raises the possibility that they also play a role in producing noninfectious sepsis-like states. Other host pattern-recognition proteins that are important for sensing microbial invasion include the intracellular NOD1 and NOD2 proteins, which recognize discrete fragments of bacterial peptidoglycan; early complement components (principally in the alternative pathway); and mannose-binding lectin and C-reactive protein, which activate the classic complement pathway.

TABLE 16-2

MICROORGANISMS INVOLVED IN EPISODES OF SEVERE SEPSIS AT EIGHT ACADEMIC MEDICAL CENTERS

MICROORGANISM	EPISODES WITH BLOOD-STREAM INFECTION, % (*n* = 436)	EPISODES WITH DOCUMENTED INFECTION BUT NO BLOODSTREAM INFECTION, % (*n* = 430)	TOTAL EPISODES, % (*n* = 866)
Gram-negative bacteria[a]	35	44	40
Gram-positive bacteria[b]	40	24	31
Fungi	7	5	6
Polymicrobial	11	21	16
Classic pathogens[c]	<5	<5	<5

[a]Enterobacteriaceae, pseudomonads, *Haemophilus* spp., other gram-negative bacteria.
[b]*Staphylococcus aureus*, coagulase-negative staphylococci, enterococci, *Streptococcus pneumoniae*, other streptococci, other gram-positive bacteria.
[c]Such as *Neisseria meningitidis*, *S. pneumoniae*, *Haemophilus influenzae*, and *Streptococcus pyogenes*.
Source: Adapted from KE Sands et al: JAMA 278:234, 1997.

A host's ability to recognize certain microbial molecules may influence both the potency of its own defenses and the pathogenesis of severe sepsis. For example, MD-2–TLR4 best senses LPS that has a hexaacyl lipid A moiety (i.e., one with six fatty acyl chains). Most of the commensal aerobic and facultatively anaerobic gram-negative bacteria that trigger severe sepsis and shock (including *E. coli*, *Klebsiella*, and *Enterobacter*) make this lipid A structure. When they invade human hosts, often through breaks in an epithelial barrier, they are typically confined to the subepithelial tissue by a localized inflammatory response. Bacteremia, if it occurs, is intermittent and low-grade, as these bacteria are efficiently cleared from the bloodstream by TLR4-expressing Kupffer cells and splenic macrophages. These mucosal commensals seem to induce severe sepsis most often by triggering severe local tissue inflammation rather than by circulating within the bloodstream. One exception is *Neisseria meningitidis*. Its hexaacyl LPS seems to be shielded from host recognition by its polysaccharide capsule. This protection may allow meningococci to transit undetected from the nasopharyngeal mucosa into the bloodstream, where they can infect vascular endothelial cells and release large amounts of endotoxin. Host recognition of lipid A may nonetheless influence pathogenesis, as meningococci that produce pentaacyl LPS were isolated from the blood of patients with less severe coagulopathy than was found in patients whose isolates produced hexaacyl lipid A. In contrast, gram-negative bacteria that make lipid A with fewer than six acyl chains (*Yersinia pestis*, *Francisella tularensis*, *Vibrio vulnificus*, *Pseudomonas aeruginosa*, and *Burkholderia pseudomallei*, among others) are poorly recognized by MD-2–TLR4. When these bacteria enter the body, they may initially induce relatively little inflammation. When they do trigger severe sepsis, it is often after they have multiplied to high density in tissues and blood. The importance of LPS recognition in disease pathogenesis has been shown by engineering a virulent strain of *Y. pestis*, which makes tetraacyl LPS at 37°C, to produce hexaacyl LPS; unlike its virulent parent, the mutant strain stimulates local inflammation and is rapidly cleared from tissues. For at least one large class of microbes—gram-negative aerobic bacteria—the pathogenesis of sepsis thus depends, at least in part, upon whether the bacterium's major signal molecule, LPS, can be sensed by the host.

Local and systemic host responses to invading microbes

Recognition of microbial molecules by tissue phagocytes triggers the production and/or release of numerous host molecules (cytokines, chemokines, prostanoids, leukotrienes, and others) that increase blood flow to the infected tissue, enhance the permeability of local blood vessels, recruit neutrophils to the site of infection, and elicit pain. These reactions are familiar elements of local inflammation, the body's frontline innate immune mechanism for eliminating microbial invaders. Systemic responses are activated by neural and/or humoral communication with the hypothalamus and brainstem; these responses enhance local defenses by increasing blood flow to the infected area, augmenting the number of circulating neutrophils, and elevating blood levels of numerous molecules (such as the microbial recognition proteins discussed earlier) that have anti-infective functions.

Cytokines and other mediators

Cytokines can exert endocrine, paracrine, and autocrine effects. TNF-α stimulates leukocytes and vascular endothelial cells to release other cytokines (as well as additional TNF-α), to express cell-surface molecules that enhance neutrophil-endothelial adhesion at sites of infection, and to increase prostaglandin and leukotriene production. Whereas blood levels of TNF-α are not elevated in individuals with localized infections, they increase in most patients with severe sepsis or septic shock. Moreover, IV infusion of TNF-α can elicit the characteristic abnormalities of SIRS. In animals, larger doses of TNF-α induce shock and death.

Although TNF-α is a central mediator, it is only one of many proinflammatory molecules that contribute to innate host defense. Chemokines, most prominently interleukin (IL)-8 and IL-17, attract circulating neutrophils to the infection site. IL-1β exhibits many of the same activities as TNF-α. TNF-α, IL-1β, interferon (IFN) γ, IL-12, IL-17, and other proinflammatory cytokines probably interact synergistically with one another and with additional mediators. The nonlinearity and multiplicity of these interactions have made it difficult to interpret the roles played by individual mediators in both tissues and blood.

Coagulation factors

Intravascular thrombosis, a hallmark of the local inflammatory response, may help wall off invading microbes and prevent infection and inflammation from spreading to other tissues. IL-6 and other mediators promote intravascular coagulation initially by inducing blood monocytes and vascular endothelial cells to express tissue factor. When tissue factor is expressed on cell surfaces, it binds to factor VIIa to form an active complex that can convert factors X and IX to their enzymatically active forms. The result is activation of both extrinsic and intrinsic clotting pathways, culminating in the generation of fibrin. Clotting is also favored by impaired function of the protein C–protein S inhibitory pathway and depletion of antithrombin and proteins C and S, while fibrinolysis is prevented by increased plasma levels of plasminogen activator inhibitor 1. Thus, there may be a striking propensity toward intravascular fibrin deposition, thrombosis, and bleeding; this propensity has been most apparent in patients with intravascular endothelial infections such as meningococcemia (Chap. 48). Evidence points to tissue factor–expressing microparticles derived from leukocytes as a potential trigger for intravascular coagulation. Contact-system activation occurs during sepsis, but contributes more to the development of hypotension than to disseminated intravascular coagulation (DIC).

Control mechanisms

Elaborate control mechanisms operate within both local sites of inflammation and the systemic compartment.

Local control mechanisms

Host recognition of invading microbes within subepithelial tissues typically ignites immune responses that rapidly kill the invader and then subside to allow tissue recovery. The anti-inflammatory forces that put out the fire and clean up the battleground include molecules that neutralize or inactivate microbial signals. Among these molecules are intracellular factors (e.g., suppressor of cytokine signaling 3 and IL-1 receptor–associated kinase 3) that diminish the production of proinflammatory mediators by neutrophils and macrophages; anti-inflammatory cytokines (IL-10, IL-4); and molecules derived from essential polyunsaturated fatty acids (lipoxins, resolvins, and protectins) that promote tissue restoration. Enzymatic inactivation of microbial signal molecules (e.g., LPS) may be required to restore homeostasis; a leukocyte enzyme, acyloxyacyl hydrolase, has been shown to prevent prolonged inflammation by inactivating LPS in mice.

Systemic control mechanisms

The signaling apparatus that links microbial recognition to cellular responses in tissues is less active in the blood. For example, whereas LPS-binding protein plays a role in recognizing the presence of LPS, in plasma it also prevents LPS signaling by transferring LPS molecules into plasma lipoprotein particles that sequester the lipid A moiety so that it cannot interact with cells. At the high concentrations found in blood, LPS-binding protein also inhibits monocyte responses to LPS, and the soluble (circulating) form of CD14 strips off LPS that has bound to monocyte surfaces.

Systemic responses to infection also diminish cellular responses to microbial molecules. Circulating levels of anti-inflammatory cytokines (e.g., IL-10) increase even in patients with mild infections. Glucocorticoids inhibit cytokine synthesis by monocytes in vitro; the increase in blood cortisol levels early in the systemic response presumably plays a similarly inhibitory role. Epinephrine inhibits the TNF-α response to endotoxin infusion in humans while augmenting and accelerating the release of IL-10; prostaglandin E_2 has a similar "reprogramming" effect on the responses of circulating monocytes to LPS and other bacterial agonists. Cortisol, epinephrine, IL-10, and C-reactive protein reduce the ability of neutrophils to attach to vascular endothelium, favoring their demargination and thus contributing to leukocytosis while preventing neutrophil-endothelial adhesion in uninflamed organs. The available evidence thus suggests that the body's systemic responses to injury and infection normally prevent inflammation within organs distant from a site of infection. There is also evidence that these responses may be immunosuppressive.

The acute-phase response increases the blood concentrations of numerous molecules that have anti-inflammatory actions. Blood levels of IL-1 receptor antagonist often greatly exceed those of circulating IL-1β, for example, and this excess may inhibit the binding of IL-1β to its receptors. High levels of soluble TNF receptors neutralize TNF-α that enters the circulation. Other acute-phase proteins are protease inhibitors or antioxidants; these may neutralize potentially harmful molecules released from neutrophils and other inflammatory cells. Increased hepatic production of hepcidin promotes the sequestration of iron in hepatocytes, intestinal epithelial cells, and erythrocytes; this effect reduces iron acquisition by invading microbes while contributing to the normocytic, normochromic anemia associated with inflammation.

It can thus be concluded that both local and systemic responses to infectious agents benefit the host in important ways. Most of these responses and the molecules responsible for them have been highly conserved during animal evolution and therefore may be adaptive. Elucidating how they contribute to lethality—i.e., become maladaptive—remains a major challenge for sepsis research.

Organ dysfunction and shock

As the body's responses to infection intensify, the mixture of circulating cytokines and other molecules becomes very complex: elevated blood levels of more than 50 molecules have been found in patients with septic shock. Although high concentrations of both pro- and anti-inflammatory molecules are found, the net mediator balance in the plasma of these extremely sick patients seems to be anti-inflammatory. For example, blood leukocytes from patients with severe sepsis are often

hyporesponsive to agonists such as LPS. In patients with severe sepsis, persistence of leukocyte hyporesponsiveness has been associated with an increased risk of dying. Apoptotic death of B cells, follicular dendritic cells, and CD4+ T lymphocytes also may contribute significantly to the immunosuppressive state.

Endothelial injury

Many investigators have favored widespread vascular endothelial injury as the major mechanism for multiorgan dysfunction. In keeping with this idea, one study found high numbers of vascular endothelial cells in the peripheral blood of septic patients. Leukocyte-derived mediators and platelet-leukocyte-fibrin thrombi may contribute to vascular injury, but the vascular endothelium also seems to play an active role. Stimuli such as TNF-α induce vascular endothelial cells to produce and release cytokines, procoagulant molecules, platelet-activating factor, nitric oxide, and other mediators. In addition, regulated cell-adhesion molecules promote the adherence of neutrophils to endothelial cells. While these responses can attract phagocytes to infected sites and activate their antimicrobial arsenals, endothelial cell activation can also promote increased vascular permeability, microvascular thrombosis, DIC, and hypotension.

Tissue oxygenation may decrease as the number of functional capillaries is reduced by luminal obstruction due to swollen endothelial cells, decreased deformability of circulating erythrocytes, leukocyte-platelet-fibrin thrombi, or compression by edema fluid. On the other hand, studies using orthogonal polarization spectral imaging of the microcirculation in the tongue found that sepsis-associated derangements in capillary flow could be reversed by applying acetylcholine to the surface of the tongue or by giving nitroprusside intravenously; these observations suggest a neuroendocrine basis for the loss of capillary filling. Oxygen utilization by tissues may also be impaired by a state of "hibernation" in which ATP production is diminished as oxidative phosphorylation decreases; nitric oxide may be responsible for inducing this response.

Remarkably, poorly functioning "septic" organs usually appear normal at autopsy. There is typically very little necrosis or thrombosis, and apoptosis is largely confined to lymphoid organs and the gastrointestinal tract. Moreover, organ function usually returns to normal if patients recover. These points suggest that organ dysfunction during severe sepsis has a basis that is principally biochemical, not structural.

Septic shock

The hallmark of septic shock is a decrease in peripheral vascular resistance that occurs despite increased levels of vasopressor catecholamines. Before this vasodilatory phase, many patients experience a period during which oxygen delivery to tissues is compromised by myocardial depression, hypovolemia, and other factors. During this "hypodynamic" period, the blood lactate concentration is elevated and central venous oxygen saturation is low. Fluid administration is usually followed by the hyperdynamic, vasodilatory phase during which cardiac output is normal (or even high) and oxygen consumption declines despite adequate oxygen delivery. The blood lactate level may be normal or increased, and normalization of central venous oxygen saturation may reflect either improved oxygen delivery or left-to-right shunting.

Prominent hypotensive molecules include nitric oxide, β-endorphin, bradykinin, platelet-activating factor, and prostacyclin. Agents that inhibit the synthesis or action of each of these mediators can prevent or reverse endotoxic shock in animals. However, in clinical trials, neither a platelet-activating factor receptor antagonist nor a bradykinin antagonist improved survival rates among patients with septic shock, and a nitric oxide synthase inhibitor, L-N^G-methylarginine HCl, actually increased the mortality rate. Remarkably, recent findings indicate that exogenous nitrite can protect mice from challenge with TNF or LPS. Nitrite provides a storage pool from which nitric oxide can be generated in hypoxic and/or acidic conditions. These findings should renew interest in the possibility of exploiting nitric oxide metabolism to improve survival rates among septic patients.

Severe sepsis: A single pathogenesis?

In some cases, circulating bacteria and their products almost certainly elicit multiorgan dysfunction and hypotension by directly stimulating inflammatory responses within the vasculature. In patients with fulminant meningococcemia, for example, mortality rates have correlated directly with blood levels of endotoxin and bacterial DNA and with the occurrence of DIC (Chap. 48). In most patients infected with other gram-negative bacteria, in contrast, circulating bacteria or bacterial molecules may reflect uncontrolled infection at a local tissue site and have little or no direct impact on distant organs; in these patients, inflammatory mediators or neural signals arising from the local site seem to be the key triggers for severe sepsis and septic shock. In a large series of patients with positive blood cultures, the risk of developing severe sepsis was strongly related to the site of primary infection: bacteremia arising from a pulmonary or abdominal source was eightfold more likely to be associated with severe sepsis than was bacteremic urinary tract infection, even after the investigators controlled for age, the kind of bacteria isolated from the blood, and other factors. A third pathogenesis may be represented by severe sepsis due to superantigen-producing *Staphylococcus aureus* or *Streptococcus pyogenes*; the T cell activation induced by these toxins produces a cytokine profile that differs substantially from that elicited by gram-negative bacterial infection. Further evidence for different pathogenetic pathways has come from observations that the pattern of mRNA expression in peripheral-blood leukocytes from children with sepsis is different for gram-positive, gram-negative, and viral pathogens.

The pathogenesis of severe sepsis thus may differ according to the infecting microbe, the ability of the

host's innate defense mechanisms to sense it, the site of the primary infection, the presence or absence of immune defects, and the prior physiologic status of the host. Genetic factors are probably important as well, yet despite much study only a few allelic polymorphisms (e.g., in the IL-1β gene) have been associated with sepsis severity in more than one or two analyses. Further studies in this area are needed.

CLINICAL MANIFESTATIONS

The manifestations of the septic response are superimposed on the symptoms and signs of the patient's underlying illness and primary infection. The rate at which severe sepsis develops may differ from patient to patient, and there are striking individual variations in presentation. For example, some patients with sepsis are normo- or hypothermic; the absence of fever is most common in neonates, in elderly patients, and in persons with uremia or alcoholism.

Hyperventilation is often an early sign of the septic response. Disorientation, confusion, and other manifestations of encephalopathy may also develop early on, particularly in the elderly and in individuals with preexisting neurologic impairment. Focal neurologic signs are uncommon, although preexisting focal deficits may become more prominent.

Hypotension and DIC predispose to acrocyanosis and ischemic necrosis of peripheral tissues, most commonly the digits. Cellulitis, pustules, bullae, or hemorrhagic lesions may develop when hematogenous bacteria or fungi seed the skin or underlying soft tissue. Bacterial toxins may also be distributed hematogenously and elicit diffuse cutaneous reactions. On occasion, skin lesions may suggest specific pathogens. When sepsis is accompanied by cutaneous petechiae or purpura, infection with *N. meningitidis* (or, less commonly, *H. influenzae*) should be suspected (Fig. 11-42); in a patient who has been bitten by a tick while in an endemic area, petechial lesions also suggest Rocky Mountain spotted fever (Fig. 79-1). A cutaneous lesion seen almost exclusively in neutropenic patients is ecthyma gangrenosum, usually caused by *P. aeruginosa*. It is a bullous lesion, surrounded by edema, that undergoes central hemorrhage and necrosis (Fig. 57-1). Histopathologic examination shows bacteria in and around the wall of a small vessel, with little or no neutrophilic response. Hemorrhagic or bullous lesions in a septic patient who has recently eaten raw oysters suggest *V. vulnificus* bacteremia, while such lesions in a patient who has recently suffered a dog bite may indicate bloodstream infection due to *Capnocytophaga canimorsus* or *C. cynodegmi*. Generalized erythroderma in a septic patient suggests the toxic shock syndrome due to *S. aureus* or *S. pyogenes*.

Gastrointestinal manifestations such as nausea, vomiting, diarrhea, and ileus may suggest acute gastroenteritis. Stress ulceration can lead to upper gastrointestinal bleeding. Cholestatic jaundice, with elevated levels of serum bilirubin (mostly conjugated) and alkaline phosphatase, may precede other signs of sepsis. Hepatocellular or canalicular dysfunction appears to underlie most cases, and the results of hepatic function tests return to normal with resolution of the infection. Prolonged or severe hypotension may induce acute hepatic injury or ischemic bowel necrosis.

Many tissues may be unable to extract oxygen normally from the blood, so that anaerobic metabolism occurs despite near-normal mixed venous oxygen saturation. Blood lactate levels rise early because of increased glycolysis as well as impaired clearance of the resulting lactate and pyruvate by the liver and kidneys. The blood glucose concentration often increases, particularly in patients with diabetes, although impaired gluconeogenesis and excessive insulin release on occasion produce hypoglycemia. The cytokine-driven acute-phase response inhibits the synthesis of transthyretin while enhancing the production of C-reactive protein, fibrinogen, and complement components. Protein catabolism is often markedly accelerated. Serum albumin levels decline as a result of decreased hepatic synthesis and the movement of albumin into interstitial spaces.

MAJOR COMPLICATIONS

Cardiopulmonary complications

Ventilation-perfusion mismatching produces a fall in arterial P_{O2} early in the course. Increasing alveolar epithelial injury and capillary permeability result in increased pulmonary water content, which decreases pulmonary compliance and interferes with oxygen exchange. In the absence of pneumonia or heart failure, progressive diffuse pulmonary infiltrates and arterial hypoxemia (Pa_{O2}/FI_{O2}, <300) indicate the development of acute lung injury; more severe hypoxemia (Pa_{O2}/FI_{O2}, <200) denotes the acute respiratory distress syndrome (ARDS). Acute lung injury or ARDS develops in ~50% of patients with severe sepsis or septic shock. Respiratory muscle fatigue can exacerbate hypoxemia and hypercapnia. An elevated pulmonary capillary wedge pressure (>18 mmHg) suggests fluid volume overload or cardiac failure rather than ARDS. Pneumonia caused by viruses or by *Pneumocystis* may be clinically indistinguishable from ARDS.

Sepsis-induced hypotension (see "Septic Shock," earlier in the chapter) usually results initially from a generalized maldistribution of blood flow and blood volume and from hypovolemia that is due, at least in part, to diffuse capillary leakage of intravascular fluid. Other factors that may decrease effective intravascular volume include dehydration from antecedent disease or insensible fluid losses, vomiting or diarrhea, and polyuria. During early septic shock, systemic vascular resistance is usually elevated and cardiac output may be low. After fluid repletion, in contrast, cardiac output typically increases and systemic vascular resistance falls. Indeed, normal or increased cardiac output and decreased systemic vascular resistance distinguish septic shock from cardiogenic, extracardiac obstructive, and hypovolemic shock; other processes that can produce this combination include anaphylaxis, beriberi, cirrhosis, and overdoses of nitroprusside or narcotics.

Depression of myocardial function, manifested as increased end-diastolic and systolic ventricular volumes with a decreased ejection fraction, develops within 24 h in most patients with severe sepsis. Cardiac output is maintained despite the low ejection fraction because ventricular dilatation permits a normal stroke volume. In survivors, myocardial function returns to normal over several days. Although myocardial dysfunction may contribute to hypotension, refractory hypotension is usually due to low systemic vascular resistance, and death results from refractory shock or the failure of multiple organs rather than from cardiac dysfunction per se.

Adrenal insufficiency

The diagnosis of adrenal insufficiency may be very difficult in critically ill patients. Whereas a plasma cortisol level of ≤15 μg/mL (≤10 μg/mL if the serum albumin concentration is <2.5 mg/dL) indicates adrenal insufficiency (inadequate production of cortisol), many experts now feel that the ACTH (CoSyntropin®) stimulation test is not useful for detecting less profound degrees of corticosteroid deficiency in patients who are critically ill. The concept of critical illness–related corticosteroid insufficiency (CIRCI; Table 16-1) was proposed to encompass the different mechanisms that may produce corticosteroid activity that is inadequate for the severity of a patient's illness. Although CIRCI may result from structural damage to the adrenal gland, it is more commonly due to reversible dysfunction of the hypothalamic-pituitary axis or to tissue corticosteroid resistance resulting from abnormalities of the glucocorticoid receptor or increased conversion of cortisol to cortisone. The major clinical manifestation of CIRCI is hypotension that is refractory to fluid replacement and requires pressor therapy. Some classic features of adrenal insufficiency, such as hyponatremia and hyperkalemia, are usually absent; others, such as eosinophilia and modest hypoglycemia, may sometimes be found. Specific etiologies include fulminant *N. meningitidis* bacteremia, disseminated tuberculosis, AIDS (with cytomegalovirus, *Mycobacterium avium-intracellulare*, or *Histoplasma capsulatum* disease), or the prior use of drugs that diminish glucocorticoid production, such as glucocorticoids, megestrol, etomidate, or ketoconazole.

Renal complications

Oliguria, azotemia, proteinuria, and nonspecific urinary casts are frequently found. Many patients are inappropriately polyuric; hyperglycemia may exacerbate this tendency. Most renal failure is due to acute tubular necrosis induced by hypotension or capillary injury, although some patients also have glomerulonephritis, renal cortical necrosis, or interstitial nephritis. Drug-induced renal damage may complicate therapy, particularly when hypotensive patients are given aminoglycoside antibiotics.

Coagulopathy

Although thrombocytopenia occurs in 10–30% of patients, the underlying mechanisms are not understood. Platelet counts are usually very low (<50,000/μL) in patients with DIC; these low counts may reflect diffuse endothelial injury or microvascular thrombosis, yet thrombi have only infrequently been found upon biopsy of septic organs.

Neurologic complications

When the septic illness lasts for weeks or months, "critical illness" polyneuropathy may prevent weaning from ventilatory support and produce distal motor weakness. Electrophysiologic studies are diagnostic. Guillain-Barré syndrome, metabolic disturbances, and toxin activity must be ruled out.

IMMUNOSUPPRESSION

Patients with severe sepsis are often profoundly immunosuppressed. Manifestations include loss of delayed-type hypersensitivity reactions to common antigens, failure to control the primary infection, and increased risk for secondary infections (e.g., by opportunists such as *Stenotrophomonas maltophilia*, *Acinetobacter calcoaceticus-baumannii*, and *Candida albicans*). Approximately one-third of patients experience reactivation of herpes simplex virus, varicella-zoster virus, or cytomegalovirus infections; the latter are thought to contribute to adverse outcomes in some instances.

LABORATORY FINDINGS

Abnormalities that occur early in the septic response may include leukocytosis with a left shift, thrombocytopenia, hyperbilirubinemia, and proteinuria. Leukopenia may develop. The neutrophils may contain toxic granulations, Döhle bodies, or cytoplasmic vacuoles. As the septic response becomes more severe, thrombocytopenia worsens (often with prolongation of the thrombin time, decreased fibrinogen, and the presence of D-dimers, suggesting DIC), azotemia and hyperbilirubinemia become more prominent, and levels of aminotransferases rise. Active hemolysis suggests clostridial bacteremia, malaria, a drug reaction, or DIC; in the case of DIC, microangiopathic changes may be seen on a blood smear.

During early sepsis, hyperventilation induces respiratory alkalosis. With respiratory muscle fatigue and the accumulation of lactate, metabolic acidosis (with increased anion gap) typically supervenes. Evaluation of arterial blood gases reveals hypoxemia that is initially correctable with supplemental oxygen but whose later refractoriness to 100% oxygen inhalation indicates right-to-left shunting. The chest radiograph may be normal or may show evidence of underlying pneumonia, volume overload, or the diffuse infiltrates of ARDS. The electrocardiogram may show only sinus tachycardia or nonspecific ST–T-wave abnormalities.

Most diabetic patients with sepsis develop hyperglycemia. Severe infection may precipitate diabetic ketoacidosis that may exacerbate hypotension. Hypoglycemia occurs rarely. The serum albumin level declines as sepsis continues. Hypocalcemia is rare.

DIAGNOSIS

There is no specific diagnostic test for the septic response. Diagnostically sensitive findings in a patient with suspected or proven infection include fever or hypothermia, tachypnea, tachycardia, and leukocytosis or leukopenia (Table 16-1); acutely altered mental status, thrombocytopenia, an elevated blood lactate level, or hypotension also should suggest the diagnosis. The septic response can be quite variable, however. In one study, 36% of patients with severe sepsis had a normal temperature, 40% had a normal respiratory rate, 10% had a normal pulse rate, and 33% had normal white blood cell counts. Moreover, the systemic responses of uninfected patients with other conditions may be similar to those characteristic of sepsis. Noninfectious etiologies of SIRS (Table 16-1) include pancreatitis, burns, trauma, adrenal insufficiency, pulmonary embolism, dissecting or ruptured aortic aneurysm, myocardial infarction, occult hemorrhage, cardiac tamponade, postcardiopulmonary bypass syndrome, anaphylaxis, tumor-associated lactic acidosis, and drug overdose.

Definitive etiologic diagnosis requires isolation of the microorganism from blood or a local site of infection. At least two blood samples should be obtained (from two different venipuncture sites) for culture; in a patient with an indwelling catheter, one sample should be collected from each lumen of the catheter and another via venipuncture. In many cases, blood cultures are negative; this result can reflect prior antibiotic administration, the presence of slow-growing or fastidious organisms, or the absence of microbial invasion of the bloodstream. In these cases, Gram's staining and culture of material from the primary site of infection or from infected cutaneous lesions may help establish the microbial etiology. Identification of microbial DNA in peripheral-blood or tissue samples by polymerase chain reaction may also be definitive. The skin and mucosae should be examined carefully and repeatedly for lesions that might yield diagnostic information. With overwhelming bacteremia (e.g., pneumococcal sepsis in splenectomized individuals; fulminant meningococcemia; or infection with *V. vulnificus*, *B. pseudomallei*, or *Y. pestis*), microorganisms are sometimes visible on buffy coat smears of peripheral blood.

TREATMENT Severe Sepsis and Septic Shock

Patients in whom sepsis is suspected must be managed expeditiously. This task is best accomplished by personnel who are experienced in the care of the critically ill. Successful management requires urgent measures to treat the infection, to provide hemodynamic and respiratory support, and to eliminate the offending microorganisms. These measures should be initiated within 1 h of the patient's presentation with severe sepsis or septic shock. Rapid assessment and diagnosis are therefore essential.

ANTIMICROBIAL AGENTS Antimicrobial chemotherapy should be started as soon as samples of blood and other relevant sites have been obtained for culture. A large retrospective review of patients who developed septic shock found that the interval between the onset of hypotension and the administration of appropriate antimicrobial chemotherapy was the major determinant of outcome; a delay of as little as 1 h was associated with lower survival rates. Use of inappropriate antibiotics, defined on the basis of local microbial susceptibilities and published guidelines for empirical therapy (see below), was associated with fivefold lower survival rates, even among patients with negative cultures.

It is therefore very important to promptly initiate empirical antimicrobial therapy that is effective against both gram-positive and gram-negative bacteria (Table 16-3). Maximal recommended doses of antimicrobial drugs should be given intravenously, with adjustment for impaired renal function when necessary. Available information about patterns of antimicrobial susceptibility among bacterial isolates from the community, the hospital, and the patient should be taken into account. When culture results become available, the regimen can often be simplified, as a single antimicrobial agent is usually adequate for the treatment of a known pathogen. Meta-analyses have concluded that, with one exception, combination antimicrobial therapy is not superior to monotherapy for treating gram-negative bacteremia; the exception is that aminoglycoside monotherapy for *P. aeruginosa* bacteremia is less effective than the combination of an aminoglycoside with an antipseudomonal β-lactam agent. Empirical antifungal therapy should be strongly considered if the septic patient is already receiving broad-spectrum antibiotics or parenteral nutrition, has been neutropenic for ≥5 days, has had a long-term central venous catheter, or has been hospitalized in an intensive care unit for a prolonged period. The chosen antimicrobial regimen should be reconsidered daily in order to provide maximal efficacy with minimal resistance, toxicity, and cost.

Most patients require antimicrobial therapy for at least 1 week. The duration of treatment is typically influenced by factors such as the site of tissue infection, the adequacy of surgical drainage, the patient's underlying disease, and the antimicrobial susceptibility of the microbial isolate(s). The absence of an identified microbial pathogen is not necessarily an indication for discontinuing antimicrobial therapy, since "appropriate" antimicrobial regimens seem to be beneficial in both culture-negative and culture-positive cases.

REMOVAL OF THE SOURCE OF INFECTION Removal or drainage of a focal source of infection is essential. In one series, a focus of ongoing infection was found in ~80% of surgical intensive care patients who died of severe sepsis or septic shock. Sites of occult infection should be sought carefully, particularly in the lungs, abdomen, and urinary tract. Indwelling IV or arterial catheters should be removed and the tip rolled over a blood agar plate for quantitative culture; after antibiotic therapy has been initiated, a new catheter should be inserted at a different site. Foley and drainage catheters should

TABLE 16-3

INITIAL ANTIMICROBIAL THERAPY FOR SEVERE SEPSIS WITH NO OBVIOUS SOURCE IN ADULTS WITH NORMAL RENAL FUNCTION

CLINICAL CONDITION	ANTIMICROBIAL REGIMENS (INTRAVENOUS THERAPY)
Immunocompetent adult	The many acceptable regimens include (1) piperacillin-tazobactam (3.375 g q4–6h); (2) imipenem-cilastatin (0.5 g q6h) or meropenem (1 g q8h); or (3) cefepime (2 g q12h). If the patient is allergic to β-lactam agents, use ciprofloxacin (400 mg q12h) or levofloxacin (500–750 mg q12h) plus clindamycin (600 mg q8h). Vancomycin (15 mg/kg q12h) should be added to each of the above regimens.
Neutropenia (<500 neutrophils/μL)	Regimens include (1) imipenem-cilastatin (0.5 g q6h) or meropenem (1 g q8h) or cefepime (2 g q8h); (2) piperacillin-tazobactam (3.375 g q4h) plus tobramycin (5–7 mg/kg q24h). Vancomycin (15 mg/kg q12h) should be added if the patient has an indwelling vascular catheter, has received quinolone prophylaxis, or has received intensive chemotherapy that produces mucosal damage; if staphylococci are suspected; if the institution has a high incidence of MRSA infections; or if there is a high prevalence of MRSA isolates in the community. Empirical antifungal therapy with an echinocandin (for caspofungin: a 70-mg loading dose, then 50 mg daily) or a lipid formulation of amphotericin B should be added if the patient is hypotensive or has been receiving broad-spectrum antibacterial drugs.
Splenectomy	Cefotaxime (2 g q6–8h) or ceftriaxone (2 g q12h) should be used. If the local prevalence of cephalosporin-resistant pneumococci is high, add vancomycin. If the patient is allergic to β-lactam drugs, vancomycin (15 mg/kg q12h) plus either moxifloxacin (400 mg q24h) or levofloxacin (750 mg q24h) or aztreonam (2 g q8h) should be used.
IV drug use	Vancomycin (15 mg/kg q12h)
AIDS	Cefepime (2 g q8h) or piperacillin-tazobactam (3.375 g q4h) plus tobramycin (5–7 mg/kg q24h) should be used. If the patient is allergic to β-lactam drugs, ciprofloxacin (400 mg q12h) or levofloxacin (750 mg q12h) plus vancomycin (15 mg/kg q12h) plus tobramycin should be used.

Abbreviation: MRSA, methicillin-resistant *Staphylococcus aureus*.
Source: Adapted in part from WT Hughes et al: Clin Infect Dis 25:551, 1997; and DN Gilbert et al: The Sanford Guide to Antimicrobial Therapy, 2009.

be replaced. The possibility of paranasal sinusitis (often caused by gram-negative bacteria) should be considered if the patient has undergone nasal intubation. Even in patients without abnormalities on chest radiographs, CT of the chest may identify unsuspected parenchymal, mediastinal, or pleural disease. In the neutropenic patient, cutaneous sites of tenderness and erythema, particularly in the perianal region, must be carefully sought. In patients with sacral or ischial decubitus ulcers, it is important to exclude pelvic or other soft tissue pus collections with CT or MRI. In patients with severe sepsis arising from the urinary tract, sonography or CT should be used to rule out ureteral obstruction, perinephric abscess, and renal abscess. Sonographic or CT imaging of the upper abdomen may disclose evidence of cholecystitis, bile duct dilatation, and pus collections in the liver, subphrenic space, or spleen.

HEMODYNAMIC, RESPIRATORY, AND METABOLIC SUPPORT The primary goals are to restore adequate oxygen and substrate delivery to the tissues as quickly as possible and to improve tissue oxygen utilization and cellular metabolism. Adequate organ perfusion is thus essential. Circulatory adequacy is assessed by measurement of arterial blood pressure and monitoring of parameters such as mentation, urine output, and skin perfusion. Indirect indices of oxygen delivery and consumption, such as central venous oxygen saturation, may also be useful. Initial management of hypotension should include the administration of IV fluids, typically beginning with 1–2 L of normal saline over 1–2 h. To avoid pulmonary edema, the central venous pressure should be maintained at 8–12 cmH_2O. The urine output rate should be kept at >0.5 mL/kg per hour by continuing fluid administration; a diuretic such as furosemide may be used if needed. In about one-third of patients, hypotension and organ hypoperfusion respond to fluid resuscitation; a reasonable goal is to maintain a mean arterial blood pressure of >65 mmHg (systolic pressure >90 mmHg). If these guidelines cannot be met by volume infusion, vasopressor therapy is indicated. Titrated doses of norepinephrine or dopamine should be administered through a central catheter. If myocardial dysfunction produces elevated cardiac filling pressures and low cardiac output, inotropic therapy with dobutamine is recommended.

In patients with septic shock, plasma vasopressin levels increase transiently but then decrease dramatically. Early studies found that vasopressin infusion can reverse septic shock in some patients, reducing or eliminating the need for catecholamine pressors. More recently,

a randomized clinical trial that compared vasopressin plus norepinephrine with norepinephrine alone in 776 patients with pressor-dependent septic shock found no difference between treatment groups in the primary study outcome, 28-day mortality. Although vasopressin may have benefited patients who required less norepinephrine, its role in the treatment of septic shock seems to be a minor one overall.

CIRCI should be strongly considered in patients who develop hypotension that does not respond to fluid replacement therapy. Hydrocortisone (50 mg IV every 6 h) should be given; if clinical improvement occurs over 24–48 h, most experts would continue hydrocortisone therapy for 5–7 days before slowly tapering and discontinuing it. Meta-analyses of recent clinical trials have concluded that hydrocortisone therapy hastens recovery from septic shock without increasing long-term survival.

Ventilator therapy is indicated for progressive hypoxemia, hypercapnia, neurologic deterioration, or respiratory muscle failure. Sustained tachypnea (respiratory rate, >30 breaths/min) is frequently a harbinger of impending respiratory collapse; mechanical ventilation is often initiated to ensure adequate oxygenation, to divert blood from the muscles of respiration, to prevent aspiration of oropharyngeal contents, and to reduce the cardiac afterload. The results of recent studies favor the use of low tidal volumes (6 mL/kg of ideal body weight, or as low as 4 mL/kg if the plateau pressure exceeds 30 cmH_2O). Patients undergoing mechanical ventilation require careful sedation, with daily interruptions; elevation of the head of the bed helps to prevent nosocomial pneumonia. Stress-ulcer prophylaxis with a histamine H_2-receptor antagonist may decrease the risk of gastrointestinal hemorrhage in ventilated patients.

Erythrocyte transfusion is generally recommended when the blood hemoglobin level decreases to ≤7 g/dL, with a target level of 9 g/dL in adults. Erythropoietin is not used to treat sepsis-related anemia. Bicarbonate is sometimes administered for severe metabolic acidosis (arterial pH <7.2), but there is little evidence that it improves either hemodynamics or the response to vasopressor hormones. DIC, if complicated by major bleeding, should be treated with transfusion of fresh-frozen plasma and platelets. Successful treatment of the underlying infection is essential to reverse both acidosis and DIC. Patients who are hypercatabolic and have acute renal failure may benefit greatly from intermittent hemodialysis or continuous veno-venous hemofiltration.

GENERAL SUPPORT In patients with prolonged severe sepsis (i.e., lasting more than 2 or 3 days), nutritional supplementation may reduce the impact of protein hypercatabolism; the available evidence, which is not strong, favors the enteral delivery route. Prophylactic heparinization to prevent deep venous thrombosis is indicated for patients who do not have active bleeding or coagulopathy; when heparin is contraindicated, compression stockings or an intermittent compression device should be used. Recovery is also assisted by prevention of skin breakdown, nosocomial infections, and stress ulcers.

The role of tight control of the blood glucose concentration in recovery from critical illness has been addressed in numerous controlled trials. Meta-analyses of these trials have concluded that use of insulin to lower blood glucose levels to 100–120 mg/dL is potentially harmful and does not improve survival rates. Most experts now recommend using insulin only if it is needed to maintain the blood glucose concentration below ~150 mg/dL. Patients receiving intravenous insulin must be monitored frequently (every 1–2 h) for hypoglycemia.

OTHER MEASURES Despite aggressive management, many patients with severe sepsis or septic shock die. Numerous interventions have been tested for their ability to improve survival rates among patients with severe sepsis. The list includes endotoxin-neutralizing proteins, inhibitors of cyclooxygenase or nitric oxide synthase, anticoagulants, polyclonal immunoglobulins, glucocorticoids, a phospholipid emulsion, and antagonists to TNF-α, IL-1, platelet-activating factor, and bradykinin. Unfortunately, none of these agents has improved rates of survival among patients with severe sepsis/septic shock in more than one large-scale, randomized, placebo-controlled clinical trial. Many factors have contributed to this lack of reproducibility, including (1) heterogeneity in the patient populations studied, the primary infection sites, the preexisting illnesses, and the inciting microbes; and (2) the nature of the "standard" therapy also used. A dramatic example of this problem was seen in a trial of tissue factor pathway inhibitor (Fig. 16-1). Whereas the drug appeared to improve

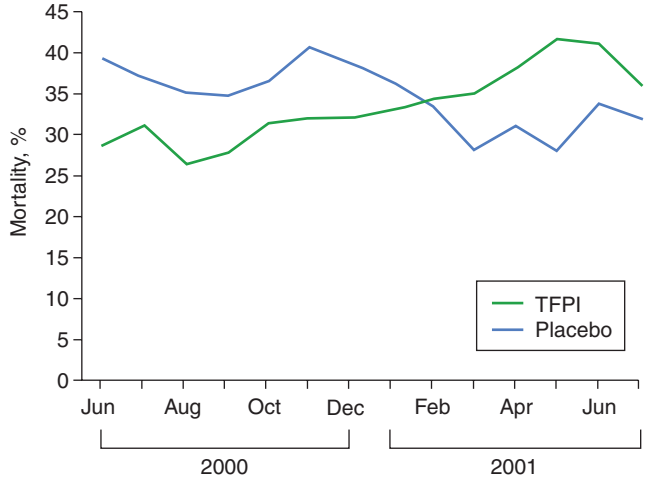


FIGURE 16-1
Mortality rates among patients who received tissue factor pathway inhibitor (TFPI) or placebo, shown as the running average over the course of the clinical trial. The drug seemed highly efficacious at the interim analysis in December 2000, but this trend reversed later in the trial. Demonstrating that therapeutic agents for sepsis have consistent, reproducible efficacy has been extremely difficult, even within well-defined patient populations. (*Reprinted with permission from E Abraham et al: JAMA 290:238, 2003.*)

survival rates after 722 patients had been studied ($p = 0.006$), it did not do so in the next 1032 patients, and the overall result was negative. This inconsistency argues that the results of a clinical trial may not apply to individual patients, even within a carefully selected patient population. It also suggests that, at a minimum, a sepsis intervention should show a significant survival benefit in more than one placebo-controlled, randomized clinical trial before it is accepted as routine clinical practice. In one prominent attempt to reduce patient heterogeneity in clinical trials, experts have called for changes that would restrict these trials to patients who have similar underlying diseases (e.g., major trauma) and inciting infections (e.g., pneumonia). The goal of the predisposition–infection–response–organ dysfunction (PIRO) grading system for classification of septic patients (Table 16-1) is similar. Other investigators have used specific biomarkers, such as IL-6 levels in blood or the expression of HLA-DR on peripheral-blood monocytes, to identify the patients most likely to benefit from certain interventions. Multivariate risk stratification based on easily measurable clinical variables should be used with each of these approaches.

Recombinant activated protein C (aPC) was the first drug to be approved by the U.S. Food and Drug Administration for the treatment of patients with severe sepsis or septic shock. Approval was based on the results of a single randomized controlled trial in which the drug was given within 24 h of the patient's first sepsis-related organ dysfunction; the 28-day survival rate was significantly higher among aPC recipients who were very sick (APACHE II score, ≥25) before infusion of the protein than among placebo-treated controls. Subsequent trials failed to show a benefit of aPC treatment in patients who were less sick (APACHE II score, <25) or in children. A second trial of aPC in high-risk patients is now under way in Europe. Given the drug's known toxicity (increased risk of severe bleeding) and uncertain performance in clinical practice, many experts are awaiting the results of the European trial before recommending further use of aPC. Other agents in ongoing or planned clinical trials include intravenous immunoglobulin, a small-molecule endotoxin antagonist (eritoran), and granulocyte-macrophage colony-stimulating factor that was recently reported to restore monocyte immunocompetence in patients with sepsis-associated immunosuppression.

A careful retrospective analysis found that the apparent efficacy of all sepsis therapeutics studied to date has been greatest among the patients at greatest risk of dying before treatment; conversely, use of many of these drugs has been associated with increased mortality rates among patients who are less ill. The authors proposed that neutralizing one of many different mediators may help patients who are very sick, whereas disrupting the mediator balance may be harmful to patients whose adaptive defense mechanisms are working well. This analysis suggests that if more aggressive early resuscitation improves survival rates among sicker patients, it will become more difficult to obtain additional benefit from other therapies; that is, if an intervention improves patients' risk status, moving them into a "less severe illness" category, it will be harder to show that adding another agent to the therapeutic regimen is beneficial.

THE SURVIVING SEPSIS CAMPAIGN An international consortium has advocated "bundling" multiple therapeutic maneuvers into a unified algorithmic approach that will become the standard of care for severe sepsis. In theory, such a strategy could improve care by mandating measures that seem to bring maximal benefit, such as the rapid administration of appropriate antimicrobial therapy; on the other hand, this approach would deemphasize physicians' experience and judgment and minimize the consideration of potentially important differences between patients. Bundling multiple therapies into a single package also obscures the efficacy and toxicity of the individual measures. Caution should be engendered by the fact that two of the key elements of the initial algorithm have now been withdrawn for lack of evidence, while a third remains unproven and controversial.

PROGNOSIS

Approximately 20–35% of patients with severe sepsis and 40–60% of patients with septic shock die within 30 days. Others die within the ensuing 6 months. Late deaths often result from poorly controlled infection, immunosuppression, complications of intensive care, failure of multiple organs, or the patient's underlying disease. Case-fatality rates are similar for culture-positive and culture-negative severe sepsis. Prognostic stratification systems such as APACHE II indicate that factoring in the patient's age, underlying condition, and various physiologic variables can yield estimates of the risk of dying of severe sepsis. Age and prior health status are probably the most important risk factors **(Fig. 16-2)**. In patients with no known preexisting morbidity, the case-fatality rate remains below 10% until the fourth decade of life, after which it gradually increases to exceed 35% in the very elderly. Death is significantly more likely in severely septic patients with preexisting illness, especially during the third to fifth decades. Septic shock is also a strong predictor of short- and long-term mortality.

PREVENTION

Prevention offers the best opportunity to reduce morbidity and mortality from severe sepsis. In developed countries, most episodes of severe sepsis and septic shock are complications of nosocomial infections. These cases might be prevented by reducing the number of invasive procedures undertaken, by limiting the use (and duration of use) of indwelling vascular and bladder catheters, by reducing the

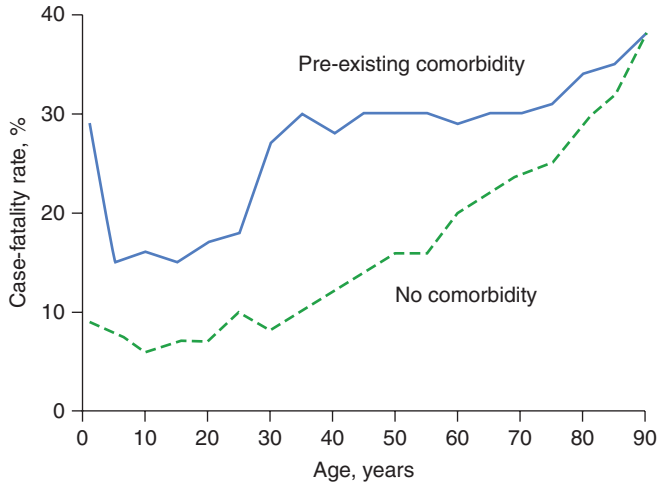


FIGURE 16-2
Influence of age and prior health status on outcome from severe sepsis. With modern therapy, fewer than 10% of previously healthy young individuals (below 35 years of age) die with severe sepsis; the case-fatality rate then increases slowly through middle and old age. The most commonly identified etiologic agents in patients who die are *Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus pneumoniae*, and *Neisseria meningitidis*. Individuals with pre-existing comorbidities are at greater risk of dying of severe sepsis at any age. The etiologic agents in these cases are likely to be *S. aureus*, *Pseudomonas aeruginosa*, various Enterobacteriaceae, enterococci, or fungi. (*Adapted from DC Angus et al: Crit Care Med 29:1303, 2001.*)

incidence and duration of profound neutropenia (<500 neutrophils/μL), and by more aggressively treating localized nosocomial infections. Indiscriminate use of antimicrobial agents and glucocorticoids should be avoided, and optimal infection-control measures (Chap. 14) should be used. Studies indicate that 50–70% of patients who develop nosocomial severe sepsis or septic shock have experienced a less severe stage of the septic response (e.g., SIRS, sepsis) on at least one previous day in the hospital. Research is needed to identify patients at increased risk and to develop adjunctive agents that can modulate the septic response before organ dysfunction or hypotension occurs.

SECTION III

INFECTIONS IN ORGAN SYSTEMS

CHAPTER 17

PHARYNGITIS, SINUSITIS, OTITIS, AND OTHER UPPER RESPIRATORY TRACT INFECTIONS

Michael A. Rubin ■ Larry C. Ford ■ Ralph Gonzales

Infections of the upper respiratory tract (URIs) have a tremendous impact on public health. They are among the most common reasons for visits to primary care providers, and although the illnesses are typically mild, their high incidence and transmission rates place them among the leading causes of time lost from work or school. Even though a minority (~25%) of cases are caused by bacteria, URIs are the leading diagnoses for which antibiotics are prescribed on an outpatient basis in the United States. The enormous consumption of antibiotics for these illnesses has contributed to the rise in antibiotic resistance among common community-acquired pathogens such as *Streptococcus pneumoniae*—a trend that in itself has had an enormous influence on public health.

Although most URIs are caused by viruses, distinguishing patients with primary viral infection from those with primary bacterial infection is difficult. Signs and symptoms of bacterial and viral URIs are typically indistinguishable. Until consistent, inexpensive, and rapid testing becomes available and is used widely, acute infections will be diagnosed largely on clinical grounds. The judicious use and potential for misuse of antibiotics in this setting pose definite challenges.

NONSPECIFIC INFECTIONS OF THE UPPER RESPIRATORY TRACT

Nonspecific URIs are a broadly defined group of disorders that collectively constitute the leading cause of ambulatory care visits in the United States. By definition, nonspecific URIs have no prominent localizing features. They are identified by a variety of descriptive names, including *acute infective rhinitis*, *acute rhinopharyngitis/nasopharyngitis*, *acute coryza*, and *acute nasal catarrh*, as well as by the inclusive label *common cold*.

Etiology

The large assortment of URI classifications reflects the wide variety of causative infectious agents and the varied manifestations of common pathogens. Nearly all nonspecific URIs are caused by viruses spanning multiple virus families and many antigenic types. For instance, there are at least 100 immunotypes of rhinovirus (Chap. 91), the most common cause of URI (~30–40% of cases); other causes include influenza virus (three immunotypes; Chap. 92) as well as parainfluenza virus (four immunotypes), coronavirus (at least three immunotypes), and adenovirus (47 immunotypes) (Chap. 91). Respiratory syncytial virus (RSV), a well-established pathogen in pediatric populations, is also a recognized cause of significant disease in elderly and immunocompromised individuals. A host of additional viruses, including some viruses not typically associated with URIs (e.g., enteroviruses, rubella virus, and varicella-zoster virus), account for a small percentage of cases in adults each year. Although new diagnostic modalities [e.g., nasopharyngeal swab for polymerase chain reaction (PCR)] can assign a viral etiology, there are few specific treatment options, and no pathogen is identified in a substantial proportion of cases. A specific diagnostic workup beyond a clinical diagnosis is generally unnecessary in an otherwise healthy adult.

Clinical manifestations

The signs and symptoms of nonspecific URI are similar to those of other URIs but lack a pronounced localization to one particular anatomic location, such as the sinuses, pharynx, or lower airway. Nonspecific URI commonly presents as an acute, mild, and self-limited catarrhal syndrome with a median duration of ~1 week (range, 2–10 days). Signs and symptoms are diverse and frequently variable across patients. The principal signs and symptoms of nonspecific URI include rhinorrhea (with or without purulence), nasal congestion, cough, and sore throat. Other manifestations, such as fever, malaise, sneezing, lymphadenopathy, and hoarseness, are more variable, with fever more common among infants and young children. This varying presentation may reflect differences in host response as well as in infecting organisms; myalgias and fatigue, for example, sometimes are

seen with influenza and parainfluenza infections, whereas conjunctivitis may suggest infection with adenovirus or enterovirus. Findings on physical examination are frequently nonspecific and unimpressive. Between 0.5% and 2% of colds are complicated by secondary bacterial infections (e.g., rhinosinusitis, otitis media, and pneumonia), particularly in higher-risk populations such as infants, elderly persons, and chronically ill individuals. Secondary bacterial infections usually are associated with a prolonged course of illness, increased severity of illness, and localization of signs and symptoms, often as a rebound after initial clinical improvement. Purulent secretions from the nares or throat often are misinterpreted as an indication of bacterial sinusitis or pharyngitis. These secretions, however, are also seen in nonspecific URI and, in the absence of other clinical features, are poor predictors of bacterial infection.

TREATMENT **Upper Respiratory Infections**

Antibiotics have no role in the treatment of uncomplicated nonspecific URI, and their misuse probably facilitates the emergence of antimicrobial resistance; even in healthy volunteers, a single course of azithromycin or clarithromycin can lead to macrolide resistance among oral streptococci months later. In the absence of clinical evidence of bacterial infection, treatment remains entirely symptom-based, with use of decongestants and nonsteroidal anti-inflammatory drugs. Other therapies directed at specific symptoms are often useful, including dextromethorphan for cough and lozenges with topical anesthetic for sore throat. Clinical trials of zinc, vitamin C, echinacea, and other alternative remedies have revealed no consistent benefit for the treatment of nonspecific URI.

INFECTIONS OF THE SINUS

Rhinosinusitis refers to an inflammatory condition involving the four paired structures surrounding the nasal cavities. Although most cases of sinusitis involve more than one sinus, the maxillary sinus is most commonly involved; next, in order of frequency, are the ethmoid, frontal, and sphenoid sinuses. Each sinus is lined with a respiratory epithelium that produces mucus, which is transported out by ciliary action through the sinus ostium and into the nasal cavity. Normally, mucus does not accumulate in the sinuses, which remain mostly sterile despite their adjacency to the bacterium-filled nasal passages. When the sinus ostia are obstructed, however, or when ciliary clearance is impaired or absent, the secretions can be retained, producing the typical signs and symptoms of sinusitis. As these secretions accumulate with obstruction, they become more susceptible to infection with a variety of pathogens, including viruses, bacteria, and fungi. Sinusitis affects a tremendous proportion of the population, accounts for millions of visits to primary care physicians each year, and is the fifth leading diagnosis for which antibiotics are prescribed. It typically is classified by duration of illness (acute vs. chronic); by etiology (infectious vs. noninfectious); and, when infectious, by the offending pathogen type (viral, bacterial, or fungal).

ACUTE RHINOSINUSITIS

Acute rhinosinusitis—defined as sinusitis of <4 weeks' duration—constitutes the vast majority of sinusitis cases. Most cases are diagnosed in the ambulatory care setting and occur primarily as a consequence of a preceding viral URI. Differentiating acute bacterial from viral sinusitis on clinical grounds is difficult. Therefore, it is perhaps not surprising that antibiotics are prescribed frequently (in 85–98% of all cases) for this condition.

Etiology

The ostial obstruction that results in rhinosinusitis can arise from both infectious and noninfectious causes. Noninfectious causes include allergic rhinitis (with either mucosal edema or polyp obstruction), barotrauma (e.g., from deep-sea diving or air travel), and exposure to chemical irritants. Obstruction also can occur with nasal and sinus tumors (e.g., squamous cell carcinoma) or granulomatous diseases (e.g., granulomatosis with polyangiitis or rhinoscleroma), and conditions leading to altered mucus content (e.g., cystic fibrosis) can cause sinusitis through impaired mucus clearance. In ICUs, nasotracheal intubation and nasogastric tubes are major risk factors for nosocomial sinusitis.

Viral rhinosinusitis is far more common than bacterial sinusitis, although relatively few studies have sampled sinus aspirates for the presence of different viruses. In the studies that have done so, the viruses most commonly isolated—both alone and with bacteria—have been rhinovirus, parainfluenza virus, and influenza virus. Bacterial causes of sinusitis have been better described. Among community-acquired cases, *S. pneumoniae* and nontypable *Haemophilus influenzae* are the most common pathogens, accounting for 50–60% of cases. *Moraxella catarrhalis* causes disease in a significant percentage (20%) of children, but a lesser percentage of adults. Other streptococcal species and *Staphylococcus aureus* cause only a small percentage of cases, although there is increasing concern about community-acquired methicillin-resistant *S. aureus* (MRSA) as an emerging cause. It is difficult to assess whether a cultured bacterium represents a true infecting organism, an insufficiently deep sample (which would not be expected to be sterile), or—especially in the case of previous sinus surgeries—a colonizing organism. Anaerobes occasionally are found in association with infections of the roots of premolar teeth that spread into the adjacent maxillary sinuses. The role of *Chlamydophila pneumoniae* and *Mycoplasma pneumoniae* in the pathogenesis of acute sinusitis is unclear. Nosocomial cases commonly are associated with bacteria found in the hospital environment, including *S. aureus*, *Pseudomonas aeruginosa*, *Serratia marcescens*, *Klebsiella pneumoniae*,

and *Enterobacter* species. Often, these infections are polymicrobial and involve organisms that are highly resistant to numerous antibiotics. Fungi are also established causes of sinusitis, although most acute cases are in immunocompromised patients and represent invasive, life-threatening infections. The best-known example is rhinocerebral mucormycosis caused by fungi of the order Mucorales, which includes *Rhizopus*, *Rhizomucor*, *Mucor*, *Mycocladus* (formerly *Absidia*), and *Cunninghamella* (Chap. 112). These infections classically occur in diabetic patients with ketoacidosis but also can develop in transplant recipients, patients with hematologic malignancies, and patients receiving chronic glucocorticoid or deferoxamine therapy. Other hyaline molds, such as *Aspergillus* and *Fusarium* species, are also occasional causes of this disease.

Clinical manifestations

Most cases of acute sinusitis present after or in conjunction with a viral URI, and it can be difficult to discriminate the clinical features of one from the other. A large proportion of patients with colds have sinus inflammation, although, as previously stated, true bacterial sinusitis complicates only 0.2–2% of these viral infections. Common presenting symptoms of sinusitis include nasal drainage and congestion, facial pain or pressure, and headache. Thick, purulent or discolored nasal discharge is often thought to indicate bacterial sinusitis but also occurs early in viral infections such as the common cold and is not specific to bacterial infection. Other nonspecific manifestations include cough, sneezing, and fever. Tooth pain, most often involving the upper molars, as well as halitosis can be associated with bacterial sinusitis.

In acute sinusitis, sinus pain or pressure often localizes to the involved sinus (particularly the maxillary sinus) and can be worse when the patient bends over or is supine. Although rare, manifestations of advanced sphenoid or ethmoid sinus infection can be profound, including severe frontal or retroorbital pain radiating to the occiput, thrombosis of the cavernous sinus, and signs of orbital cellulitis. Acute focal sinusitis is uncommon, but should be considered over the maxillary sinus and fever in patients with severe symptoms, regardless of illness duration. Similarly, patients with advanced frontal sinusitis can present with a condition known as *Pott's puffy tumor*, with soft tissue swelling and pitting edema over the frontal bone from a communicating subperiosteal abscess. Life-threatening complications of sinusitis include meningitis, epidural abscess, and cerebral abscess.

Patients with acute fungal rhinosinusitis (such as mucormycosis; Chap. 112) often present with symptoms related to pressure effects, particularly when the infection has spread to the orbits and cavernous sinus. Signs such as orbital swelling and cellulitis, proptosis, ptosis, and decreased extraocular movement are common, as is retroorbital or periorbital pain. Nasopharyngeal ulcerations, epistaxis, and headaches are also common, and involvement of cranial nerves V and VII has been described in more advanced cases. Bony erosion may be evident on examination. Often the patient does not appear seriously ill despite the rapidly progressive nature of these infections.

Patients with acute nosocomial sinusitis are often critically ill and, thus, do not manifest the typical clinical features of sinus disease. This diagnosis should be suspected, however, when hospitalized patients who have appropriate risk factors (e.g., nasotracheal intubation) develop fever without another apparent cause.

Diagnosis

Distinguishing viral from bacterial rhinosinusitis in the ambulatory setting is usually difficult because of the relatively low sensitivity and specificity of the common clinical features. One clinical feature that has been used to help guide diagnostic and therapeutic decision making is illness duration. Because acute bacterial sinusitis is uncommon in patients whose symptoms have lasted <10 days, expert panels now recommend reserving this diagnosis for patients with "persistent" symptoms (i.e., symptoms lasting >10 days in adults or >10–14 days in children) accompanied by the three cardinal signs of purulent nasal discharge, nasal obstruction, and facial pain **(Table 17-1)**. Even among patients who meet these criteria, only 40–50% have true bacterial sinusitis. The use of CT or sinus radiography is not recommended for acute disease, particularly early in the course of illness (i.e., at <10 days) in light of the high prevalence of similar abnormalities among patients with acute viral rhinosinusitis. In the evaluation of persistent, recurrent, or chronic sinusitis, CT of the sinuses is the radiographic study of choice.

The clinical history and/or setting often can identify cases of acute anaerobic bacterial sinusitis, acute fungal sinusitis, or sinusitis from noninfectious causes (e.g., allergic rhinosinusitis). In the case of an immunocompromised patient with acute fungal sinus infection, immediate examination by an otolaryngologist is required. Biopsy specimens from involved areas should be examined by a pathologist for evidence of fungal hyphal elements and tissue invasion. Cases of suspected acute nosocomial sinusitis should be confirmed by sinus CT. Because therapy should target the offending organism, a sinus aspirate for culture and susceptibility testing should be obtained, if possible, before the initiation of antimicrobial therapy.

TREATMENT **Acute Sinusitis**

Most patients with a clinical diagnosis of acute rhinosinusitis improve without antibiotic therapy. The preferred initial approach in patients with mild to moderate symptoms of short duration is therapy aimed at symptom relief and facilitation of sinus drainage, such as with oral and topical decongestants, nasal saline lavage, and—at least in patients with a history of chronic sinusitis or allergies—nasal glucocorticoids. Newer studies have cast doubt on the role of antibiotics and inhaled glucocorticoids in acute rhinosinusitis. In one notable double-blind, randomized,

TABLE 17-1

GUIDELINES FOR THE DIAGNOSIS AND TREATMENT OF ACUTE SINUSITIS

AGE GROUP	DIAGNOSTIC CRITERIA	TREATMENT RECOMMENDATIONS[a]
Adults	Moderate symptoms (e.g., nasal purulence/congestion or cough) for >10 d *or* Severe symptoms of any duration, including unilateral/focal facial swelling or tooth pain	*Initial therapy:* Amoxicillin, 500 mg PO tid or 875 mg PO bid *Penicillin allergy:* TMP-SMX, 1 DS tablet PO bid for 10–14 d *Exposure to antibiotics within 30 d or >30% prevalence of penicillin-resistant Streptococcus pneumoniae:* Amoxicillin/clavulanate (extended release), 2000 mg PO bid; *or* Antipneumococcal fluoroquinolone (e.g., levofloxacin, 500 mg PO qd) *Recent treatment failure:* Amoxicillin/clavulanate (extended release), 2000 mg PO bid; *or* Amoxicillin, 1500 mg bid, plus clindamycin, 300 mg PO qid; *or* Antipneumococcal fluoroquinolone (e.g., levofloxacin, 500 mg PO qd)
Children	Moderate symptoms (e.g., nasal purulence/congestion or cough) for >10–14 d *or* Severe symptoms of any duration, including fever (>102°F), unilateral/focal facial swelling or pain	*Initial therapy:* Amoxicillin, 45–90 mg/kg qd (up to 2 g) PO in divided doses (bid or tid); *or* Cefuroxime axetil, 30 mg/kg qd PO in divided doses (bid); *or* Cefdinir, 14 mg/kg PO qd *Exposure to antibiotics within 30 d, recent treatment failure, or >30% prevalence of penicillin-resistant S. pneumoniae:* Amoxicillin, 90 mg/kg qd (up to 2 g) PO in divided doses (bid), plus clavulanate, 6.4 mg/kg qd PO in divided doses (bid) (extra-strength suspension); *or* Cefuroxime axetil, 30 mg/kg qd PO in divided doses (bid); *or* Cefdinir, 14 mg/kg PO qd

[a]Unless otherwise specified, the duration of therapy is generally 10 days, with appropriate follow-up.
Abbreviations: DS, double-strength; TMP-SMX, trimethoprim-sulfamethoxazole.
Sources: American Academy of Pediatrics Subcommittee on Management of Sinusitis and Committee on Quality Improvement: Pediatrics 108:798, 2001; RM Rosenfeld et al: Otolaryngol Head Neck Surg 137(3 Suppl):S1, 2007.

placebo-controlled trial, neither antibiotics nor topical glucocorticoids had a significant impact on cure in the study population of patients, the majority of whom had had symptoms for <7 days. Adult patients whose condition does not improve after 7 days, children whose condition does not improve after 10–14 days, and patients with more severe symptoms (regardless of duration) should be treated with antibiotics (Table 17-1). Empirical therapy for adults with community-acquired sinusitis should consist of the narrowest-spectrum agent active against the most common bacterial pathogens, including *S. pneumoniae* and *H. influenzae* (e.g., amoxicillin). No clinical trials support the use of broad-spectrum agents for routine cases of bacterial sinusitis, even in the current era of drug-resistant *S. pneumoniae*. Up to 10% of patients do not respond to initial antimicrobial therapy; sinus aspiration and/or lavage by an otolaryngologist should be considered in these cases. Antibiotic prophylaxis to prevent episodes of recurrent acute bacterial sinusitis is not recommended.

Surgical intervention and IV antibiotic administration usually are reserved for patients with severe disease or those with intracranial complications such as abscess and orbital involvement. Immunocompromised patients with acute invasive fungal sinusitis usually

require extensive surgical debridement and treatment with IV antifungal agents active against fungal hyphal forms, such as amphotericin B. Specific therapy should be individualized according to the fungal species and its susceptibilities as well as the individual patient's characteristics.

Treatment of nosocomial sinusitis should begin with broad-spectrum antibiotics to cover common and often resistant pathogens such as *S. aureus* and gram-negative bacilli. Therapy then should be tailored to the results of culture and susceptibility testing of sinus aspirates.

CHRONIC SINUSITIS

Chronic sinusitis is characterized by symptoms of sinus inflammation lasting >12 weeks. This illness is most commonly associated with either bacteria or fungi, and clinical cure in most cases is very difficult. Many patients have undergone treatment with repeated courses of antibacterial agents and multiple sinus surgeries, increasing their risk of colonization with antibiotic-resistant pathogens and of surgical complications. These patients often have high rates of morbidity, sometimes over many years.

In *chronic bacterial sinusitis*, infection is thought to be due to the impairment of mucociliary clearance from repeated infections rather than to persistent bacterial infection. The pathogenesis of this condition, however, is poorly understood. Although certain conditions (e.g., cystic fibrosis) can predispose patients to chronic bacterial sinusitis, most patients with chronic rhinosinusitis do not have obvious underlying conditions that result in the obstruction of sinus drainage, the impairment of ciliary action, or immune dysfunction. Patients experience constant nasal congestion and sinus pressure, with intermittent periods of greater severity, which may persist for years. CT can be helpful in determining the extent of disease, detecting an underlying anatomic defect or obstructing process (e.g., a polyp), and assessing the response to therapy. The management team should include an otolaryngologist to conduct endoscopic examinations and obtain tissue samples for histologic examination and culture. An endoscopy-derived culture not only has a higher yield but also allows direct visualization for abnormal anatomy.

Chronic fungal sinusitis is a disease of immunocompetent hosts and is usually noninvasive, although slowly progressive invasive disease sometimes is seen. Noninvasive disease, which typically is associated with hyaline molds such as *Aspergillus* species and dematiaceous molds such as *Curvularia* or *Bipolaris* species, can present as a number of different scenarios. In mild, indolent disease, which usually occurs in the setting of repeated failures of antibacterial therapy, only nonspecific mucosal changes may be seen on sinus CT. Although there is some controversy on this point, endoscopic surgery is usually curative in these cases, with no need for antifungal therapy. Another form of disease presents as longstanding, often unilateral symptoms and opacification of a single sinus on imaging studies as a result of a mycetoma (fungus ball) within the sinus. Treatment for this condition is also surgical, although systemic antifungal therapy may be warranted in the rare case in which bony erosion occurs. A third form of disease, known as *allergic fungal sinusitis*, is seen in patients with a history of nasal polyposis and asthma, who often have had multiple sinus surgeries. Patients with this condition produce a thick, eosinophil-laden mucus with the consistency of peanut butter that contains sparse fungal hyphae on histologic examination. These patients often present with pansinusitis.

TREATMENT Chronic Sinusitis

Treatment of chronic bacterial sinusitis can be challenging and consists primarily of repeated culture-guided courses of antibiotics, sometimes for 3–4 weeks at a time; administration of intranasal glucocorticoids; and mechanical irrigation of the sinus with sterile saline solution. When this management approach fails, sinus surgery may be indicated and sometimes provides significant, albeit short-term, alleviation. Treatment of chronic fungal sinusitis consists of surgical removal of impacted mucus. Recurrence, unfortunately, is common.

INFECTIONS OF THE EAR AND MASTOID

Infections of the ear and associated structures can involve both the middle and the external ear, including the skin, cartilage, periosteum, ear canal, and tympanic and mastoid cavities. Both viruses and bacteria are known causes of these infections, some of which result in significant morbidity if not treated appropriately.

INFECTIONS OF THE EXTERNAL EAR STRUCTURES

Infections involving the structures of the external ear are often difficult to differentiate from noninfectious inflammatory conditions with similar clinical manifestations. Clinicians should consider inflammatory disorders as possible causes of external ear irritation, particularly in the absence of local or regional adenopathy. Aside from the more salient causes of inflammation, such as trauma, insect bite, and overexposure to sunlight or extreme cold, the differential diagnosis should include less common conditions such as autoimmune disorders (e.g., lupus or relapsing polychondritis) and vasculitides (e.g., granulomatosis with polyangiitis).

Auricular cellulitis

Auricular cellulitis is an infection of the skin overlying the external ear and typically follows minor local trauma.

It presents as the typical signs and symptoms of cellulitis, with tenderness, erythema, swelling, and warmth of the external ear (particularly the lobule), but without apparent involvement of the ear canal or inner structures. Treatment consists of warm compresses and oral antibiotics such as dicloxacillin that are active against typical skin and soft tissue pathogens (specifically, *S. aureus* and streptococci). IV antibiotics such as a first-generation cephalosporin (e.g., cefazolin) or a penicillinase-resistant penicillin (e.g., nafcillin) occasionally are needed for more severe cases, with consideration of MRSA if either risk factors or failure of therapy point to this organism.

Perichondritis

Perichondritis, an infection of the perichondrium of the auricular cartilage, typically follows local trauma (e.g., ear piercing, burns, or lacerations). Occasionally, when the infection spreads down to the cartilage of the pinna itself, patients may develop chondritis. The infection may closely resemble auricular cellulitis, with erythema, swelling, and extreme tenderness of the pinna, although the lobule is less often involved in perichondritis. The most common pathogens are *P. aeruginosa* and *S. aureus*, although other gram-negative and gram-positive organisms occasionally are involved. Treatment consists of systemic antibiotics active against both *P. aeruginosa* and *S. aureus*. An antipseudomonal penicillin (e.g., piperacillin) or a combination of a penicillinase-resistant penicillin and an antipseudomonal quinolone (e.g., nafcillin plus ciprofloxacin) is typically used. Incision and drainage may be helpful for culture and for resolution of infection, which often takes weeks. When perichondritis fails to respond to adequate antimicrobial therapy, clinicians should consider a noninfectious inflammatory etiology such as relapsing polychondritis.

Otitis externa

The term *otitis externa* refers to a collection of diseases involving primarily the auditory meatus. Otitis externa usually results from a combination of heat and retained moisture, with desquamation and maceration of the epithelium of the outer ear canal. The disease exists in several forms: localized, diffuse, chronic, and invasive. All forms are predominantly bacterial in origin, with *P. aeruginosa* and *S. aureus* the most common pathogens.

Acute localized otitis externa (*furunculosis*) can develop in the outer third of the ear canal, where skin overlies cartilage and hair follicles are numerous. As in furunculosis elsewhere on the body, *S. aureus* is the usual pathogen, and treatment typically consists of an oral antistaphylococcal penicillin (e.g., dicloxacillin), with incision and drainage in cases of abscess formation.

Acute diffuse otitis externa is also known as *swimmer's ear*, although it can develop in patients who have not recently been swimming. Heat, humidity, and the loss of protective cerumen lead to excessive moisture and elevation of the pH in the ear canal, which in turn lead to skin maceration and irritation. Infection may then occur; the predominant pathogen is *P. aeruginosa*, although other gram-negative and gram-positive organisms—and rarely yeasts—have been recovered from patients with this condition. The illness often starts with itching and progresses to severe pain, which usually is elicited by manipulation of the pinna or tragus. The onset of pain generally is accompanied by the development of an erythematous, swollen ear canal, often with scant white, clumpy discharge. Treatment consists of cleansing the canal to remove debris and enhance the activity of topical therapeutic agents—usually hypertonic saline or mixtures of alcohol and acetic acid. Inflammation also can be decreased by adding glucocorticoids to the treatment regimen or by using Burow's solution (aluminum acetate in water). Antibiotics are most effective when given topically. Otic mixtures provide adequate pathogen coverage; these preparations usually combine neomycin with polymyxin, with or without glucocorticoids. Systemic antimicrobial agents typically are reserved for severe disease or infections in immunocompromised hosts.

Chronic otitis externa is caused primarily by repeated local irritation, most commonly arising from persistent drainage from a chronic middle-ear infection. Other causes of repeated irritation, such as insertion of cotton swabs or other foreign objects into the ear canal, can lead to this condition, as can rare chronic infections such as syphilis, tuberculosis, and leprosy. Chronic otitis externa typically presents as erythematous, scaling dermatitis in which the predominant symptom is pruritus rather than pain; this condition must be differentiated from several others that produce a similar clinical picture, such as atopic dermatitis, seborrheic dermatitis, psoriasis, and dermatomycosis. Therapy consists of identifying and treating or removing the offending process, although successful resolution is frequently difficult.

Invasive otitis externa, also known as *malignant* or *necrotizing* otitis externa, is an aggressive and potentially life-threatening disease that occurs predominantly in elderly diabetic patients and other immunocompromised persons. The disease begins in the external canal as a soft tissue infection that progresses slowly over weeks to months and often is difficult to distinguish from a severe case of chronic otitis externa because of the presence of purulent otorrhea and an erythematous swollen ear and external canal. Severe, deep-seated otalgia, frequently out of proportion to findings on examination, is often noted and can help differentiate invasive from chronic otitis externa. The characteristic finding on examination is granulation tissue in the posteroinferior wall of the external canal, near the junction of bone and cartilage. If left unchecked, the infection can migrate to the base of the skull (resulting in skull-base osteomyelitis) and onto the meninges and brain, with a high-associated mortality rate. Cranial nerve involvement is seen occasionally, with the facial nerve usually affected first and most often. Thrombosis of the sigmoid sinus can occur if the infection extends to that area. CT, which can reveal osseous erosion of the temporal bone and

skull base, can be used to help determine the extent of disease, as can gallium and technetium-99 scintigraphy studies. *P. aeruginosa* is by far the most common pathogen, although *S. aureus*, *S. epidermidis*, *Aspergillus*, *Actinomyces*, and some gram-negative bacteria have also been associated with this disease. In all cases, the external ear canal should be cleansed and a biopsy specimen of the granulation tissue within the canal (or of deeper tissues) obtained for culture of the offending organism. IV antibiotic therapy should be given for a prolonged course (6–8 weeks) and directed specifically toward the recovered pathogen. For *P. aeruginosa*, the regimen typically includes an antipseudomonal penicillin or cephalosporin (e.g., piperacillin or ceftazidime) with an aminoglycoside. A fluoroquinolone antibiotic is frequently used in place of the aminoglycoside and can even be administered orally because of the excellent bioavailability of this drug class. In addition, antibiotic drops containing an agent active against *Pseudomonas* (e.g., ciprofloxacin) usually are prescribed and are combined with glucocorticoids to reduce inflammation. Cases of invasive *Pseudomonas* otitis externa recognized in the early stages sometimes can be treated with oral and otic fluoroquinolones alone, albeit with close follow-up. Extensive surgical debridement, once an important component of the treatment approach, is now rarely indicated.

In necrotizing otitis externa, recurrence is documented up to 20% of the time. Aggressive glycemic control in diabetics is important not only for effective treatment but also for prevention of recurrence. The role of hyperbaric oxygen has not been clearly established.

INFECTIONS OF MIDDLE-EAR STRUCTURES

Otitis media is an inflammatory condition of the middle ear that results from dysfunction of the eustachian tube in association with a number of illnesses, including URIs and chronic rhinosinusitis. The inflammatory response to these conditions leads to the development of a sterile transudate within the middle ear and mastoid cavities. Infection may occur if bacteria or viruses from the nasopharynx contaminate this fluid, producing an acute (or sometimes chronic) illness.

Acute otitis media

Acute otitis media results when pathogens from the nasopharynx are introduced into the inflammatory fluid collected in the middle ear (e.g., by nose blowing during a URI). The proliferation of these pathogens in this space leads to the development of the typical signs and symptoms of acute middle-ear infection. The diagnosis of acute otitis media requires the demonstration of fluid in the middle ear [with tympanic membrane (TM) immobility] and the accompanying signs or symptoms of local or systemic illness **(Table 17-2)**.

Etiology

Acute otitis media typically follows a viral URI. The causative viruses (most commonly RSV, influenza virus, rhinovirus, and enterovirus) can themselves cause subsequent acute otitis media; more often, they predispose the patient to bacterial otitis media. Studies using tympanocentesis have consistently found *S. pneumoniae* to be the most important bacterial cause, isolated in up to 35% of cases. *H. influenzae* (nontypable strains) and *M. catarrhalis* are also common bacterial causes of acute otitis media, and concern is increasing about community strains of MRSA as an emerging etiologic agent. Viruses, such as those mentioned earlier, have been recovered either alone or with bacteria in 17–40% of cases.

Clinical manifestations

Fluid in the middle ear is typically demonstrated or confirmed with pneumatic otoscopy. In the absence of fluid, the tympanic membrane moves visibly with the application of positive and negative pressure, but this movement is dampened when fluid is present. With bacterial infection, the tympanic membrane can also be erythematous, bulging, or retracted and occasionally can perforate spontaneously. The signs and symptoms accompanying infection can be local or systemic, including otalgia, otorrhea, diminished hearing, fever, and irritability. Erythema of the tympanic membrane is often evident but is nonspecific as it frequently is seen in association with inflammation of the upper respiratory mucosa (e.g., during examination of young children). Other signs and symptoms that are occasionally reported include vertigo, nystagmus, and tinnitus.

TREATMENT **Acute Otitis Media**

There has been considerable debate on the usefulness of antibiotics for the treatment of acute otitis media. A higher proportion of treated than untreated patients are free of illness 3–5 days after diagnosis. The difficulty of predicting which patients will benefit from antibiotic therapy has led to different approaches. In the Netherlands, for instance, physicians typically manage acute otitis media with initial observation, administering anti-inflammatory agents for aggressive pain management and reserving antibiotics for high-risk patients, patients with complicated disease, or patients whose condition does not improve after 48–72 h. In contrast, many experts in the United States continue to recommend antibiotic therapy for children <6 months old in light of the higher frequency of secondary complications in this young and functionally immunocompromised population. However, observation without antimicrobial therapy is now the recommended option in the United States for acute otitis media in children ≥2 years of age and for mild to moderate disease without middle-ear effusion in children 6 months to 2 years of age. Treatment is typically indicated for patients <6 months old; for children 6 months to 2 years old who have middle-ear effusion and signs/symptoms of middle-ear

TABLE 17-2

GUIDELINES FOR THE DIAGNOSIS AND TREATMENT OF ACUTE OTITIS MEDIA

ILLNESS SEVERITY	DIAGNOSTIC CRITERIA	TREATMENT RECOMMENDATIONS
Mild to moderate	>2 yrs or 6 mo to 2 yrs without middle-ear effusion	*Observation alone* (deferring antibiotic therapy for 48–72 h and limiting management to symptom relief)
	<6 mo; *or* 6 mo to 2 yrs with middle-ear effusion (fluid in the middle ear, evidenced by decreased TM mobility, air/fluid level behind TM, bulging TM, purulent otorrhea) *and* acute onset of signs and symptoms of middle-ear inflammation, including fever, otalgia, decreased hearing, tinnitus, vertigo, erythematous TM; *or* >2 yrs with bilateral disease, TM perforation, high fever, immunocompromise, emesis	*Initial therapy*[a] Amoxicillin, 80–90 mg/kg qd (up to 2 g) PO in divided doses (bid or tid); *or* Cefdinir, 14 mg/kg qd PO in 1 dose or divided doses (bid); *or* Cefuroxime, 30 mg/kg qd PO in divided doses (bid); *or* Azithromycin, 10 mg/kg qd PO on day 1 followed by 5 mg/kg qd PO for 4 d *Exposure to antibiotics within 30 d or recent treatment failure*[a,b]*:* Amoxicillin, 90 mg/kg qd (up to 2 g) PO in divided doses (bid), plus clavulanate, 6.4 mg/kg qd PO in divided doses (bid); *or* Ceftriaxone, 50 mg/kg IV/IM qd for 3 d; *or* Clindamycin, 30–40 mg/kg qd PO in divided doses (tid)
Severe	As above, with temperature ≥39.0°C (102°F) *or* Moderate to severe otalgia	*Initial therapy*[a] Amoxicillin, 90 mg/kg qd (up to 2 g) PO in divided doses (bid), plus clavulanate, 6.4 mg/kg qd PO in divided doses (bid); *or* Ceftriaxone, 50 mg/kg IV/IM qd for 3 d *Exposure to antibiotics within 30 d or recent treatment failure*[a,b] Ceftriaxone, 50 mg/kg IV/IM qd for 3 d; *or* Clindamycin, 30–40 mg/kg qd PO in divided doses (tid); *or* Consider tympanocentesis with culture

[a]Duration (unless otherwise specified): 10 days for patients <6 years old and patients with severe disease; 5–7 days (with consideration of observation only in previously healthy individuals with mild disease) for patients ≥6 years old.
[b]Failure to improve and/or clinical worsening after 48–72 h of observation or treatment.
Abbreviation: TM, tympanic membrane.
Source: American Academy of Pediatrics Subcommittee on Management of Acute Otitis Media: Pediatrics 113:1451, 2004.

inflammation; for all patients >2 years old who have bilateral disease, tympanic membrane perforation, immunocompromise, or emesis; and for any patient who has severe symptoms, including a fever ≥39°C or moderate to severe otalgia (Table 17-2).

Because most studies of the etiologic agents of acute otitis media consistently document similar pathogen profiles, therapy is generally empirical except in those few cases in which tympanocentesis is warranted—e.g., cases in newborns, cases refractory to therapy, and cases in patients who are severely ill or immunodeficient. Despite resistance to penicillin and amoxicillin in roughly one-quarter of *S. pneumoniae* isolates, one-third of *H. influenzae* isolates, and nearly all *M. catarrhalis* isolates, outcome studies continue to find that amoxicillin is as successful as any other agent, and it remains the drug of first choice in recommendations from multiple sources (Table 17-2). Therapy for uncomplicated acute otitis media typically is administered for 5–7 days to patients ≥6 years old; longer courses (e.g., 10 days) should be reserved for children <6 years old and patients with severe disease, in whom short-course therapy may be inadequate.

A switch in regimen is recommended if there is no clinical improvement by the third day of therapy in light of the possibility of infection with a β-lactamase-producing strain of *H. influenzae* or *M. catarrhalis* or with a strain of penicillin-resistant *S. pneumoniae*. Decongestants and antihistamines are frequently used as adjunctive agents to reduce congestion and relieve obstruction of the eustachian tube, but clinical trials have yielded no significant evidence of benefit with either class of agents.

Recurrent acute otitis media

Recurrent acute otitis media (more than three episodes within 6 months or four episodes within 12 months) generally is due to relapse or reinfection, although data indicate that the majority of early recurrences are new infections. In general, the same pathogens responsible for acute otitis media cause recurrent disease; even so, the recommended treatment consists of antibiotics active against β-lactamase-producing organisms. Antibiotic prophylaxis [e.g., with trimethoprim-sulfamethoxazole (TMP-SMX) or amoxicillin] can reduce recurrences in patients with recurrent acute otitis media by an average of one episode per year, but this benefit is small compared with the cost of the drug and the high likelihood of colonization with antibiotic-resistant pathogens. Other approaches, including placement of tympanostomy tubes, adenoidectomy, and tonsillectomy plus adenoidectomy, are of questionable overall value in light of the relatively small benefit compared with the potential for complications.

Serous otitis media

In serous otitis media (otitis media with effusion), fluid is present in the middle ear for an extended period in the absence of signs and symptoms of infection. In general, acute effusions are self-limited; most resolve in 2–4 weeks. In some cases, however (in particular after an episode of acute otitis media), effusions can persist for months. These chronic effusions are often associated with significant hearing loss in the affected ear. In younger children, persistent effusions and decreased hearing can be associated with impairment of language acquisition skills. The great majority of cases of otitis media with effusion resolve spontaneously within 3 months without antibiotic therapy. Antibiotic therapy or myringotomy with insertion of tympanostomy tubes typically is reserved for patients in whom bilateral effusion (1) has persisted for at least 3 months and (2) is associated with significant bilateral hearing loss. With this conservative approach and the application of strict diagnostic criteria for acute otitis media and otitis media with effusion, it is estimated that 6–8 million courses of antibiotics could be avoided each year in the United States.

Chronic otitis media

Chronic suppurative otitis media is characterized by persistent or recurrent purulent otorrhea in the setting of tympanic membrane perforation. Usually, there is also some degree of conductive hearing loss. This condition can be categorized as active or inactive. Inactive disease is characterized by a central perforation of the tympanic membrane, which allows drainage of purulent fluid from the middle ear. When the perforation is more peripheral, squamous epithelium from the auditory canal may invade the middle ear through the perforation, forming a mass of keratinaceous debris (*cholesteatoma*) at the site of invasion. This mass can enlarge and has the potential to erode bone and promote further infection, which can lead to meningitis, brain abscess, or paralysis of cranial nerve VII. Treatment of chronic active otitis media is surgical; mastoidectomy, myringoplasty, and tympanoplasty can be performed as outpatient surgical procedures, with an overall success rate of ~80%. Chronic inactive otitis media is more difficult to cure, usually requiring repeated courses of topical antibiotic drops during periods of drainage. Systemic antibiotics may offer better cure rates, but their role in the treatment of this condition remains unclear.

Mastoiditis

Acute mastoiditis was relatively common among children before the introduction of antibiotics. Because the mastoid air cells connect with the middle ear, the process of fluid collection and infection is usually the same in the mastoid as in the middle ear. Early and frequent treatment of acute otitis media is most likely the reason that the incidence of acute mastoiditis has declined to only 1.2–2.0 cases per 100,000 person-years in countries with high prescribing rates for acute otitis media.

In countries such as the Netherlands, where antibiotics are used sparingly for acute otitis media, the incidence rate of acute mastoiditis is roughly twice that in countries like the United States. However, neighboring Denmark has a rate of acute mastoiditis similar to that in the Netherlands but an antibiotic-prescribing rate for acute otitis media more similar to that in the United States.

In typical acute mastoiditis, purulent exudate collects in the mastoid air cells **(Fig. 17-1)**, producing pressure that may result in erosion of the surrounding bone and formation of abscess-like cavities that are usually evident on CT. Patients typically present with pain, erythema, and swelling of the mastoid process along with displacement of the pinna, usually in conjunction with the typical signs and symptoms of acute middle-ear infection. Rarely, patients can develop severe complications if the infection tracks under the periosteum of the temporal bone to cause a subperiosteal abscess, erodes through the mastoid tip to cause a deep neck abscess, or extends posteriorly to cause septic thrombosis of the lateral sinus.

Purulent fluid should be cultured whenever possible to help guide antimicrobial therapy. Initial empirical therapy usually is directed against the typical organisms associated with acute otitis media, such as *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*. Some patients with more severe or prolonged courses of illness should be treated

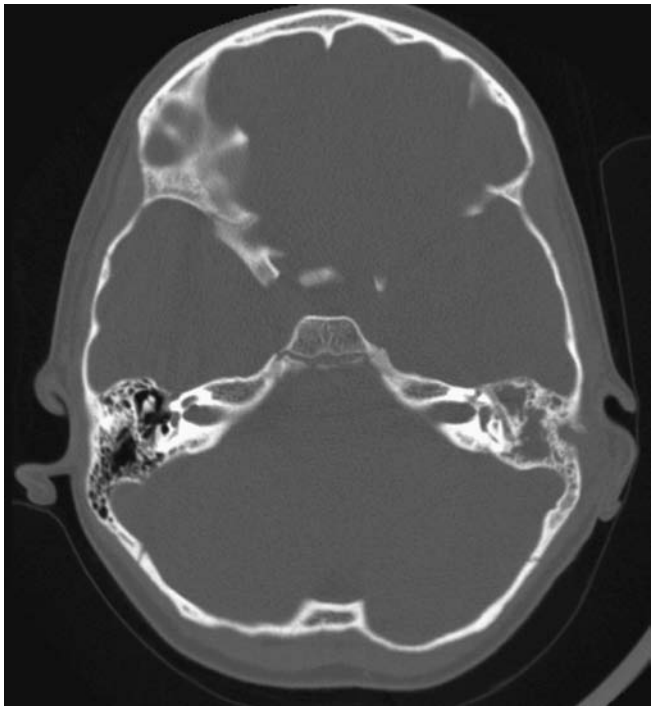


FIGURE 17-1
Acute mastoiditis. Axial CT image shows an acute fluid collection within the mastoid air cells on the left.

for infection with *S. aureus* and gram-negative bacilli (including *Pseudomonas*). Broad empirical therapy is usually narrowed once culture results become available. Most patients can be treated conservatively with IV antibiotics; surgery (cortical mastoidectomy) can be reserved for complicated cases and those in which conservative treatment has failed.

INFECTIONS OF THE PHARYNX AND ORAL CAVITY

Oropharyngeal infections range from mild, self-limited viral illnesses to serious, life-threatening bacterial infections. The most common presenting symptom is sore throat—one of the most common reasons for ambulatory care visits by both adults and children. Although sore throat is a symptom in many noninfectious illnesses as well, the overwhelming majority of patients with a new sore throat have acute pharyngitis of viral or bacterial etiology.

ACUTE PHARYNGITIS

Millions of visits to primary care providers each year are for sore throat; the majority of cases of acute pharyngitis are caused by typical respiratory viruses. The most important source of concern is infection with group A β-hemolytic *Streptococcus* (*S. pyogenes*) that is associated with acute glomerulonephritis and acute rheumatic fever. The risk of rheumatic fever can be reduced by timely penicillin therapy.

Etiology

A wide variety of organisms cause acute pharyngitis. The relative importance of the different pathogens can only be estimated, since a significant proportion of cases (~30%) have no identified cause. Together, respiratory viruses are the most common identifiable cause of acute pharyngitis, with rhinoviruses and coronaviruses accounting for large proportions of cases (~20% and at least 5%, respectively). Influenza virus, parainfluenza virus, and adenovirus also account for a measurable share of cases, the latter as part of the more clinically severe syndrome of pharyngoconjunctival fever. Other important but less common viral causes include herpes simplex virus (HSV) types 1 and 2, coxsackievirus A, cytomegalovirus (CMV), and Epstein-Barr virus (EBV). Acute HIV infection can present as acute pharyngitis and should be considered in at-risk populations.

Acute bacterial pharyngitis is typically caused by *S. pyogenes*, which accounts for ~5–15% of all cases of acute pharyngitis in adults; rates vary with the season and with utilization of the health care system. Group A streptococcal pharyngitis is primarily a disease of children 5–15 years of age; it is uncommon among children <3 years old, as is rheumatic fever. Streptococci of groups C and G account for a minority of cases, although these serogroups are nonrheumatogenic. *Fusobacterium necrophorum* has been increasingly recognized as a cause of pharyngitis in adolescents and young adults and is isolated nearly as often as group A streptococci. This information is important because of the rare but life-threatening Lemierre's disease, which is generally associated with *F. necrophorum* and is usually preceded by pharyngitis (see "Oral Infections," later in the chapter). The remaining bacterial causes of acute pharyngitis are seen infrequently (<1% of cases each) but should be considered in appropriate exposure groups because of the severity of illness if left untreated; these etiologic agents include *Neisseria gonorrhoeae*, *Corynebacterium diphtheriae*, *Corynebacterium ulcerans*, *Yersinia enterocolitica*, and *Treponema pallidum* (in secondary syphilis). Anaerobic bacteria can also cause acute pharyngitis (*Vincent's angina*) and can contribute to more serious polymicrobial infections, such as peritonsillar or retropharyngeal abscess (see below). Atypical organisms such as *M. pneumoniae* and *C. pneumoniae* have been recovered from patients with acute pharyngitis; whether these agents are commensals or causes of acute infection is debatable.

Clinical manifestations

Although the signs and symptoms accompanying acute pharyngitis are not reliable predictors of the etiologic agent, the clinical presentation occasionally suggests that one etiology is more likely than another. Acute pharyngitis due to respiratory viruses such as rhinovirus or coronavirus is usually not severe and typically is associated with a constellation of coryzal symptoms better characterized as nonspecific URI. Findings on physical examination are uncommon; fever is rare, and tender cervical adenopathy and pharyngeal exudates are not seen. In contrast,

acute pharyngitis from influenza virus can be severe and is much more likely to be associated with fever as well as with myalgias, headache, and cough. The presentation of pharyngoconjunctival fever due to adenovirus infection is similar. Since pharyngeal exudate may be present on examination, this condition can be difficult to differentiate from streptococcal pharyngitis. However, adenoviral pharyngitis is distinguished by the presence of conjunctivitis in one-third to one-half of patients. Acute pharyngitis from primary HSV infection can also mimic streptococcal pharyngitis in some cases, with pharyngeal inflammation and exudate, but the presence of vesicles and shallow ulcers on the palate can help differentiate the two diseases. This HSV syndrome is distinct from pharyngitis caused by coxsackievirus (*herpangina*), which is associated with small vesicles that develop on the soft palate and uvula and then rupture to form shallow white ulcers. Acute exudative pharyngitis coupled with fever, fatigue, generalized lymphadenopathy, and (on occasion) splenomegaly is characteristic of infectious mononucleosis due to EBV or CMV. Acute primary infection with HIV is frequently associated with fever and acute pharyngitis as well as with myalgias, arthralgias, malaise, and occasionally a nonpruritic maculopapular rash, which may be followed by lymphadenopathy and mucosal ulcerations without exudate.

The clinical features of acute pharyngitis caused by streptococci of groups A, C, and G are all similar, ranging from a relatively mild illness without many accompanying symptoms to clinically severe cases with profound pharyngeal pain, fever, chills, and abdominal pain. A hyperemic pharyngeal membrane with tonsillar hypertrophy and exudate is usually seen, along with tender anterior cervical adenopathy. Coryzal manifestations, including cough, are typically absent; when present, they suggest a viral etiology. Strains of *S. pyogenes* that generate erythrogenic toxin can also produce scarlet fever characterized by an erythematous rash and strawberry tongue. The other types of acute bacterial pharyngitis (e.g., gonococcal, diphtherial, and yersinial) often present as exudative pharyngitis with or without other clinical features. Their etiologies are often suggested only by the clinical history.

Diagnosis

The primary goal of diagnostic testing is to separate acute streptococcal pharyngitis from pharyngitis of other etiologies (particularly viral) so that antibiotics can be prescribed more efficiently for patients to whom they may be beneficial. The most appropriate standard for the diagnosis of streptococcal pharyngitis, however, has not been established definitively. Throat swab culture is generally regarded as the most appropriate but cannot distinguish between infection and colonization and requires 24–48 h to yield results that vary with technique and culture conditions. Rapid antigen-detection tests offer good specificity (>90%) but lower sensitivity when implemented in routine practice. The sensitivity has also been shown to vary across the clinical spectrum of disease (65–90%). Several clinical prediction systems **(Table 17-3)** can increase the sensitivity

TABLE 17-3

GUIDELINES FOR THE DIAGNOSIS AND TREATMENT OF ACUTE PHARYNGITIS

AGE GROUP	DIAGNOSTIC CRITERIA	TREATMENT RECOMMENDATIONS[a]
Adults	Clinical suspicion of streptococcal pharyngitis (e.g., fever, tonsillar swelling, exudate, enlarged/tender anterior cervical lymph nodes, absence of cough or coryza)[b] *with:* History of rheumatic fever *or* Documented household exposure *or* Positive rapid strep screen	Penicillin VK, 500 mg PO tid; *or* Amoxicillin, 500 mg PO bid; *or* Erythromycin, 250 mg PO qid; *or* Benzathine penicillin G, single dose of 1.2 million units IM
Children	Clinical suspicion of streptococcal pharyngitis (e.g., tonsillar swelling, exudate, enlarged/tender anterior cervical lymph nodes, absence of coryza) *with:* History of rheumatic fever *or* Documented household exposure *or* Positive rapid strep screen *or* Positive throat culture (for patients with negative rapid strep screen)	Amoxicillin, 45 mg/kg qd PO in divided doses (bid or tid); *or* Penicillin VK, 50 mg/kg qd PO in divided doses (bid); *or* Cephalexin, 50 mg/kg qd PO in divided doses (qid); *or* Benzathine penicillin G, single dose of 25,000 units/kg IM

[a]Unless otherwise specified, the duration of therapy is generally 10 days, with appropriate follow-up.
[b]Some organizations support treating adults who have these symptoms and signs without administering a rapid streptococcal antigen test.
Sources: RJ Cooper et al: Ann Intern Med 134:509, 2001; B Schwartz et al: Pediatrics 101:171, 1998.

of rapid antigen-detection tests to >90% in controlled settings. Since the sensitivities achieved in routine clinical practice are often lower, several medical and professional societies continue to recommend that all negative rapid antigen-detection tests in children be confirmed by a throat culture to limit transmission and complications of illness caused by group A streptococci. The Centers for Disease Control and Prevention, the Infectious Diseases Society of America, and the American Academy of Family Physicians do not recommend backup culture when adults have negative results in a highly sensitive rapid antigen-detection test, however, because of the lower prevalence and smaller benefit in this age group.

Cultures and rapid diagnostic tests for other causes of acute pharyngitis, such as influenza virus, adenovirus, HSV, EBV, CMV, and *M. pneumoniae*, are available in some locations and can be used when these infections are suspected. The diagnosis of acute EBV infection depends primarily on the detection of antibodies to the virus with a heterophile agglutination assay (monospot slide test) or enzyme-linked immunosorbent assay. Testing for HIV RNA or antigen (p24) should be performed when acute primary HIV infection is suspected. If other bacterial causes are suspected (particularly *N. gonorrhoeae*, *C. diphtheriae*, or *Y. enterocolitica*), specific cultures should be requested since these organisms may be missed on routine throat swab culture.

TREATMENT **Pharyngitis**

Antibiotic treatment of pharyngitis due to *S. pyogenes* confers numerous benefits, including a decrease in the risk of rheumatic fever. The magnitude of this benefit is fairly small, since rheumatic fever is now a rare disease, even among untreated patients. Nevertheless, when therapy is started within 48 h of illness onset, symptom duration is decreased. An additional benefit of therapy is the potential to reduce the transmission of streptococcal pharyngitis, particularly in areas of overcrowding or close contact. Antibiotic therapy for acute pharyngitis is, therefore, recommended in cases in which *S. pyogenes* is confirmed as the etiologic agent by rapid antigen-detection test or throat swab culture. Otherwise, antibiotics should be given in routine cases only when another bacterial cause has been identified. Effective therapy for streptococcal pharyngitis consists of either a single dose of IM benzathine penicillin or a full 10-day course of oral penicillin (Table 17-3).

Erythromycin can be used in place of penicillin, although resistance to erythromycin among *S. pyogenes* strains in some parts of the world (particularly Europe) can prohibit the use of this drug. Newer (and more expensive) antibiotics are also active against streptococci, but offer no greater efficacy than the agents mentioned above. Testing for cure is unnecessary and may reveal only chronic colonization. There is no evidence to support antibiotic treatment of group C or G streptococcal pharyngitis or pharyngitis in which mycoplasmas or chlamydiae have been recovered.

Penicillin prophylaxis (benzathine penicillin G, 1.2 million units IM every 3–4 weeks) is indicated for patients at risk of recurrent rheumatic fever.

Treatment of viral pharyngitis is entirely symptom-based except in infection with influenza virus or HSV. For influenza, the repertoire of therapeutic agents includes the adamantanes amantadine and rimantadine and the neuraminidase inhibitors oseltamivir and zanamivir. Administration of all these agents needs to be started within 36–48 h of symptom onset to reduce illness duration meaningfully. Among these agents, only oseltamivir and zanamivir are active against both influenza A and influenza B and, therefore, can be used when local patterns of infection and antiviral resistance are unknown. Oropharyngeal HSV infection sometimes responds to treatment with antiviral agents such as acyclovir, although these drugs are often reserved for immunosuppressed patients.

Complications

Although rheumatic fever is the best-known complication of acute streptococcal pharyngitis, the risk of its following acute infection remains quite low. Other complications include acute glomerulonephritis and numerous suppurative conditions, such as peritonsillar abscess (*quinsy*), otitis media, mastoiditis, sinusitis, bacteremia, and pneumonia—all of which occur at low rates. Although antibiotic treatment of acute streptococcal pharyngitis can prevent the development of rheumatic fever, there is no evidence that it can prevent acute glomerulonephritis. Some evidence supports antibiotic use to prevent the suppurative complications of streptococcal pharyngitis, particularly peritonsillar abscess, which can also involve oral anaerobes such as *Fusobacterium*. Abscesses usually are accompanied by severe pharyngeal pain, dysphagia, fever, and dehydration; in addition, medial displacement of the tonsil and lateral displacement of the uvula are often evident on examination. Although early use of IV antibiotics (e.g., clindamycin, penicillin G with metronidazole) may obviate the need for surgical drainage in some cases, treatment typically involves needle aspiration or incision and drainage.

ORAL INFECTIONS

Aside from periodontal disease such as gingivitis, infections of the oral cavity most commonly involve HSV or *Candida* species. In addition to causing painful cold sores on the lips, HSV can infect the tongue and buccal mucosa, causing the formation of irritating vesicles. Although topical antiviral agents (e.g., acyclovir and penciclovir) can be used externally for cold sores, oral or IV acyclovir is often needed for primary infections, extensive oral infections, and infections in immunocompromised patients. Oropharyngeal candidiasis (*thrush*) is caused by a variety of *Candida* species, most often *C. albicans*. Thrush occurs predominantly in neonates, immunocompromised patients (especially those with AIDS), and recipients

of prolonged antibiotic or glucocorticoid therapy. In addition to sore throat, patients often report a burning tongue, and physical examination reveals friable white or gray plaques on the gingiva, tongue, and oral mucosa. Treatment that usually consists of an oral antifungal suspension (nystatin or clotrimazole) or oral fluconazole, is frequently successful. In the uncommon cases of fluconazole-refractory thrush that are seen in some patients with AIDS, other therapeutic options include oral formulations of itraconazole, amphotericin B, posaconazole, or voriconazole as well as an IV echinocandin (caspofungin, micafungin, or anidulafungin) or amphotericin B deoxycholate, if needed. In these cases, therapy based on culture and susceptibility test results is ideal.

Vincent's angina, also known as *acute necrotizing ulcerative gingivitis* or *trench mouth*, is a unique and dramatic form of gingivitis characterized by painful, inflamed gingiva with ulcerations of the interdental papillae that bleed easily. Since oral anaerobes are the cause, patients typically have halitosis and frequently present with fever, malaise, and lymphadenopathy. Treatment consists of debridement and oral administration of penicillin plus metronidazole, with clindamycin alone as an alternative.

Ludwig's angina is a rapidly progressive, potentially fulminant form of cellulitis that involves the bilateral sublingual and submandibular spaces and that typically originates from an infected or recently extracted tooth, most commonly the lower second and third molars. Improved dental care has reduced the incidence of this disorder substantially. Infection in these areas leads to dysphagia, odynophagia, and "woody" edema in the sublingual region, forcing the tongue up and back with the potential for airway obstruction. Fever, dysarthria, and drooling also may be noted, and patients may speak in a "hot potato" voice. Intubation or tracheostomy may be necessary to secure the airway, as asphyxiation is the most common cause of death. Patients should be monitored closely and treated promptly with IV antibiotics directed against streptococci and oral anaerobes. Recommended agents include ampicillin/sulbactam and high-dose penicillin plus metronidazole.

Postanginal septicemia (*Lemierre's disease*) is a rare anaerobic oropharyngeal infection caused predominantly by *F. necrophorum*. The illness typically starts as a sore throat (most commonly in adolescents and young adults), which may present as exudative tonsillitis or peritonsillar abscess. Infection of the deep pharyngeal tissue allows organisms to drain into the lateral pharyngeal space, which contains the carotid artery and internal jugular vein. Septic thrombophlebitis of the internal jugular vein can result, with associated pain, dysphagia, and neck swelling and stiffness. Sepsis usually occurs 3–10 days after the onset of sore throat and is often coupled with metastatic infection to the lung and other distant sites. Occasionally, the infection can extend along the carotid sheath and into the posterior mediastinum, resulting in mediastinitis, or it can erode into the carotid artery, with the early sign of repeated small bleeds into the mouth. The mortality rate from these invasive infections can be as high as 50%. Treatment consists of IV antibiotics (penicillin G or clindamycin) and surgical drainage of any purulent collections. The concomitant use of anticoagulants to prevent embolization remains controversial but is often advised, with careful consideration of both the risks and the benefits.

INFECTIONS OF THE LARYNX AND EPIGLOTTIS

LARYNGITIS

Laryngitis is defined as any inflammatory process involving the larynx and can be caused by a variety of infectious and noninfectious processes. The vast majority of laryngitis cases seen in clinical practice in developed countries are acute. Acute laryngitis is a common syndrome caused predominantly by the same viruses responsible for many other URIs. In fact, most cases of acute laryngitis occur in the setting of a viral URI.

Etiology

Nearly all major respiratory viruses have been implicated in acute viral laryngitis, including rhinovirus, influenza virus, parainfluenza virus, adenovirus, coxsackievirus, coronavirus, and RSV. Acute laryngitis can also be associated with acute bacterial respiratory infections such as those caused by group A *Streptococcus* or *C. diphtheriae* (although diphtheria has been virtually eliminated in the United States). Another bacterial pathogen thought to play a role (albeit unclear) in the pathogenesis of acute laryngitis is *M. catarrhalis*, which has been recovered on nasopharyngeal culture in a significant percentage of cases.

Chronic laryngitis of infectious etiology is much less common in developed than in developing countries. Laryngitis due to *Mycobacterium tuberculosis* is often difficult to distinguish from laryngeal cancer, in part because of the frequent absence of signs, symptoms, and radiographic findings typical of pulmonary disease. *Histoplasma* and *Blastomyces* may cause laryngitis, often as a complication of systemic infection. *Candida* species can cause laryngitis as well, often in association with thrush or esophagitis and particularly in immunosuppressed patients. Rare cases of chronic laryngitis are due to *Coccidioides* and *Cryptococcus*.

Clinical manifestations

Laryngitis is characterized by hoarseness and also can be associated with reduced vocal pitch or aphonia. As acute laryngitis is caused predominantly by respiratory viruses, these symptoms usually occur in association with other symptoms and signs of URI, including rhinorrhea, nasal congestion, cough, and sore throat. Direct laryngoscopy often reveals diffuse laryngeal erythema and edema, along with vascular engorgement of the vocal folds. In addition, chronic disease (e.g., tuberculous laryngitis) often includes mucosal nodules and ulcerations visible on laryngoscopy; these lesions sometimes are mistaken for laryngeal cancer.

TREATMENT Laryngitis

Acute laryngitis usually is treated with humidification and voice rest alone. Antibiotics are not recommended except when group A *Streptococcus* is cultured, in which case penicillin is the drug of choice. The choice of therapy for chronic laryngitis depends on the pathogen, whose identification usually requires biopsy with culture. Patients with laryngeal tuberculosis are highly contagious because of the large number of organisms that are easily aerosolized. These patients should be managed in the same way as patients with active pulmonary disease.

CROUP

The term *croup* actually denotes a group of diseases collectively referred to as "croup syndrome," all of which are acute and predominantly viral respiratory illnesses characterized by marked swelling of the subglottic region of the larynx. Croup primarily affects children <6 years old. For a detailed discussion of this entity, the reader should consult a textbook of pediatric medicine.

EPIGLOTTITIS

Acute epiglottitis (supraglottitis) is an acute, rapidly progressive form of cellulitis of the epiglottis and adjacent structures that can result in complete—and potentially fatal—airway obstruction in both children and adults. Before the widespread use of *H. influenzae* type b (Hib) vaccine, this entity was much more common among children, with a peak incidence at ~3.5 years of age. In some countries, mass vaccination against Hib has reduced the annual incidence of acute epiglottitis in children by >90%; in contrast, the annual incidence in adults has changed little since the introduction of Hib vaccine. Because of the danger of airway obstruction, acute epiglottitis constitutes a medical emergency, particularly in children, and prompt diagnosis and airway protection are of the utmost importance.

Etiology

After the introduction of the Hib vaccine in the mid-1980s, disease incidence among children in the United States declined dramatically. Nevertheless, lack of vaccination or vaccine failure has meant that many pediatric cases seen today are still due to Hib. In adults and (more recently) in children, a variety of other bacterial pathogens have been associated with epiglottitis, the most common being group A *Streptococcus*. Other pathogens seen less frequently include *S. pneumoniae*, *Haemophilus parainfluenzae*, and *S. aureus* (including MRSA). Viruses have not been established as causes of acute epiglottitis.

Clinical manifestations and diagnosis

Epiglottitis typically presents more acutely in young children than in adolescents or adults. On presentation, most children have had symptoms for <24 h, including high fever, severe sore throat, tachycardia, systemic toxicity, and (in many cases) drooling while sitting forward. Symptoms and signs of respiratory obstruction may also be present and may progress rapidly. The somewhat milder illness in adolescents and adults often follows 1–2 days of severe sore throat and is commonly accompanied by dyspnea, drooling, and stridor. Physical examination of patients with acute epiglottitis may reveal moderate or severe respiratory distress, with inspiratory stridor and retractions of the chest wall. These findings *diminish* as the disease progresses and the patient tires. Conversely, oropharyngeal examination reveals infection that is much less severe than would be predicted from the symptoms—a finding that should alert the clinician to a cause of symptoms and obstruction that lies beyond the tonsils. The diagnosis often is made on clinical grounds, although direct fiberoptic laryngoscopy is frequently performed in a controlled environment (e.g., an operating room) to visualize and culture the typical edematous "cherry-red" epiglottis and facilitate placement of an endotracheal tube. Direct visualization in an examination room (i.e., with a tongue blade and indirect laryngoscopy) is not recommended because of the risk of immediate laryngospasm and complete airway obstruction. Lateral neck radiographs and laboratory tests can assist in the diagnosis but may delay the critical securing of the airway and cause the patient to be moved or repositioned more than is necessary, thereby increasing the risk of further airway compromise. Neck radiographs typically reveal an enlarged edematous epiglottis (the "thumbprint sign," **Fig. 17-2**), usually with a dilated hypopharynx

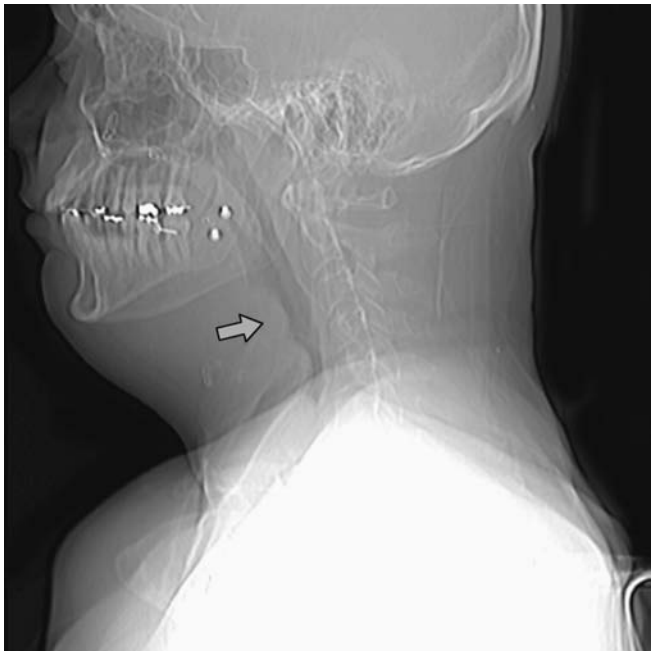


FIGURE 17-2
Acute epiglottitis. In this lateral soft tissue radiograph of the neck, the arrow indicates the enlarged edematous epiglottis (the "thumbprint sign").

and normal subglottic structures. Laboratory tests characteristically document mild to moderate leukocytosis with a predominance of neutrophils. Blood cultures are positive in a significant proportion of cases.

TREATMENT **Epiglottitis**

Security of the airway is always of primary concern in acute epiglottitis, even if the diagnosis is only suspected. Mere observation for signs of impending airway obstruction is not routinely recommended, particularly in children. Many adults have been managed with observation only since the illness is perceived to be milder in this age group, but some data suggest that this approach may be risky and probably should be reserved only for adult patients who have yet to develop dyspnea or stridor. Once the airway has been secured and specimens of blood and epiglottis tissue have been obtained for culture, treatment with IV antibiotics should be given to cover the most likely organisms, particularly *H. influenzae*. Because rates of ampicillin resistance in this organism have risen significantly in recent years, therapy with a β-lactam/β-lactamase inhibitor combination or a second- or third-generation cephalosporin is recommended. Typically, ampicillin/sulbactam, cefuroxime, cefotaxime, or ceftriaxone is given, with clindamycin and TMP-SMX reserved for patients allergic to β-lactams. Antibiotic therapy should be continued for 7–10 days and should be tailored to the organism recovered in culture. If the household contacts of a patient with *H. influenzae* epiglottitis include an unvaccinated child under age 4, all members of the household (including the patient) should receive prophylactic rifampin for 4 days to eradicate carriage of *H. influenzae*.

INFECTIONS OF THE DEEP NECK STRUCTURES

Deep neck infections are usually extensions of infection from other primary sites, most often within the pharynx or oral cavity. Many of these infections are life threatening but are difficult to detect at early stages, when they may be more easily managed. Three of the most clinically relevant spaces in the neck are the submandibular (and sublingual) space, the lateral pharyngeal (or parapharyngeal) space, and the retropharyngeal space. These spaces communicate with one another and with other important structures in the head, neck, and thorax, providing pathogens with easy access to areas that include the mediastinum, carotid sheath, skull base, and meninges. Once infection reaches these sensitive areas, mortality rates can be as high as 20–50%.

Infection of the submandibular and/or sublingual space typically originates from an infected or recently extracted lower tooth. The result is the severe, life-threatening infection referred to as Ludwig's angina (see "Oral Infections," earlier in the chapter). Infection of the lateral pharyngeal (or parapharyngeal) space is most often a complication of common infections of the oral cavity and upper respiratory tract, including tonsillitis, peritonsillar abscess, pharyngitis, mastoiditis, and periodontal infection. This space, situated deep in the lateral wall of the pharynx, contains a number of sensitive structures, including the carotid artery, internal jugular vein, cervical sympathetic chain, and portions of cranial nerves IX through XII; at its distal end, it opens into the posterior mediastinum. Involvement of this space with infection can therefore be rapidly fatal. Examination may reveal some tonsillar displacement, trismus, and neck rigidity, but swelling of the lateral pharyngeal wall can easily be missed. The diagnosis can be confirmed by CT. Treatment consists of airway management, operative drainage of fluid collections, and at least 10 days of IV therapy with an antibiotic active against streptococci and oral anaerobes (e.g., ampicillin/sulbactam). A particularly severe form of this infection involving the components of the carotid sheath (postanginal septicemia, Lemierre's disease) is described above (see "Oral Infections"). Infection of the retropharyngeal space can also be extremely dangerous, as this space runs posterior to the pharynx from the skull base to the superior mediastinum. Infections in this space are more common among children <5 years old because of the presence of several small retropharyngeal lymph nodes that typically atrophy by age 4 years. Infection is usually a consequence of extension from another site of infection, most commonly acute pharyngitis. Other sources include otitis media, tonsillitis, dental infections, Ludwig's angina, and anterior extension of vertebral osteomyelitis. Retropharyngeal space infection also can follow penetrating trauma to the posterior pharynx (e.g., from an endoscopic procedure). Infections are commonly polymicrobial, involving a mixture of aerobes and anaerobes; group A β-hemolytic streptococci and *S. aureus* are the most common pathogens. *M. tuberculosis* was a common cause in the past but now is rarely involved in the United States.

Patients with retropharyngeal abscess typically present with sore throat, fever, dysphagia, and neck pain and are often drooling because of difficulty and pain with swallowing. Examination may reveal tender cervical adenopathy, neck swelling, and diffuse erythema and edema of the posterior pharynx as well as a bulge in the posterior pharyngeal wall that may not be obvious on routine inspection. A soft tissue mass is usually demonstrable by lateral neck radiography or CT. Because of the risk of airway obstruction, treatment begins with securing of the airway, followed by a combination of surgical drainage and IV antibiotic administration. Initial empirical therapy should cover streptococci, oral anaerobes, and *S. aureus*; ampicillin/sulbactam, clindamycin alone, or clindamycin plus ceftriaxone is usually effective. Complications result primarily from extension to other areas (e.g., rupture into the posterior pharynx may lead to aspiration pneumonia and empyema). Extension may also occur to the lateral pharyngeal space and mediastinum, resulting in mediastinitis and pericarditis, or into nearby major blood vessels. All these events are associated with a high mortality rate.

CHAPTER 18

PNEUMONIA

Lionel A. Mandell ■ Richard Wunderink

DEFINITION

Pneumonia is an infection of the pulmonary parenchyma. Despite being the cause of significant morbidity and mortality, pneumonia is often misdiagnosed, mistreated, and underestimated. In the past, pneumonia was typically classified as community-acquired (CAP), hospital-acquired (HAP), or ventilator-associated (VAP). Over the past two decades, however, some persons presenting as outpatients with onset of pneumonia have been found to be infected with the multidrug-resistant (MDR) pathogens previously associated with HAP. Factors responsible for this phenomenon include the development and widespread use of potent oral antibiotics, earlier transfer of patients out of acute-care hospitals to their homes or various lower-acuity facilities, increased use of outpatient IV antibiotic therapy, general aging of the population, and more extensive immunomodulatory therapies. The potential involvement of these MDR pathogens has led to a new category of pneumonia—termed *health care–associated pneumonia* (HCAP)—distinct from CAP. Conditions associated with HCAP and the likely pathogens are listed in Table 18-1.

Although the new classification system has been helpful in designing empirical antibiotic strategies, it is not without disadvantages. Not all MDR pathogens are associated with all risk factors (Table 18-1). Moreover, HCAP is a distillation of multiple risk factors, and each patient must be considered individually. For example, the risk of infection with MDR pathogens for a nursing home resident who has dementia but can independently dress, ambulate, and eat is quite different from the risk for a patient who is in a chronic vegetative state with a tracheostomy and a percutaneous feeding tube in place. In addition, risk factors for MDR infection do not preclude the development of pneumonia caused by the usual CAP pathogens.

This chapter deals with pneumonia in patients who are not considered to be immunocompromised. Pneumonia in severely immunocompromised patients, some

TABLE 18-1

CLINICAL CONDITIONS ASSOCIATED WITH AND LIKELY PATHOGENS IN HEALTH CARE–ASSOCIATED PNEUMONIA

	PATHOGEN			
CONDITION	MRSA	*PSEUDOMONAS AERUGINOSA*	*ACINETOBACTER* SPP.	MDR ENTEROBACTERIACEAE
Hospitalization for ≥48 h	X	X	X	X
Hospitalization for ≥2 days in prior 3 months	X	X	X	X
Nursing home or extended-care-facility residence	X	X	X	X
Antibiotic therapy in preceding 3 months		X		X
Chronic dialysis	X			
Home infusion therapy	X			
Home wound care	X			
Family member with MDR infection	X			X

Abbreviations: MDR, multidrug-resistant; MRSA, methicillin-resistant *Staphylococcus aureus.*

of whom overlap with the groups of patients considered in this chapter, warrants separate discussion (see Chaps. 12, 13, and 93).

PATHOPHYSIOLOGY

Pneumonia results from the proliferation of microbial pathogens at the alveolar level and the host's response to those pathogens. Microorganisms gain access to the lower respiratory tract in several ways. The most common is by aspiration from the oropharynx. Small-volume aspiration occurs frequently during sleep (especially in the elderly) and in patients with decreased levels of consciousness. Many pathogens are inhaled as contaminated droplets. Rarely, pneumonia occurs via hematogenous spread (e.g., from tricuspid endocarditis) or by contiguous extension from an infected pleural or mediastinal space.

Mechanical factors are critically important in host defense. The hairs and turbinates of the nares capture larger inhaled particles before they reach the lower respiratory tract. The branching architecture of the tracheobronchial tree traps particles on the airway lining, where mucociliary clearance and local antibacterial factors either clear or kill the potential pathogen. The gag reflex and the cough mechanism offer critical protection from aspiration. In addition, the normal flora adhering to mucosal cells of the oropharynx, whose components are remarkably constant, prevents pathogenic bacteria from binding and thereby decreases the risk of pneumonia caused by these more virulent bacteria.

When these barriers are overcome or when the microorganisms are small enough to be inhaled to the alveolar level, resident alveolar macrophages are extremely efficient at clearing and killing pathogens. Macrophages are assisted by local proteins (e.g., surfactant proteins A and D) that have intrinsic opsonizing properties or antibacterial or antiviral activity. Once engulfed by the macrophage, the pathogens—even if they are not killed—are eliminated via either the mucociliary elevator or the lymphatics and no longer represent an infectious challenge. Only when the capacity of the alveolar macrophages to ingest or kill the microorganisms is exceeded does clinical pneumonia become manifest. In that situation, the alveolar macrophages initiate the inflammatory response to bolster lower respiratory tract defenses. The host inflammatory response, rather than the proliferation of microorganisms, triggers the clinical syndrome of pneumonia. The release of inflammatory mediators, such as interleukin (IL)-1 and tumor necrosis factor (TNF), results in fever. Chemokines, such as IL-8 and granulocyte colony-stimulating factor, stimulate the release of neutrophils and their attraction to the lung, producing both peripheral leukocytosis and increased purulent secretions. Inflammatory mediators released by macrophages and the newly recruited neutrophils create an alveolar capillary leak equivalent to that seen in the acute respiratory distress syndrome (ARDS), although in pneumonia this leak is localized (at least initially). Even erythrocytes can cross the alveolar-capillary membrane, with consequent hemoptysis. The capillary leak results in a radiographic infiltrate and rales detectable on auscultation, and hypoxemia results from alveolar filling. Moreover, some bacterial pathogens appear to interfere with the hypoxemic vasoconstriction that would normally occur with fluid-filled alveoli, and this interference can result in severe hypoxemia. Increased respiratory drive in the systemic inflammatory response syndrome (SIRS; Chap. 16) leads to respiratory alkalosis. Decreased compliance due to capillary leak, hypoxemia, increased respiratory drive, increased secretions, and occasionally infection-related bronchospasm all lead to dyspnea. If severe enough, the changes in lung mechanics secondary to reductions in lung volume and compliance and the intrapulmonary shunting of blood may cause the patient's death.

PATHOLOGY

Classic pneumonia evolves through a series of pathologic changes. The initial phase is one of *edema*, with the presence of a proteinaceous exudate—and often of bacteria—in the alveoli. This phase is rarely evident in clinical or autopsy specimens because it is so rapidly followed by a *red hepatization* phase. The presence of erythrocytes in the cellular intraalveolar exudate gives this second stage its name, but neutrophil influx is more important from the standpoint of host defense. Bacteria are occasionally seen in pathologic specimens collected during this phase. In the third phase, *gray hepatization*, no new erythrocytes are extravasating, and those already present have been lysed and degraded. The neutrophil is the predominant cell, fibrin deposition is abundant, and bacteria have disappeared. This phase corresponds with successful containment of the infection and improvement in gas exchange. In the final phase, *resolution*, the macrophage reappears as the dominant cell type in the alveolar space, and the debris of neutrophils, bacteria, and fibrin has been cleared, as has the inflammatory response.

This pattern has been described best for lobar pneumococcal pneumonia and may not apply to pneumonias of all etiologies, especially viral or *Pneumocystis* pneumonia. In VAP, respiratory bronchiolitis may precede the development of a radiologically apparent infiltrate. Because of the microaspiration mechanism, a bronchopneumonia pattern is most common in nosocomial pneumonias, whereas a lobar pattern is more common in bacterial CAP. Despite the radiographic appearance, viral and *Pneumocystis* pneumonias represent alveolar rather than interstitial processes.

COMMUNITY-ACQUIRED PNEUMONIA

ETIOLOGY

The extensive list of potential etiologic agents in CAP includes bacteria, fungi, viruses, and protozoa. Newly identified pathogens include hantaviruses, metapneumoviruses, the coronavirus responsible for severe acute respiratory syndrome (SARS), and community-acquired

strains of methicillin-resistant *Staphylococcus aureus* (MRSA). Most cases of CAP, however, are caused by relatively few pathogens **(Table 18-2)**. Although *Streptococcus pneumoniae* is most common, other organisms must also be considered in light of the patient's risk factors and severity of illness. In most cases, it is most useful to think of the potential causes as either "typical" bacterial pathogens or "atypical" organisms. The former category includes *S. pneumoniae*, *Haemophilus influenzae*, and (in selected patients) *S. aureus* and gram-negative bacilli such as *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*. The "atypical" organisms include *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* (in outpatients) and *Legionella* spp. (in inpatients) as well as respiratory viruses such as influenza viruses, adenoviruses, and respiratory syncytial viruses. Data suggest that a virus may be responsible for up to 18% of cases of CAP that require admission to the hospital. The atypical organisms cannot be cultured on standard media, nor can they be seen on Gram's stain. The frequency and importance of atypical pathogens have significant implications for therapy. These organisms are intrinsically resistant to all β-lactam agents and must be treated with a macrolide, a fluoroquinolone, or a tetracycline. In the ~10–15% of CAP cases that are polymicrobial, the etiology often includes a combination of typical and atypical pathogens.

Anaerobes play a significant role only when an episode of aspiration has occurred days to weeks before presentation for pneumonia. The combination of an unprotected airway (e.g., in patients with alcohol or drug overdose or a seizure disorder) and significant gingivitis constitutes the major risk factor. Anaerobic pneumonias are often complicated by abscess formation and significant empyemas or parapneumonic effusions.

S. aureus pneumonia is well known to complicate influenza infection. However, MRSA has been reported as the primary etiologic agent of CAP. While this entity is still relatively uncommon, clinicians must be aware of its potentially serious consequences such as necrotizing pneumonia. Two important developments have led to this problem: the spread of MRSA from the hospital setting to the community and the emergence of genetically distinct strains of MRSA in the community. The former circumstance is more likely to result in HCAP, whereas the novel community-acquired MRSA (CA-MRSA) strains have infected healthy individuals who have had no association with health care.

Unfortunately, despite a careful history and physical examination as well as routine radiographic studies, the causative pathogen in a case of CAP is difficult to predict with any degree of certainty; in more than one-half of cases, a specific etiology is never determined. Nevertheless, epidemiologic and risk factors may suggest the involvement of certain pathogens **(Table 18-3)**.

TABLE 18-2

MICROBIAL CAUSES OF COMMUNITY-ACQUIRED PNEUMONIA, BY SITE OF CARE

	HOSPITALIZED PATIENTS	
OUTPATIENTS	**NON-ICU**	**ICU**
Streptococcus pneumoniae	*S. pneumoniae*	*S. pneumoniae*
Mycoplasma pneumoniae	*M. pneumoniae*	*Staphylococcus aureus*
Haemophilus influenzae	*Chlamydia pneumoniae*	*Legionella* spp.
C. pneumoniae		Gram-negative bacilli
Respiratory viruses[a]	*H. influenzae*	*H. influenzae*
	Legionella spp.	
	Respiratory viruses[a]	

[a]Influenza A and B viruses, adenoviruses, respiratory syncytial viruses, parainfluenza viruses.

Note: Pathogens are listed in descending order of frequency. ICU, intensive care unit.

EPIDEMIOLOGY

In the United States, ~80% of the 4 million CAP cases that occur annually are treated on an outpatient basis, and ~20% are treated in the hospital. CAP results in more than 600,000 hospitalizations, 64 million days of restricted activity, and 45,000 deaths annually. The overall yearly cost associated with CAP is estimated at $9–10 billion. The incidence rates are highest at the extremes of age. The overall annual rate in the United States is 12 cases per 1000 persons, but the figure increases to 12–18 per 1000 among children <4 years of age and to 20 per 1000 among persons >60 years of age.

The risk factors for CAP in general and for pneumococcal pneumonia in particular have implications for treatment regimens. Risk factors for CAP include alcoholism, asthma, immunosuppression, institutionalization, and an age of ≥70 years versus 60–69 years. Risk factors for pneumococcal pneumonia include dementia, seizure disorders, heart failure, cerebrovascular disease, alcoholism, tobacco smoking, chronic obstructive pulmonary disease (COPD), and HIV infection. CA-MRSA pneumonia is more likely in patients with skin colonization or infection with CA-MRSA. Enterobacteriaceae tend to infect patients who have recently been hospitalized and/or received antibiotic therapy or who have comorbidities such as alcoholism, heart failure, or renal failure. *P. aeruginosa* is a particular problem in patients with severe structural lung disease, such as bronchiectasis, cystic fibrosis, or severe COPD. Risk factors for *Legionella* infection include diabetes, hematologic malignancy, cancer, severe renal disease, HIV infection, smoking, male gender, and a recent hotel stay or ship cruise. (Many of these risk factors would now reclassify as HCAP some cases that were previously designated CAP.)

CLINICAL MANIFESTATIONS

CAP can vary from indolent to fulminant in presentation and from mild to fatal in severity. The various signs and symptoms that depend on the progression and severity of the infection include both constitutional findings and manifestations limited to the lung and

TABLE 18-3

EPIDEMIOLOGIC FACTORS SUGGESTING POSSIBLE CAUSES OF COMMUNITY-ACQUIRED PNEUMONIA

FACTOR	POSSIBLE PATHOGEN(S)
Alcoholism	*Streptococcus pneumoniae,* oral anaerobes, *Klebsiella pneumoniae, Acinetobacter* spp., *Mycobacterium tuberculosis*
COPD and/or smoking	*Haemophilus influenzae, Pseudomonas aeruginosa, Legionella* spp., *S. pneumoniae, Moraxella catarrhalis, Chlamydia pneumoniae*
Structural lung disease (e.g., bronchiectasis)	*P. aeruginosa, Burkholderia cepacia, Staphylococcus aureus*
Dementia, stroke, decreased level of consciousness	Oral anaerobes, gram-negative enteric bacteria
Lung abscess	CA-MRSA, oral anaerobes, endemic fungi, *M. tuberculosis*, atypical mycobacteria
Travel to Ohio or St. Lawrence river valleys	*Histoplasma capsulatum*
Travel to southwestern United States	Hantavirus, *Coccidioides* spp.
Travel to Southeast Asia	*Burkholderia pseudomallei,* avian influenza virus
Stay in hotel or on cruise ship in previous 2 weeks	*Legionella* spp.
Local influenza activity	Influenza virus, *S. pneumoniae*, *S. aureus*
Exposure to bats or birds	*H. capsulatum*
Exposure to birds	*Chlamydia psittaci*
Exposure to rabbits	*Francisella tularensis*
Exposure to sheep, goats, parturient cats	*Coxiella burnetii*

Abbreviations: CA-MRSA, community-acquired methicillin-resistant *Staphylococcus aureus;* COPD, chronic obstructive pulmonary disease.

associated structures. In light of the pathobiology of the disease, many of the findings are to be expected.

The patient is frequently febrile with tachycardia or may have a history of chills and/or sweats. Cough may be either nonproductive or productive of mucoid, purulent, or blood-tinged sputum. Depending on severity, the patient may be able to speak in full sentences or may be very short of breath. If the pleura is involved, the patient may experience pleuritic chest pain. Up to 20% of patients may have gastrointestinal symptoms such as nausea, vomiting, and/or diarrhea. Other symptoms may include fatigue, headache, myalgias, and arthralgias.

Findings on physical examination vary with the degree of pulmonary consolidation and the presence or absence of a significant pleural effusion. An increased respiratory rate and use of accessory muscles of respiration are common. Palpation may reveal increased or decreased tactile fremitus, and the percussion note can vary from dull to flat, reflecting underlying consolidated lung and pleural fluid, respectively. Crackles, bronchial breath sounds, and possibly a pleural friction rub may be heard on auscultation. The clinical presentation may not be so obvious in the elderly, who may initially display new-onset or worsening confusion and few other manifestations. Severely ill patients may have septic shock and evidence of organ failure.

DIAGNOSIS

When confronted with possible CAP, the physician must ask two questions: Is this pneumonia, and, if so, what is the likely etiology? The former question is typically answered by clinical and radiographic methods, whereas the latter requires the aid of laboratory techniques.

Clinical diagnosis

The differential diagnosis includes both infectious and noninfectious entities such as acute bronchitis, acute exacerbations of chronic bronchitis, heart failure, pulmonary embolism, and radiation pneumonitis. The importance of a careful history cannot be overemphasized. For example, known cardiac disease may suggest worsening pulmonary edema, while underlying carcinoma may suggest lung injury secondary to irradiation. Epidemiologic clues, such as recent travel to areas with known endemic pathogens (e.g., the U.S. Southwest), may alert the physician to specific possibilities (Table 18-3).

Unfortunately, the sensitivity and specificity of the findings on physical examination are less than ideal, averaging 58% and 67%, respectively. Therefore, chest radiography is often necessary to differentiate CAP from other conditions. Radiographic findings may include risk factors for increased severity (e.g., cavitation or multilobar involvement). Occasionally, radiographic results suggest an etiologic diagnosis. For example, pneumatoceles suggest infection with *S. aureus*, and an upper-lobe cavitating lesion suggests tuberculosis. CT is rarely necessary, but may be of value in a patient with suspected postobstructive pneumonia caused by a tumor or foreign body. For outpatients, the clinical and radiologic assessments are usually all that is done before treatment for CAP is started since most laboratory results are not available soon enough to influence initial management significantly. In certain cases, the availability of rapid point-of-care outpatient diagnostic tests can be very important (e.g., rapid diagnosis of influenza virus infection can prompt specific anti-influenza drug treatment and secondary prevention).

Etiologic diagnosis

The etiology of pneumonia usually cannot be determined solely on the basis of clinical presentation; instead,

the physician must rely upon the laboratory for support. Except for the 2% of CAP patients who are admitted to the intensive care unit (ICU), no data exist to show that treatment directed at a specific pathogen is statistically superior to empirical therapy. The benefit of establishing a microbial etiology can therefore be questioned, particularly in light of the cost of diagnostic testing. However, a number of reasons can be advanced for attempting an etiologic diagnosis. Identification of an unexpected pathogen allows narrowing of the initial empirical regimen that decreases antibiotic selection pressure, lessening the risk of resistance. Pathogens with important public safety implications, such as *Mycobacterium tuberculosis* and influenza virus, may be found in some cases. Finally, without culture and susceptibility data, trends in resistance cannot be followed accurately, and appropriate empirical therapeutic regimens are harder to devise.

Gram's stain and culture of sputum

The main purpose of the sputum Gram's stain is to ensure that a sample is suitable for culture. However, Gram's staining may also identify certain pathogens (e.g., *S. pneumoniae*, *S. aureus*, and gram-negative bacteria) by their characteristic appearance. To be adequate for culture, a sputum sample must have >25 neutrophils and <10 squamous epithelial cells per low-power field. The sensitivity and specificity of the sputum Gram's stain and culture are highly variable. Even in cases of proven bacteremic pneumococcal pneumonia, the yield of positive cultures from sputum samples is ≤50%.

Some patients, particularly elderly individuals, may not be able to produce an appropriate expectorated sputum sample. Others may already have started a course of antibiotics that can interfere with culture results at the time a sample is obtained. Inability to produce sputum can be a consequence of dehydration, and the correction of this condition may result in increased sputum production and a more obvious infiltrate on chest radiography. For patients admitted to the ICU and intubated, a deep-suction aspirate or bronchoalveolar lavage sample (obtained either via bronchoscopy or nonbronchoscopically) has a high yield on culture when sent to the microbiology laboratory as soon as possible. Since the etiologies in severe CAP are somewhat different from those in milder disease (Table 18-2), the greatest benefit of staining and culturing respiratory secretions is to alert the physician of unsuspected and/or resistant pathogens and to permit appropriate modification of therapy. Other stains and cultures (e.g., specific stains for *M. tuberculosis* or fungi) may be useful as well.

Blood cultures

The yield from blood cultures, even when samples are collected before antibiotic therapy, is disappointingly low. Only ~5–14% of cultures of blood from patients hospitalized with CAP are positive, and the most frequently isolated pathogen is *S. pneumoniae*. Since recommended empirical regimens all provide pneumococcal coverage, a blood culture positive for this pathogen has little, if any, effect on clinical outcome. However, susceptibility data may allow narrowing of antibiotic therapy in appropriate cases. Because of the low yield and the lack of significant impact on outcome, blood cultures are no longer considered *de rigueur* for all hospitalized CAP patients. Certain high-risk patients—including those with neutropenia secondary to pneumonia, asplenia, or complement deficiencies; chronic liver disease; or severe CAP—should have blood cultured.

Antigen tests

Two commercially available tests detect pneumococcal and certain *Legionella* antigens in urine. The test for *L. pneumophila* detects only serogroup 1, but this serogroup accounts for most community-acquired cases of Legionnaires' disease. The sensitivity and specificity of the *Legionella* urine antigen test are as high as 90% and 99%, respectively. The pneumococcal urine antigen test is also quite sensitive and specific (80% and >90%, respectively). Although false-positive results can be obtained with samples from pneumococcus-colonized children, the test is generally reliable. Both tests can detect antigen even after the initiation of appropriate antibiotic therapy. Other antigen tests include a rapid test for influenza virus and direct fluorescent antibody tests for influenza virus and respiratory syncytial virus; the latter tests are only poorly sensitive.

Polymerase chain reaction

Polymerase chain reaction (PCR) tests, which amplify a microorganism's DNA or RNA, are available for a number of pathogens, including *L. pneumophila* and mycobacteria. In addition, a multiplex PCR can detect the nucleic acid of *Legionella* spp., *M. pneumoniae*, and *C. pneumoniae*. However, the use of these PCR assays is generally limited to research studies. In patients with pneumococcal pneumonia, an increased bacterial load documented by PCR is associated with an increased risk of septic shock, need for mechanical ventilation, and death. Such a test could conceivably help identify patients suitable for ICU admission.

Serology

A fourfold rise in specific IgM antibody titer between acute- and convalescent-phase serum samples is generally considered diagnostic of infection with the pathogen in question. In the past, serologic tests were used to help identify atypical pathogens as well as selected unusual organisms such as *Coxiella burnetii*. Recently, however, they have fallen out of favor because of the time required to obtain a final result for the convalescent-phase sample.

TREATMENT Community-Acquired Pneumonia

SITE OF CARE The cost of inpatient management exceeds that of outpatient treatment by a factor of 20, and hospitalization accounts for most CAP-related expenditures. Thus the decision to admit a patient with CAP to the hospital has considerable implications.

Certain patients clearly can be managed at home, and others clearly require treatment in the hospital, but the choice is sometimes difficult. Tools that objectively assess the risk of adverse outcomes, including severe illness and death, can minimize unnecessary hospital admissions. There are currently two sets of criteria: the Pneumonia Severity Index (PSI), a prognostic model used to identify patients at low risk of dying; and the CURB-65 criteria, a severity-of-illness score.

To determine the PSI, points are given for 20 variables, including age, coexisting illness, and abnormal physical and laboratory findings. On the basis of the resulting score, patients are assigned to one of five classes with the following mortality rates: class 1, 0.1%; class 2, 0.6%; class 3, 2.8%; class 4, 8.2%; and class 5, 29.2%. Clinical trials demonstrate that routine use of the PSI results in lower admission rates for class 1 and class 2 patients. Patients in classes 4 and 5 should be admitted to the hospital, while those in class 3 should ideally be admitted to an observation unit until a further decision can be made.

The CURB-65 criteria include five variables: confusion (C); urea >7 mmol/L (U); respiratory rate ≥30/min (R); blood pressure, systolic ≤90 mmHg or diastolic ≤60 mmHg (B); and age ≥65 years (65). Patients with a score of 0, among whom the 30-day mortality rate is 1.5%, can be treated outside the hospital. With a score of 2, the 30-day mortality rate is 9.2%, and patients should be admitted to the hospital. Among patients with scores of ≥3, mortality rates are 22% overall; these patients may require admission to an ICU.

It is not clear which assessment tool is superior. The PSI is less practical in a busy emergency room setting because of the need to assess 20 variables. While the CURB-65 criteria are easily remembered, they have not been studied as extensively. Whichever system is used, these objective criteria must always be tempered by careful consideration of factors relevant to individual patients, including the ability to comply reliably with an oral antibiotic regimen and the resources available to the patient outside the hospital. In fact, neither the PSI nor CURB-65 is ideal for determining the need for ICU care. The severity criteria proposed by the Infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATS) in their guidelines for the management of CAP are better suited to this purpose.

ANTIBIOTIC RESISTANCE Antimicrobial resistance is a significant problem that threatens to diminish our therapeutic armamentarium. Misuse of antibiotics results in increased antibiotic selection pressure that can affect resistance locally or even globally by clonal dissemination. For CAP, the main resistance issues currently involve *S. pneumoniae* and CA-MRSA.

S. pneumoniae In general, pneumococcal resistance is acquired (1) by direct DNA incorporation and remodeling resulting from contact with closely related oral commensal bacteria, (2) by the process of natural transformation, or (3) by mutation of certain genes.

The cutoff for penicillin susceptibility in pneumonia has recently been raised from a minimal inhibitory concentration (MIC) of ≤0.6 μg/mL to an MIC of ≤2 μg/mL. Cutoffs for intermediate and resistant pneumococci have been raised to 4 μg/mL (from 0.1–1 μg/mL) and ≥8 μg/mL (from ≥2 μg/mL), respectively. These changes in susceptibility thresholds have resulted in a dramatic decrease in the proportion of pneumococcal isolates considered nonsusceptible. For meningitis, MIC thresholds remain at the former levels. Fortunately, resistance to penicillin appeared to plateau even before the change in MIC thresholds. Pneumococcal resistance to β-lactam drugs is due solely to low-affinity penicillin-binding proteins. Risk factors for penicillin-resistant pneumococcal infection include recent antimicrobial therapy, an age of <2 years or >65 years, attendance at day-care centers, recent hospitalization, and HIV infection.

In contrast to penicillin resistance, resistance to macrolides is increasing through several mechanisms. *Target-site modification* is caused by ribosomal methylation in 23S rRNA encoded by the *ermB* gene, resulting in resistance to macrolides, lincosamides, and streptogramin B–type antibiotics. This MLSb phenotype is associated with high-level resistance, with typical MICs of ≥64 μg/mL. The *efflux mechanism* encoded by the *mef* gene (*M phenotype*) is usually associated with low-level resistance (MICs, 1–32 μg/mL). These two mechanisms account for ~45% and ~65%, respectively, of resistant pneumococcal isolates in the United States. High-level resistance to macrolides is more common in Europe, whereas lower-level resistance seems to predominate in North America. Although clinical failures with macrolides have been reported, many experts think that these drugs still have a role to play in the management of pneumococcal pneumonia in North America.

Pneumococcal resistance to fluoroquinolones (e.g., ciprofloxacin and levofloxacin) has been reported. Changes can occur in one or both target sites (topoisomerases II and IV); changes in these two sites usually result from mutations in the *gyrA* and *parC* genes, respectively. The increasing number of pneumococcal isolates that, although still testing susceptible to fluoroquinolones, already have a mutation in one target site is of concern. Such organisms may be more likely to undergo a second step mutation that will render them fully resistant to fluoroquinolones. In addition, an efflux pump may play a role in pneumococcal resistance to fluoroquinolones.

Isolates resistant to drugs from three or more antimicrobial classes with different mechanisms of action are considered MDR. The propensity for an association of pneumococcal resistance to penicillin with reduced susceptibility to other drugs such as macrolides, tetracyclines, and trimethoprim-sulfamethoxazole, is also of concern. In the United States, 58.9% of penicillin-resistant pneumococcal isolates from blood are also resistant to macrolides.

The most important risk factor for antibiotic-resistant pneumococcal infection is use of a specific antibiotic within the previous 3 months. Therefore, a patient's history of prior antibiotic treatment is a critical factor in avoiding the use of an inappropriate antibiotic.

CA-MRSA CAP due to MRSA may be caused by infection with the classic hospital-acquired strains or with the more recently identified, genotypically and phenotypically distinct community-acquired strains. Most infections with the former strains have been acquired either directly or indirectly by contact with the health care environment and would now be classified as HCAP. In some hospitals, CA-MRSA strains are displacing the classic hospital-acquired strains—a trend suggesting that the newer strains may be more robust.

Methicillin resistance in *S. aureus* is determined by the *mecA* gene, which encodes for resistance to all β-lactam drugs. At least five *staphylococcal chromosomal cassette mec* (*SCCmec*) types have been described. The typical hospital-acquired strain usually has type II or III, whereas CA-MRSA has a type IV SCC*mec* element. CA-MRSA isolates tend to be less resistant than the older hospital-acquired strains and are often susceptible to trimethoprim-sulfamethoxazole, clindamycin, and tetracycline in addition to vancomycin and linezolid. However, CA-MRSA strains may also carry genes for superantigens, such as enterotoxins B and C and Panton-Valentine leukocidin, a membrane-tropic toxin that can create cytolytic pores in polymorphonuclear neutrophils, monocytes, and macrophages.

Gram-Negative Bacilli A detailed discussion of resistance among gram-negative bacilli is beyond the scope of this chapter (see Chap. 54). Fluoroquinolone resistance among isolates of *Escherichia coli* from the community appears to be increasing. *Enterobacter* spp. are typically resistant to cephalosporins; the drugs of choice for use against these bacteria are usually fluoroquinolones or carbapenems. Similarly, when infections due to bacteria producing extended-spectrum β-lactamases are documented or suspected, a fluoroquinolone or a carbapenem should be used; these MDR strains are more likely to be involved in HCAP.

INITIAL ANTIBIOTIC MANAGEMENT Since the physician rarely knows the etiology of CAP at the outset of treatment, initial therapy is usually empirical and is designed to cover the most likely pathogens (Table 18-4). In all cases, antibiotic treatment should be initiated as expeditiously as possible. The CAP treatment guidelines in the United States (summarized in Table 18-4) represent joint statements from the IDSA and the ATS; the Canadian guidelines come from the Canadian Infectious Disease Society and the Canadian Thoracic Society. In these guidelines, coverage is always provided for the pneumococcus and the atypical pathogens. In contrast, guidelines from some European countries do not always include atypical coverage based on local epidemiologic data. The U.S.–Canadian approach is supported by retrospective data from several studies of administrative databases including thousands of patients. Atypical pathogen coverage provided by the addition of a macrolide to a cephalosporin or by the use of a fluoroquinolone alone has been consistently associated with a significant reduction in mortality rates compared with those for β-lactam coverage alone.

TABLE 18-4

EMPIRICAL ANTIBIOTIC TREATMENT OF COMMUNITY-ACQUIRED PNEUMONIA

Outpatients
Previously healthy and no antibiotics in past 3 months • A macrolide [clarithromycin (500 mg PO bid) or azithromycin (500 mg PO once, then 250 mg qd)] ***or*** • Doxycycline (100 mg PO bid)
Comorbidities or antibiotics in past 3 months: select an alternative from a different class • A respiratory fluoroquinolone [moxifloxacin (400 mg PO qd), gemifloxacin (320 mg PO qd), levofloxacin (750 mg PO qd)] ***or*** • A β-lactam [preferred: high-dose amoxicillin (1 g tid) or amoxicillin/clavulanate (2 g bid); alternatives: ceftriaxone (1–2 g IV qd), cefpodoxime (200 mg PO bid), cefuroxime (500 mg PO bid)] ***plus*** a macrolide[a]
In regions with a high rate of "high-level" pneumococcal macrolide resistance,[b] consider alternatives listed above for patients with comorbidities.
Inpatients, Non-ICU
• A respiratory fluoroquinolone [moxifloxacin (400 mg PO or IV qd), gemifloxacin (320 mg PO qd), levofloxacin (750 mg PO or IV qd)] • A β-lactam[c] [cefotaxime (1–2 g IV q8h), ceftriaxone (1–2 g IV qd), ampicillin (1–2 g IV q4–6h), ertapenem (1 g IV qd in selected patients)] ***plus*** a macrolide[d] [oral clarithromycin or azithromycin (as listed above for previously healthy patients) or IV azithromycin (1 g once, then 500 mg qd)]
Inpatients, ICU
• A β-lactam[e] [cefotaxime (1–2 g IV q8h), ceftriaxone (2 g IV qd), ampicillin-sulbactam (2 g IV q8h)] ***plus*** • Azithromycin or a fluoroquinolone (as listed above for inpatients, non-ICU)
Special Concerns
If *Pseudomonas* is a consideration • An antipneumococcal, antipseudomonal β-lactam [piperacillin/tazobactam (4.5 g IV q6h), cefepime (1–2 g IV q12h), imipenem (500 mg IV q6h), meropenem (1 g IV q8h)] ***plus*** either ciprofloxacin (400 mg IV q12h) or levofloxacin (750 mg IV qd) • The above β-lactams ***plus*** an aminoglycoside [amikacin (15 mg/kg qd) or tobramycin (1.7 mg/kg qd) and azithromycin] • The above β-lactams[f] ***plus*** an aminoglycoside ***plus*** an antipneumococcal fluoroquinolone
If CA-MRSA is a consideration • Add linezolid (600 mg IV q12h) or vancomycin (1 g IV q12h).

[a]Doxycycline (100 mg PO bid) is an alternative to the macrolide.
[b]MICs of >16 μg/mL in 25% of isolates.
[c]A respiratory fluoroquinolone should be used for penicillin-allergic patients.
[d]Doxycycline (100 mg IV q12h) is an alternative to the macrolide.
[e]For penicillin-allergic patients, use a respiratory fluoroquinolone and aztreonam (2 g IV q8h).
[f]For penicillin-allergic patients, substitute aztreonam.
Abbreviations: CA-MRSA, community-acquired methicillin-resistant *Staphylococcus aureus;* ICU, intensive care unit.

Therapy with a macrolide or a fluoroquinolone within the previous 3 months is associated with an increased likelihood of infection with a resistant strain of *S. pneumoniae*. For this reason, a fluoroquinolone-based regimen should be used for patients recently given a macrolide, and vice versa (Table 18-4).

Once the etiologic agent(s) and susceptibilities are known, therapy may be altered to target the specific pathogen(s). However, this decision is not always straightforward. If blood cultures yield *S. pneumoniae* sensitive to penicillin after 2 days of treatment with a macrolide plus a β-lactam or with a fluoroquinolone alone, should therapy be switched to penicillin alone? The concern here is that a β-lactam alone would not be effective in the potential 15% of cases with atypical co-infection. No standard approach exists. In all cases, the individual patient and the various risk factors must be considered.

Management of bacteremic pneumococcal pneumonia is also controversial. Data from nonrandomized studies suggest that combination therapy (especially with a macrolide and a β-lactam) is associated with a lower mortality rate than monotherapy, particularly in severely ill patients. The exact reason is unknown, but possible explanations include an additive or synergistic antibacterial effect, antimicrobial tolerance, atypical co-infection, or the immunomodulatory effects of the macrolides.

For patients with CAP who are admitted to the ICU, the risk of infection with *P. aeruginosa* or CA-MRSA is increased, and coverage should be considered when a patient has risk factors or a Gram's stain suggestive of these pathogens (Table 18-4). If CA-MRSA infection is suspected, either linezolid or vancomycin should be added to the initial empirical regimen. There is concern about vancomycin's loss of potency against MRSA; in addition, vancomycin does not reach significant concentrations in epithelial lining fluid, whereas concentrations of linezolid at this site exceed the MIC for MRSA during the entire dosing interval.

Although hospitalized patients have traditionally received initial therapy by the IV route, some drugs—particularly the fluoroquinolones—are very well absorbed and can be given orally from the outset to select patients. For patients initially treated IV, a switch to oral treatment is appropriate as long as the patient can ingest and absorb the drugs, is hemodynamically stable, and is showing clinical improvement.

The duration of treatment for CAP has generated considerable interest. Patients were previously treated for 10–14 days, but studies with fluoroquinolones and telithromycin suggest that a 5-day course is sufficient for otherwise uncomplicated CAP. Even a single dose of ceftriaxone has been associated with a significant cure rate. A longer course is required for patients with bacteremia, metastatic infection, or infection with a virulent pathogen such as *P. aeruginosa* or CA-MRSA.

GENERAL CONSIDERATIONS In addition to appropriate antimicrobial therapy, certain general considerations apply in dealing with CAP, HCAP, or HAP/VAP. Adequate hydration, oxygen therapy for hypoxemia, and assisted ventilation when necessary are critical to the success of therapy. Patients with severe CAP who remain hypotensive despite fluid resuscitation may have adrenal insufficiency and may respond to glucocorticoid treatment. Immunomodulatory therapy in the form of drotrecogin alfa (activated) should be considered for CAP patients with persistent septic shock and APACHE II scores of ≥25, particularly if the infection is caused by *S. pneumoniae*. The value of other forms of adjunctive therapy, including glucocorticoids, statins, and angiotensin-converting enzyme inhibitors, remains unproven in the management of CAP.

Failure to Improve Patients who are slow to respond to therapy should be reevaluated at about day 3 (sooner if their condition is worsening rather than simply not improving), and a number of possible scenarios should be considered. A number of noninfectious conditions can mimic pneumonia, including pulmonary edema, pulmonary embolism, lung carcinoma, radiation and hypersensitivity pneumonitis, and connective tissue disease involving the lungs. If the patient has CAP and treatment is aimed at the correct pathogen, the lack of response may be explained in a number of ways. The pathogen may be resistant to the drug selected, or a sequestered focus (e.g., a lung abscess or empyema) may be blocking access of the antibiotic(s) to the pathogen. The patient may be getting either the wrong drug or the correct drug at the wrong dose or frequency of administration. It is also possible that CAP is the correct diagnosis but that an unsuspected pathogen (e.g., CA-MRSA, *M. tuberculosis*, or a fungus) is the cause. Nosocomial superinfections—both pulmonary and extrapulmonary—are possible explanations for failure to improve or worsening. In all cases of delayed response or deteriorating condition, the patient must be carefully reassessed and appropriate studies initiated. These studies may include such diverse procedures as CT and bronchoscopy.

Complications As in other severe infections, common complications of severe CAP include respiratory failure, shock and multiorgan failure, coagulopathy, and exacerbation of comorbid illnesses. Three particularly noteworthy conditions are metastatic infection, lung abscess, and complicated pleural effusion. Metastatic infection (e.g., brain abscess or endocarditis), although unusual, deserves immediate attention by the physician, with a detailed workup and proper treatment. Lung abscess may occur in association with aspiration or with infection caused by a single CAP pathogen such as CA-MRSA, *P. aeruginosa*, or (rarely) *S. pneumoniae*. Aspiration pneumonia is typically a mixed polymicrobial infection involving both aerobes and anaerobes. In either scenario, drainage should be established, and antibiotics that cover the known or suspected pathogens should be administered. A significant pleural effusion should be tapped for both diagnostic and therapeutic purposes. If the fluid has a pH of <7, a glucose level of <2.2 mmol/L, and a lactate dehydrogenase concentration of >1000 U/L or if bacteria are seen or

cultured, then the fluid should be drained; a chest tube is usually required.

Follow-Up Fever and leukocytosis usually resolve within 2–4 days in otherwise healthy patients with CAP, but physical findings may persist longer. Chest radiographic abnormalities are slowest to resolve and may require 4–12 weeks to clear, with the speed of clearance depending on the patient's age and underlying lung disease. Patients may be discharged from the hospital once their clinical conditions are stable, with no active medical problems requiring hospital care. The site of residence after discharge (nursing home, home with family, home alone) is an important consideration, particularly for elderly patients. For a patient whose condition is improving and who (if hospitalized) has been discharged, a follow-up radiograph can be done ~4–6 weeks later. If relapse or recurrence is documented, particularly in the same lung segment, the possibility of an underlying neoplasm must be considered.

PROGNOSIS

The prognosis of CAP depends on the patient's age, comorbidities, and site of treatment (inpatient or outpatient). Young patients without comorbidity do well and usually recover fully after ~2 weeks. Older patients and those with comorbid conditions can take several weeks longer to recover fully. The overall mortality rate for the outpatient group is <1%. For patients requiring hospitalization, the overall mortality rate is estimated at 10%, with ~50% of deaths directly attributable to pneumonia.

PREVENTION

The main preventive measure is vaccination. The recommendations of the Advisory Committee on Immunization Practices should be followed for influenza and pneumococcal vaccines. In the event of an influenza outbreak, unprotected patients at risk from complications should be vaccinated immediately and given chemoprophylaxis with either oseltamivir or zanamivir for 2 weeks—i.e., until vaccine-induced antibody levels are sufficiently high. Because of an increased risk of pneumococcal infection, even among patients without obstructive lung disease, smokers should be strongly encouraged to stop smoking.

An available 7-valent pneumococcal conjugate vaccine produces T cell–dependent antigens that result in long-term immunologic memory. Administration of this vaccine to children has led to an overall decrease in the prevalence of antimicrobial-resistant pneumococci and in the incidence of invasive pneumococcal disease among both children and adults. However, vaccination can be followed by the replacement of vaccine serotypes with nonvaccine serotypes (e.g., 19A and 35B).

HEALTH CARE–ASSOCIATED PNEUMONIA

HCAP represents a transition between classic CAP and typical HAP. The definition of HCAP is still in some degree of flux because of a lack of large-scale studies. Several of the studies that are available have been limited to patients with culture-positive pneumonia. In these studies, the incidence of MDR pathogens in HCAP was as high as or higher than in HAP/VAP. MRSA in particular was more common in HCAP than in traditional HAP/VAP. Conversely, prospective studies in nontertiary-care centers have found a low incidence of MDR pathogens in HCAP.

The patients at greatest risk for HCAP are not well defined. Patients from nursing homes are not always at elevated risk for infection with MDR pathogens. Careful evaluation of nursing home residents with pneumonia suggests that their risk of MDR infection is low if they have not recently received antibiotics and are independent in most activities of daily living. Conversely, nursing home patients are at increased risk of infection with influenza virus and other atypical pneumonia pathogens. Undue concern about MDR pathogens occasionally results in a failure to cover atypical pathogens in treating nursing home patients. In addition, patients receiving home infusion therapy or undergoing chronic dialysis are probably at particular risk for MRSA pneumonia but may not be at greater risk for infection with *Pseudomonas* or *Acinetobacter* than are other patients who develop CAP.

In general, the management of HCAP due to MDR pathogens is similar to that of MDR HAP/VAP. This topic will therefore be covered in subsequent sections on HAP and VAP. The prognosis of HCAP is intermediate between that of CAP and VAP and is closer to that of HAP.

VENTILATOR-ASSOCIATED PNEUMONIA

Most research on VAP has focused on illness in the hospital setting. However, the information and principles based on this research can be applied to non-ICU HAP and HCAP as well. The greatest difference between VAP and HCAP/HAP is the return to dependence on expectorated sputum for a microbiologic diagnosis of VAP (as for that of CAP), which is further complicated by frequent colonization by pathogens in patients with HAP or HCAP.

Etiology

Potential etiologic agents of VAP include both MDR and non-MDR bacterial pathogens **(Table 18-5)**. The non-MDR group is nearly identical to the pathogens found in severe CAP (Table 18-2); it is not surprising that such pathogens predominate if VAP develops in the first 5–7 days of the hospital stay. However, if patients have other risk factors for HCAP, MDR pathogens are a consideration, even early in the hospital course. The relative frequency of individual MDR

TABLE 18-5

MICROBIOLOGIC CAUSES OF VENTILATOR-ASSOCIATED PNEUMONIA

NON-MDR PATHOGENS	MDR PATHOGENS
Streptococcus pneumoniae	*Pseudomonas aeruginosa*
Other *Streptococcus* spp.	MSSA
Haemophilus influenzae	*Acinetobacter* spp.
MRSA	Antibiotic-resistant Enterobacteriaceae
Antibiotic-sensitive Enterobacteriaceae	*Enterobacter* spp.
Escherichia coli	ESBL-positive strains
Klebsiella pneumoniae	*Klebsiella* spp.
Proteus spp.	*Legionella pneumophila*
Enterobacter spp.	*Burkholderia cepacia*
Serratia marcescens	*Aspergillus* spp.

Abbreviations: ESBL, extended-spectrum β-lactamase; MDR, multidrug-resistant; MRSA, methicillin-resistant *Staphylococcus aureus;* MSSA, methicillin-sensitive *S. aureus.*

pathogens can vary significantly from hospital to hospital and even between different critical care units within the same institution. Most hospitals have problems with *P. aeruginosa* and MRSA, but other MDR pathogens are often institution-specific. Less commonly, fungal and viral pathogens cause VAP, usually affecting severely immunocompromised patients. Rarely, community-associated viruses cause mini-epidemics, usually when introduced by ill health care workers.

Epidemiology

Pneumonia is a common complication among patients requiring mechanical ventilation. Prevalence estimates vary between 6 and 52 cases per 100 patients, depending on the population studied. On any given day in the ICU, an average of 10% of patients will have pneumonia—VAP in the overwhelming majority of cases. The frequency of diagnosis is not static but changes with the duration of mechanical ventilation, with the highest hazard ratio in the first 5 days and a plateau in additional cases (1% per day) after ~2 weeks. However, the cumulative rate among patients who remain ventilated for as long as 30 days is as high as 70%. These rates often do not reflect the recurrence of VAP in the same patient. Once a ventilated patient is transferred to a chronic-care facility or to home, the incidence of pneumonia drops significantly, especially in the absence of other risk factors for pneumonia. However, in chronic ventilator units, purulent tracheobronchitis becomes a significant issue, often interfering with efforts to wean patients off mechanical ventilation.

Three factors are critical in the pathogenesis of VAP: colonization of the oropharynx with pathogenic microorganisms, aspiration of these organisms from the oropharynx into the lower respiratory tract, and compromise of the normal host defense mechanisms. Most risk factors and their corresponding prevention strategies pertain to one of these three factors **(Table 18-6)**.

TABLE 18-6

PATHOGENIC MECHANISMS AND CORRESPONDING PREVENTION STRATEGIES FOR VENTILATOR-ASSOCIATED PNEUMONIA

PATHOGENIC MECHANISM	PREVENTION STRATEGY
Oropharyngeal colonization with pathogenic bacteria	
Elimination of normal flora	Avoidance of prolonged antibiotic courses
Large-volume oropharyngeal aspiration around time of intubation	Short course of prophylactic antibiotics for comatose patients[a]
Gastroesophageal reflux	Postpyloric enteral feeding[b]; avoidance of high gastric residuals, prokinetic agents
Bacterial overgrowth of stomach	Prophylactic agents that raise gastric pH[b]; selective decontamination of digestive tract with nonabsorbable antibiotics[b]
Cross-infection from other colonized patients	Hand washing, especially with alcohol-based hand rub; intensive infection control education[a]; isolation; proper cleaning of reusable equipment
Large-volume aspiration	Endotracheal intubation; avoidance of sedation; decompression of small-bowel obstruction
Microaspiration around endotracheal tube	
Endotracheal intubation	Noninvasive ventilation[a]
Prolonged duration of ventilation	Daily awakening from sedation,[a] weaning protocols[a]
Abnormal swallowing function	Early percutaneous tracheostomy[a]
Secretions pooled above endotracheal tube	Head of bed elevated[a]; continuous aspiration of subglottic secretions with specialized endotracheal tube[a]; avoidance of reintubation; minimization of sedation and patient transport
Altered lower respiratory host defenses	Tight glycemic control[b]; lowering of hemoglobin transfusion threshold; specialized enteral feeding formula

[a]Strategies demonstrated to be effective in at least one randomized controlled trial.
[b]Strategies with negative randomized trials or conflicting results.

The most obvious risk factor is the endotracheal tube, which bypasses the normal mechanical factors preventing aspiration. While the presence of an endotracheal tube may prevent large-volume aspiration, microaspiration is

actually exacerbated by secretions pooling above the cuff. The endotracheal tube and the concomitant need for suctioning can damage the tracheal mucosa, thereby facilitating tracheal colonization. In addition, pathogenic bacteria can form a glycocalyx biofilm on the tube's surface that protects them from both antibiotics and host defenses. The bacteria can also be dislodged during suctioning and can reinoculate the trachea, or tiny fragments of glycocalyx can embolize to distal airways, carrying bacteria with them.

In a high percentage of critically ill patients, the normal oropharyngeal flora is replaced by pathogenic microorganisms. The most important risk factors are antibiotic selection pressure, cross-infection from other infected/colonized patients or contaminated equipment, and malnutrition. Of these factors, antibiotic exposure poses the greatest risk by far. Pathogens such as *P. aeruginosa* almost never cause infection in patients without prior exposure to antibiotics. The recent emphasis on hand hygiene has lowered the cross-infection rate.

How the lower respiratory tract defenses become overwhelmed remains poorly understood. Almost all intubated patients experience microaspiration and are at least transiently colonized with pathogenic bacteria. However, only around one-third of colonized patients develop VAP. Colony counts increase to high levels, sometimes days before the development of clinical pneumonia; these increases suggest that the final step in VAP development, independent of aspiration and oropharyngeal colonization, is the overwhelming of host defenses. Severely ill patients with sepsis and trauma appear to enter a state of immunoparalysis several days after admission to the ICU—a time that corresponds to the greatest risk of developing VAP. The mechanism of this immunosuppression is not clear, although several factors have been suggested. Hyperglycemia affects neutrophil function, and trials suggest that keeping the blood sugar close to normal with exogenous insulin may have beneficial effects, including a decreased risk of infection. More frequent transfusions also adversely affect the immune response.

Clinical manifestations

The clinical manifestations are generally the same in VAP as in all other forms of pneumonia: fever, leukocytosis, increase in respiratory secretions, and pulmonary consolidation on physical examination, along with a new or changing radiographic infiltrate. The frequency of abnormal chest radiographs before the onset of pneumonia in intubated patients and the limitations of portable radiographic technique make interpretation of radiographs more difficult than in patients who are not intubated. Other clinical features may include tachypnea, tachycardia, worsening oxygenation, and increased minute ventilation.

Diagnosis

No single set of criteria is reliably diagnostic of pneumonia in a ventilated patient. The inability to identify such patients compromises efforts to prevent and treat VAP and even calls into question estimates of the impact of VAP on mortality rates.

Application of clinical criteria consistently results in overdiagnosis of VAP, largely because of three common findings in at-risk patients: (1) tracheal colonization with pathogenic bacteria in patients with endotracheal tubes, (2) multiple alternative causes of radiographic infiltrates in mechanically ventilated patients, and (3) the high frequency of other sources of fever in critically ill patients. The differential diagnosis of VAP includes a number of entities such as atypical pulmonary edema, pulmonary contusion, alveolar hemorrhage, hypersensitivity pneumonitis, ARDS, and pulmonary embolism. Clinical findings in ventilated patients with fever and/or leukocytosis may have alternative causes, including antibiotic-associated diarrhea, sinusitis, urinary tract infection, pancreatitis, and drug fever. Conditions mimicking pneumonia are often documented in patients in whom VAP has been ruled out by accurate diagnostic techniques. Most of these alternative diagnoses do not require antibiotic treatment; require antibiotics different from those used to treat VAP; or require some additional intervention, such as surgical drainage or catheter removal, for optimal management.

This diagnostic dilemma has led to debate and controversy. The major question is whether a quantitative-culture approach as a means of eliminating false-positive clinical diagnoses is superior to the clinical approach enhanced by principles learned from quantitative-culture studies. The most recent IDSA/ATS guidelines for HCAP suggest that either approach is clinically valid.

Quantitative-culture approach

The essence of the quantitative-culture approach is to discriminate between colonization and true infection by determining the bacterial burden. The more distal in the respiratory tree the diagnostic sampling, the more specific the results and therefore the lower the threshold of growth necessary to diagnose pneumonia and exclude colonization. For example, a quantitative endotracheal aspirate yields proximate samples, and the diagnostic threshold is 10^6 cfu/mL. The protected specimen brush method, in contrast, obtains distal samples and has a threshold of 10^3 cfu/mL. Conversely, sensitivity declines as more distal secretions are obtained, especially when they are collected blindly (i.e., by a technique other than bronchoscopy). Additional tests that may increase the diagnostic yield include Gram's stain, differential cell counts, staining for intracellular organisms, and detection of local protein levels elevated in response to infection.

Several studies have compared patient cohorts managed by the various quantitative-culture methods. While these studies documented issues of relative sensitivity and specificity, outcomes were not significantly different for the various groups of patients. The IDSA/ATS guidelines suggest that all these methods are appropriate and that the choice depends on availability and local expertise.

The Achilles heel of the quantitative approach is the effect of antibiotic therapy. With sensitive microorganisms, a single antibiotic dose can reduce colony counts below the diagnostic threshold. Recent changes in antibiotic therapy are the most significant. After 3 days, the operating characteristics of the tests are almost the same

as if no antibiotic therapy has been given. Conversely, colony counts above the diagnostic threshold during antibiotic therapy suggest that the current antibiotics are ineffective. Even the normal host response may be sufficient to reduce quantitative-culture counts below the diagnostic threshold if sampling is delayed. In short, expertise in quantitative-culture techniques is critical, with a specimen obtained as soon as pneumonia is suspected and before antibiotic therapy is initiated or changed.

In a study comparing the quantitative with the clinical approach, use of bronchoscopic quantitative cultures resulted in significantly less antibiotic use at 14 days after study entry and lower rates of mortality and severity-adjusted mortality at 28 days. In addition, more alternative sites of infection were found in patients randomized to the quantitative-culture strategy. A critical aspect of this study was that antibiotic treatment was initiated only in patients whose gram-stained respiratory sample was positive or who displayed signs of hemodynamic instability. Fewer than one-half as many patients were treated for pneumonia in the bronchoscopy group, and only one-third as many microorganisms were cultured. Other studies that did not demonstrate a similar beneficial impact of quantitative culture on outcomes did not tightly link antibiotic treatment to the results of quantitative culture and other tests.

Clinical approach

The lack of specificity of a clinical diagnosis of VAP has led to efforts to improve the diagnostic criteria. The Clinical Pulmonary Infection Score (CPIS) was developed by weighting of the various clinical criteria usually used for the diagnosis of VAP **(Table 18-7)**. Use of the CPIS allows the selection of low-risk patients who may need only short-course antibiotic therapy or no treatment at all. Moreover, studies have demonstrated that the absence of bacteria in gram-stained endotracheal aspirates makes pneumonia an unlikely cause of fever or pulmonary infiltrates. These findings, coupled with a heightened awareness of the alternative diagnoses possible in patients with suspected VAP, can prevent inappropriate treatment for this disease. Furthermore, data show that the absence of an MDR pathogen in tracheal aspirate cultures eliminates the need for MDR coverage when empirical antibiotic therapy is narrowed. Since the most likely explanations for the mortality benefit of bronchoscopic quantitative cultures are decreased antibiotic selection pressure (which reduces the risk of subsequent infection with MDR pathogens) and identification of alternative sources of infection, a clinical diagnostic approach that incorporates such principles may result in similar outcomes.

TABLE 18-7

CLINICAL PULMONARY INFECTION SCORE (CPIS)

CRITERION	SCORE
Fever (°C)	
≥38.5 but ≤38.9	1
>39 or <36	2
Leukocytosis	
<4000 or >11,000/μL	1
Bands >50%	1 (additional)
Oxygenation (mmHg)	
Pa_{O_2}/FI_{O_2} <250 and no ARDS	2
Chest radiograph	
Localized infiltrate	2
Patchy or diffuse infiltrate	1
Progression of infiltrate (no ARDS or CHF)	2
Tracheal aspirate	
Moderate or heavy growth	1
Same morphology on Gram's stain	1 (additional)
Maximal score[a]	12

[a]At the time of the original diagnosis, the progression of the infiltrate is not known and tracheal aspirate culture results are often unavailable; thus, the maximal score is initially 8–10.
Abbreviations: ARDS, acute respiratory distress syndrome; CHF, congestive heart failure.

ANTIBIOTIC RESISTANCE If it were not for the risk of infection with MDR pathogens (Table 18-1), VAP could be treated with the same antibiotics used for severe CAP. However, antibiotic selection pressure leads to the frequent involvement of MDR pathogens by selecting either for drug-resistant isolates of common pathogens (MRSA and extended-spectrum β-lactamase–positive Enterobacteriaceae) or for intrinsically resistant pathogens (*P. aeruginosa* and *Acinetobacter* spp.). Frequent use of β-lactam drugs, especially cephalosporins, appears to be the major risk factor for infection with MRSA and extended spectrum β-lactamase–positive strains.

P. aeruginosa has demonstrated the ability to develop resistance to all routinely used antibiotics. Unfortunately, even if initially sensitive, *P. aeruginosa* isolates have also shown a propensity to develop resistance during treatment. Either derepression of resistance genes or selection of resistant clones within the large bacterial inoculum associated with most pneumonias may be the cause. *Acinetobacter* spp., *Stenotrophomonas maltophilia*, and *Burkholderia cepacia* are intrinsically resistant to many of the empirical antibiotic regimens employed (see below). VAP caused by these pathogens emerges during treatment of other infections, and resistance is always evident at initial diagnosis.

EMPIRICAL THERAPY Recommended options for empirical therapy are listed in Table 18-8. Treatment

TREATMENT Ventilator-Associated Pneumonia

Many studies have demonstrated higher mortality rates with inappropriate than with appropriate empirical antibiotic therapy. The key to appropriate antibiotic management of VAP is an appreciation of the patterns of resistance of the most likely pathogens in any given patient.

TABLE 18-8

EMPIRICAL ANTIBIOTIC TREATMENT OF HEALTH CARE–ASSOCIATED PNEUMONIA

Patients without Risk Factors for MDR Pathogens
Ceftriaxone (2 g IV q24h) ***or***
Moxifloxacin (400 mg IV q24h), ciprofloxacin (400 mg IV q8h), or levofloxacin (750 mg IV q24h) ***or***
Ampicillin/sulbactam (3 g IV q6h) ***or***
Ertapenem (1 g IV q24h)
Patients with Risk Factors for MDR Pathogens
1. A β-lactam: Ceftazidime (2 g IV q8h) or cefepime (2 g IV q8–12h) ***or*** Piperacillin/tazobactam (4.5 g IV q6h), imipenem (500 mg IV q6h or 1 g IV q8h), or meropenem (1 g IV q8h) ***plus***
2. A second agent active against gram-negative bacterial pathogens: Gentamicin or tobramycin (7 mg/kg IV q24h) or amikacin (20 mg/kg IV q24h) ***or*** Ciprofloxacin (400 mg IV q8h) or levofloxacin (750 mg IV q24h) ***plus***
3. An agent active against gram-positive bacterial pathogens: Linezolid (600 mg IV q12h) *or* Vancomycin (15 mg/kg, up to 1 g IV, q12h)

Abbreviation: MDR, multidrug-resistant.

should be started once diagnostic specimens have been obtained. The major factor in the selection of agents is the presence of risk factors for MDR pathogens. Choices among the various options listed depend on local patterns of resistance and the patient's prior antibiotic exposure.

The majority of patients *without* risk factors for MDR infection can be treated with a single agent. The major difference from CAP is the markedly lower incidence of atypical pathogens in VAP; the exception is *Legionella*, which can be a nosocomial pathogen, especially with breakdowns in the treatment of potable water in the hospital.

The standard recommendation for patients *with* risk factors for MDR infection is for three antibiotics: two directed at *P. aeruginosa* and one at MRSA. The choice of a β-lactam agent provides the greatest variability in coverage, yet the use of the broadest-spectrum agent—a carbapenem, even in an antibiotic combination—still represents inappropriate initial therapy in 10–15% of cases.

SPECIFIC TREATMENT Once an etiologic diagnosis is made, broad-spectrum empirical therapy can be modified to address the known pathogen specifically. For patients with MDR risk factors, antibiotic regimens can be reduced to a single agent in more than one-half of cases and to a two-drug combination in more than one-quarter of cases. Only a minority of cases require a complete course with three drugs. A negative tracheal-aspirate culture or growth below the threshold for quantitative cultures, especially if the sample was obtained before any antibiotic change, strongly suggests that antibiotics should be discontinued. Identification of other confirmed or suspected sites of infection may require ongoing antibiotic therapy, but the spectrum of pathogens (and the corresponding antibiotic choices) may be different from those for VAP. If the CPIS decreases over the first 3 days, antibiotics should be stopped after 8 days. An 8-day course of therapy is just as effective as a 2-week course and is associated with less frequent emergence of antibiotic-resistant strains.

The major controversy regarding specific therapy for VAP concerns the need for ongoing combination treatment of *Pseudomonas* infection. No randomized controlled trials have demonstrated a benefit of combination therapy with a β-lactam and an aminoglycoside, nor have subgroup analyses in other trials found a survival benefit with such a regimen. The unacceptably high rates of clinical failure and death for VAP caused by *P. aeruginosa* despite combination therapy (see "Failure to Improve," later) indicate that better regimens are needed—including, perhaps, aerosolized antibiotics.

VAP caused by MRSA is associated with a 40% clinical failure rate when treated with standard-dose vancomycin. One proposed solution is the use of high-dose individualized treatment, although the risk of renal toxicity increases with this strategy. In addition, the MIC of vancomycin has been increasing, and a high percentage of clinical failures occur when the MIC is in the upper range of sensitivity (i.e., 1.5–2 μg/mL). Linezolid appears to be more efficacious than the standard dose of vancomycin and may be the preferred agent in patients with renal insufficiency and in those infected with high-MIC isolates of MRSA.

FAILURE TO IMPROVE Treatment failure is not uncommon in VAP, especially in that caused by MDR pathogens. In addition to the 40% failure rate for MRSA infection treated with vancomycin, VAP due to *Pseudomonas* has a 50% failure rate, no matter what the regimen. The causes of clinical failure vary with the pathogen(s) and the antibiotic(s). Inappropriate therapy can usually be minimized by use of the recommended triple-drug regimen (Table 18-8). However, the emergence of β-lactam resistance during therapy is an important problem, especially in infection with *Pseudomonas* and *Enterobacter* spp. Recurrent VAP caused by the same pathogen is possible because the biofilm on endotracheal tubes allows reintroduction of the microorganism. However, studies of VAP caused by *Pseudomonas* show that approximately one-half of recurrent cases are caused by a new strain. Inadequate local levels of vancomycin are the likely cause of treatment failure in VAP due to MRSA.

Treatment failure is very difficult to diagnose. Pneumonia due to a new superinfection, the presence of extrapulmonary infection, and drug toxicity must be considered in the differential diagnosis of treatment failure.

Serial CPIS appears to track the clinical response accurately, while repeat quantitative cultures may clarify the microbiologic response. A persistently elevated or rising CPIS value by day 3 of therapy is likely to indicate failure. The most sensitive component of the CPIS is improvement in oxygenation.

COMPLICATIONS Apart from death, the major complication of VAP is prolongation of mechanical ventilation, with corresponding increases in length of stay in the ICU and in the hospital. In most studies, an additional week of mechanical ventilation because of VAP is common. The additional expense of this complication often warrants costly and aggressive efforts at prevention.

In rare cases, some types of necrotizing pneumonia (e.g., that due to *P. aeruginosa*) result in significant pulmonary hemorrhage. More commonly, necrotizing infections result in the long-term complications of bronchiectasis and parenchymal scarring leading to recurrent pneumonias. The long-term complications of pneumonia are underappreciated. Pneumonia results in a catabolic state in a patient already nutritionally at risk. The muscle loss and general debilitation from an episode of VAP often require prolonged rehabilitation and, in the elderly, commonly result in an inability to return to independent function and the need for nursing home placement.

FOLLOW-UP Clinical improvement, if it occurs, is usually evident within 48–72 h of the initiation of antimicrobial treatment. Because findings on chest radiography often worsen initially during treatment, they are less helpful than clinical criteria as an indicator of clinical response in severe pneumonia. Seriously ill patients with pneumonia often undergo follow-up chest radiography daily, at least until they are being weaned off mechanical ventilation. Once a patient has been extubated and is in stable condition, follow-up radiographs may not be necessary for a few weeks.

Prognosis

VAP is associated with significant mortality. Crude mortality rates of 50–70% have been reported, but the real issue is attributable mortality. Many patients with VAP have underlying diseases that would result in death even if VAP did not occur. Attributable mortality exceeded 25% in one matched cohort study. Patients who develop VAP are at least twice as likely to die as those who do not. Some of the variability in VAP mortality rates is clearly related to the type of patient and ICU studied. VAP in trauma patients is not associated with attributable mortality, possibly because many of the patients were otherwise healthy before being injured. However, the causative pathogen also plays a major role. Generally, MDR pathogens are associated with significantly greater attributable mortality than non-MDR pathogens. Pneumonia caused by some pathogens (e.g., *S. maltophilia*) is simply a marker for a patient whose immune system is so compromised that death is almost inevitable.

Prevention

(Table 18-6) Because of the significance of the endotracheal tube as a risk factor for VAP, the most important preventive intervention is to avoid endotracheal intubation or at least to minimize its duration. Successful use of noninvasive ventilation via a nasal or full-face mask avoids many of the problems associated with endotracheal tubes. Strategies that minimize the duration of ventilation through daily holding of sedation and formal weaning protocols have also been highly effective in preventing VAP.

Unfortunately, a tradeoff in risks is sometimes required. Aggressive attempts to extubate early may result in reintubation(s) and increase aspiration, posing a risk of VAP. Heavy continuous sedation increases the risk, but self-extubation because of too little sedation is also a risk. The tradeoffs also apply to antibiotic therapy. Short-course antibiotic prophylaxis can decrease the risk of VAP in comatose patients requiring intubation, and data suggest that antibiotics decrease VAP rates in general. However, the major benefit appears to be a decrease in the incidence of early-onset VAP, which is usually caused by the less pathogenic non-MDR microorganisms. Conversely, prolonged courses of antibiotics consistently increase the risk of VAP caused by the more lethal MDR pathogens. Despite its virulence and associated mortality, VAP caused by *Pseudomonas* is rare among patients who have not recently received antibiotics.

Minimizing the amount of microaspiration around the endotracheal tube cuff is also a strategy for avoidance of VAP. Simply elevating the head of the bed (at least 30° above horizontal but preferably 45°) decreases VAP rates. Specially modified endotracheal tubes that allow removal of the secretions pooled above the cuff may also prevent VAP. The risk-to-benefit ratio of transporting the patient outside the ICU for diagnostic tests or procedures should be carefully considered, since VAP rates are increased among transported patients.

Emphasis on the avoidance of agents that raise gastric pH and on oropharyngeal decontamination has been diminished by the equivocal and conflicting results of more recent clinical trials. The role in the pathogenesis of VAP that is played by the overgrowth of bacterial components of the bowel flora in the stomach has also been downplayed. MRSA and the nonfermenters *P. aeruginosa* and *Acinetobacter* spp. are not normally part of the bowel flora but reside primarily in the nose and on the skin, respectively. Therefore, an emphasis on controlling overgrowth of the bowel flora may be relevant only in certain populations, such as liver transplant recipients and patients who have undergone other major intraabdominal procedures or who have bowel obstruction.

In outbreaks of VAP due to specific pathogens, the possibility of a breakdown in infection control measures (particularly contamination of reusable equipment) should be investigated. Even high rates of pathogens that are already common in a particular ICU may be a result of cross-infection. Education and reminders of the need for consistent hand washing and other infection control practices can minimize this risk.

HOSPITAL-ACQUIRED PNEUMONIA

While significantly less well studied than VAP, HAP in nonintubated patients—both inside and outside the ICU—is similar to VAP. The main differences are in the higher frequency of non-MDR pathogens and the better underlying host immunity in nonintubated patients. The lower frequency of MDR pathogens allows monotherapy in a larger proportion of cases of HAP than of VAP.

The only pathogens that may be more common in the non-VAP population are anaerobes. The greater risk of macroaspiration by nonintubated patients and the lower oxygen tensions in the lower respiratory tract of these patients increase the likelihood of a role for anaerobes. While more common in patients with HAP, anaerobes are usually only contributors to polymicrobial pneumonias except in patients with large-volume aspiration or in the setting of bowel obstruction/ileus. As in the management of CAP, specific therapy targeting anaerobes probably is not indicated (unless gross aspiration is a concern) since many of the recommended antibiotics are active against anaerobes.

Diagnosis is even more difficult for HAP in the nonintubated patient than for VAP. Lower respiratory tract samples appropriate for culture are considerably more difficult to obtain from nonintubated patients. Many of the underlying diseases that predispose a patient to HAP are also associated with an inability to cough adequately. Since blood cultures are infrequently positive (<15% of cases), the majority of patients with HAP do not have culture data on which antibiotic modifications can be based. Therefore, de-escalation of therapy is less likely in patients with risk factors for MDR pathogens. Despite these difficulties, the better host defenses in non-ICU patients result in lower mortality rates than are documented for VAP. In addition, the risk of antibiotic failure is lower in HAP.

CHAPTER 19

BRONCHIECTASIS AND LUNG ABSCESS

Rebecca M. Baron ■ John G. Bartlett

BRONCHIECTASIS

Bronchiectasis refers to an irreversible airway dilation that involves the lung in either a focal or a diffuse manner and that classically has been categorized as cylindrical or tubular (the most common form), varicose, or cystic.

ETIOLOGY

Bronchiectasis can arise from infectious or noninfectious causes **(Table 19-1)**. Clues to the underlying etiology are often provided by the pattern of lung involvement. *Focal bronchiectasis* refers to bronchiectatic changes in a localized area of the lung and can be a consequence of obstruction of the airway—either extrinsic (e.g., due to compression by adjacent lymphadenopathy or parenchymal tumor mass) or intrinsic (e.g., due to an airway tumor or aspirated foreign body, a scarred/stenotic airway, or bronchial atresia from congenital underdevelopment of the airway). *Diffuse bronchiectasis* is characterized by widespread bronchiectatic changes throughout the lung and often arises from an underlying systemic or infectious disease process.

More pronounced involvement of the upper lung fields is most common in cystic fibrosis (CF) and is also observed in postradiation fibrosis, corresponding to the lung region encompassed by the radiation port. Bronchiectasis with predominant involvement of the lower lung fields usually has its source in chronic recurrent aspiration (e.g., due to esophageal motility disorders like those in scleroderma), end-stage fibrotic lung disease (e.g., traction bronchiectasis from idiopathic pulmonary fibrosis), or recurrent immunodeficiency-associated infections (e.g., hypogammaglobulinemia). Bronchiectasis resulting from infection by nontuberculous mycobacteria [NTM; most commonly the *Mycobacterium avium-intracellulare* complex (MAC)] often preferentially affects the midlung fields. Congenital causes of bronchiectasis with predominant midlung field involvement include the dyskinetic/immotile cilia syndrome. Finally, predominant involvement of the central airways is reported in association with allergic

TABLE 19-1

MAJOR ETIOLOGIES OF BRONCHIECTASIS AND PROPOSED WORKUP

PATTERN OF LUNG INVOLVEMENT BY BRONCHIECTASIS	ETIOLOGY BY CATEGORIES (WITH SPECIFIC EXAMPLES)	WORKUP
Focal	Obstruction (e.g., aspirated foreign body, tumor mass)	Chest imaging (chest x-ray and/or chest CT); bronchoscopy
Diffuse	Infection (e.g., bacterial, nontuberculous mycobacterial)	Gram's stain/culture; stains/cultures for acid-fast bacilli and fungi. If no pathogen is identified, consider bronchoscopy with bronchoalveolar lavage (BAL).
	Immunodeficiency (e.g., hypogammaglobulinemia, HIV infection, bronchiolitis obliterans after lung transplantation)	Complete blood count with differential; immunoglobulin measurement; HIV testing
	Genetic causes (e.g., cystic fibrosis, Kartagener's syndrome, α_1 antitrypsin deficiency)	Measurement of chloride levels in sweat (for cystic fibrosis), α_1 antitrypsin levels; nasal or respiratory tract brush/biopsy (for dyskinetic/immotile cilia syndrome); genetic testing
	Autoimmune or rheumatologic causes (e.g., rheumatoid arthritis, Sjögren's syndrome, inflammatory bowel disease); immune-mediated disease (e.g., allergic bronchopulmonary aspergillosis)	Clinical examination with careful joint exam, serologic testing (e.g., for rheumatoid factor). Consider workup for allergic bronchopulmonary aspergillosis, especially in patients with refractory asthma.[a]
	Recurrent aspiration	Test of swallowing function and general neuromuscular strength
	Miscellaneous (e.g., yellow nail syndrome; traction bronchiectasis from postradiation fibrosis or idiopathic pulmonary fibrosis)	Guided by clinical condition
	Idiopathic	Exclusion of other causes

[a]Skin testing for *Aspergillus* reactivity; measurement of serum precipitins for *Aspergillus*, serum IgE levels, serum eosinophils, etc.

bronchopulmonary aspergillosis (ABPA), in which an immune-mediated reaction to *Aspergillus* damages the bronchial wall. Congenital causes of central airway–predominant bronchiectasis resulting from cartilage deficiency include tracheobronchomegaly (Mounier-Kuhn syndrome) and Williams-Campbell syndrome.

In many cases, the etiology of bronchiectasis is not determined. In case series, as many as 25–50% of patients referred for bronchiectasis have idiopathic disease.

EPIDEMIOLOGY

The epidemiology of bronchiectasis varies greatly with the underlying etiology. For example, patients born with CF often develop significant clinical bronchiectasis in late adolescence or early adulthood, although atypical presentations of CF in adults in their thirties and forties are also possible. In contrast, bronchiectasis resulting from MAC infection classically affects nonsmoking women older than age 50 years. In general, the incidence of bronchiectasis increases with age. Bronchiectasis is more common among women than among men.

In areas where tuberculosis is prevalent, bronchiectasis more frequently occurs as a sequela of granulomatous infection. Focal bronchiectasis can arise from extrinsic compression of the airway by enlarged granulomatous lymph nodes and/or from development of intrinsic obstruction as a result of erosion of a calcified lymph node through the airway wall (e.g., broncholithiasis). Especially in reactivated tuberculosis, parenchymal destruction from infection can result in areas of more diffuse bronchiectasis. Apart from cases associated with tuberculosis, an increased incidence of non-CF bronchiectasis with an unclear underlying mechanism has been reported as a significant problem in developing nations. It has been suggested that the high incidence of malnutrition in certain areas may predispose to immune dysfunction and development of bronchiectasis.

PATHOGENESIS AND PATHOLOGY

The most widely cited mechanism of infectious bronchiectasis is the "vicious cycle hypothesis," in which susceptibility to infection and poor mucociliary clearance result in microbial colonization of the bronchial tree. Some organisms, such as *Pseudomonas aeruginosa*, exhibit a particular propensity for colonizing damaged airways and evading host defense mechanisms. Impaired mucociliary clearance can result from inherited conditions such as CF or dyskinetic cilia syndrome,

and it has been proposed that a single severe infection (e.g., pneumonia caused by *Bordetella pertussis* or *Mycoplasma pneumoniae*) can result in significant airway damage and poor secretion clearance. The presence of the microbes incites continued chronic inflammation, with consequent damage to the airway wall, continued impairment of secretion and microbial clearance, and ongoing propagation of the infectious/inflammatory cycle. Moreover, it has been proposed that mediators released directly from bacteria can interfere with mucociliary clearance.

Classic studies of the pathology of bronchiectasis from the 1950s demonstrated significant small-airway wall inflammation and larger-airway wall destruction as well as dilation, with loss of elastin, smooth muscle, and cartilage. It has been proposed that inflammatory cells in the small airways release proteases and other mediators, such as reactive oxygen species and proinflammatory cytokines, that damage the larger-airway walls. Furthermore, the ongoing inflammatory process in the smaller airways results in airflow obstruction. It is believed that antiproteases, such as α_1 antitrypsin, play an important role in neutralizing the damaging effects of neutrophil elastase and in enhancing bacterial killing. In addition to emphysema, bronchiectasis has been observed in patients with α_1 antitrypsin deficiency.

Proposed mechanisms for noninfectious bronchiectasis include immune-mediated reactions that damage the bronchial wall (e.g., those associated with systemic autoimmune conditions such as Sjögren's syndrome and rheumatoid arthritis). *Traction bronchiectasis* refers to dilated airways arising from parenchymal distortion as a result of lung fibrosis (e.g., postradiation fibrosis or idiopathic pulmonary fibrosis).

CLINICAL MANIFESTATIONS

The most common clinical presentation is a persistent productive cough with ongoing production of thick, tenacious sputum. Physical findings often include crackles and wheezing on lung auscultation, and some patients with bronchiectasis exhibit clubbing of the digits. Mild to moderate airflow obstruction is often detected on pulmonary function tests, overlapping with that seen at presentation with other conditions, such as chronic obstructive pulmonary disease (COPD). Acute exacerbations of bronchiectasis are usually characterized by changes in the nature of sputum production, with increased volume and purulence. However, typical signs and symptoms of lung infection, such as fever and new infiltrates, may not be present.

DIAGNOSIS

The diagnosis is usually based on presentation with a persistent chronic cough and sputum production accompanied by consistent radiographic features. While chest radiographs lack sensitivity, the presence of "tram tracks" indicating dilated airways is consistent with bronchiectasis. Chest CT is more specific for bronchiectasis and is the imaging modality of choice for confirming the diagnosis. CT findings include airway dilation (detected as parallel "tram tracks" or as the "signet-ring sign"—a cross-sectional area of the airway with a diameter at least 1.5 times that of the adjacent vessel), lack of bronchial tapering (including the presence of tubular structures within 1 cm from the pleural surface), bronchial wall thickening in dilated airways, inspissated secretions (e.g., the "tree-in-bud" pattern), or cysts emanating from the bronchial wall (especially pronounced in cystic bronchiectasis; **Fig. 19-1**).

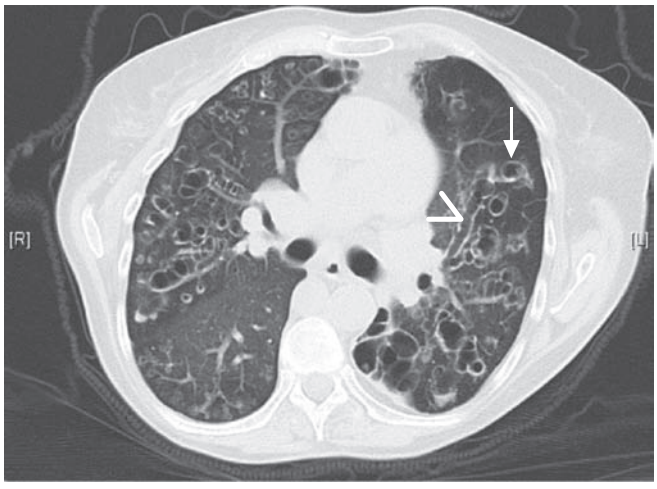


FIGURE 19-1
Representative chest CT image of severe bronchiectasis. This patient's CT demonstrates many severely dilated airways, seen both longitudinally (arrowhead) and in cross-section (arrow).

APPROACH TO THE PATIENT **Bronchiectasis**

The evaluation of a patient with bronchiectasis entails elicitation of a clinical history, chest imaging, and a workup to determine the underlying etiology. Evaluation of focal bronchiectasis almost always requires bronchoscopy to exclude airway obstruction by an underlying mass or foreign body. A workup for diffuse bronchiectasis includes analysis for the major etiologies (Table 19-1). Pulmonary function testing is an important component of a functional assessment of the patient.

TREATMENT **Bronchiectasis**

Treatment of infectious bronchiectasis is directed at the control of active infection and improvements in secretion clearance and bronchial hygiene so as to decrease the microbial load within the airways and minimize the risk of repeated infections.

ANTIBIOTIC TREATMENT Antibiotics targeting the causative or presumptive pathogen (with *Haemophilus influenzae* and *P. aeruginosa* isolated commonly) should be administered in acute exacerbations, usually for a minimum of 7–10 days. Decisions about treatment of NTM infection can be difficult, given that these organisms can be colonizers as well as pathogens and the prolonged treatment course often is not well tolerated. Consensus guidelines have advised that diagnostic criteria for true clinical infection with NTM should be considered in patients with symptoms and radiographic findings of lung disease who have at least two sputum samples positive on culture; at least one bronchoalveolar lavage (BAL) fluid sample positive on culture; a biopsy sample displaying histopathologic features of NTM infection (e.g., granuloma or a positive stain for acid-fast bacilli) along with one positive sputum culture; or a pleural fluid sample (or a sample from another sterile extrapulmonary site) positive on culture. MAC strains are the most common NTM pathogens, and the recommended regimen for HIV-negative patients includes a macrolide combined with rifampin and ethambutol. Consensus guidelines also recommend macrolide susceptibility testing for clinically significant MAC isolates.

BRONCHIAL HYGIENE The numerous approaches employed to enhance secretion clearance in bronchiectasis include hydration and mucolytic administration, aerosolization of bronchodilators and hyperosmolar agents (e.g., hypertonic saline), and chest physiotherapy (e.g., postural drainage, traditional mechanical chest percussion via hand clapping to the chest, or use of devices such as an oscillatory positive expiratory pressure flutter valve or a high-frequency chest wall oscillation vest). The mucolytic dornase (DNase) is recommended routinely in CF-related bronchiectasis but not in non-CF bronchiectasis, given concerns about lack of efficacy and potential harm in the non-CF population.

ANTI-INFLAMMATORY THERAPY It has been proposed that control of the inflammatory response may be of benefit in bronchiectasis, and relatively small-scale trials have yielded evidence of alleviated dyspnea, decreased need for inhaled β-agonists, and reduced sputum production with inhaled glucocorticoids. However, no significant differences in lung function or bronchiectasis exacerbation rates have been observed. Risks of immunosuppression and adrenal suppression must be carefully considered with use of anti-inflammatory therapy in infectious bronchiectasis. Nevertheless, administration of oral/systemic glucocorticoids may be important in treating bronchiectasis due to certain etiologies, such as ABPA, or noninfectious bronchiectasis due to underlying conditions, especially that in which an autoimmune condition is believed to be active (e.g., rheumatoid arthritis or Sjögren's syndrome). Patients with ABPA may also benefit from a prolonged course of treatment with the oral antifungal agent itraconazole.

REFRACTORY CASES In select cases, surgery can be considered, with resection of a focal area of suppuration. In advanced cases, lung transplantation can be considered.

COMPLICATIONS

In more severe cases of infectious bronchiectasis, recurrent infections and repeated courses of antibiotics can lead to microbial resistance to antibiotics. In certain cases, combinations of antibiotics that have their own independent toxicity profiles may be necessary to treat resistant organisms.

Recurrent infections can result in injury to superficial mucosal vessels, with bleeding and, in severe cases, life-threatening hemoptysis. Management of massive hemoptysis usually requires intubation to stabilize the patient, identifying the source of bleeding, and protecting the nonbleeding lung. Control of bleeding often necessitates bronchial artery embolization and, in severe cases, surgery.

PROGNOSIS

Outcomes of bronchiectasis vary widely with the underlying etiology and may also be influenced by the frequency of exacerbations and (in infectious cases) the specific pathogens involved. In one study, the decline of lung function in patients with non-CF bronchiectasis was similar to that in patients with COPD, with the forced expiratory volume in 1 s (FEV_1) declining by 50–55 mL per year as opposed to 20–30 mL per year for healthy controls.

PREVENTION

Reversal of an underlying immunodeficient state (e.g., by administration of gamma globulin for immunoglobulin-deficient patients) and vaccination of patients with chronic respiratory conditions (e.g., influenza and pneumococcal vaccines) can decrease the risk of recurrent infections. Patients who smoke should be counseled about smoking cessation.

After resolution of an acute infection in patients with recurrences (e.g., ≥3 episodes per year), the use of suppressive antibiotics to minimize the microbial load and reduce the frequency of exacerbations has been proposed, although there is less consensus with regard to this approach in non-CF-associated bronchiectasis than there is in patients with CF-related bronchiectasis. Possible suppressive treatments include (1) administration of an oral antibiotic (e.g., ciprofloxacin) daily for 1–2 weeks per month; (2) use of a rotating schedule of oral antibiotics (to minimize the risk of development of drug resistance); (3) administration of a macrolide antibiotic daily or three times per week (with mechanisms of possible benefit related to non-antimicrobial properties, such as anti-inflammatory effects and reduction of gram-negative bacillary biofilms); (4) inhalation of aerosolized antibiotics

[e.g., tobramycin inhalation solution (TOBI)] by select patients on a rotating schedule (e.g., 30 days on, 30 days off) with the goal of decreasing the microbial load without encountering the side effects of systemic drug administration; and (5) intermittent administration of IV antibiotics (e.g., "clean-outs") for patients with more severe bronchiectasis and/or resistant pathogens.

In addition, ongoing, consistent attention to bronchial hygiene can promote secretion clearance and decrease the microbial load in the airways.

LUNG ABSCESS

The term *lung abscess* refers to a microbial infection of the lung that results in necrosis of the pulmonary parenchyma. *Necrotizing pneumonia* or *lung gangrene* refers to multiple small pulmonary abscesses in contiguous areas of the lung, usually resulting from a more virulent infection.

CLASSIFICATION

Lung abscesses are classified by clinical and pathologic features including the tempo of progression, the presence or absence of an associated underlying lesion, and the microbial pathogen responsible. Duration defines the infection as *acute* versus *chronic*, with the dividing line usually at 4–6 weeks. Abscesses occurring in the presence of underlying pulmonary lesions, including tumors or systemic conditions (e.g., HIV infection), are referred to as *secondary*; those that occur in the absence of underlying pulmonary lesions are considered *primary*. The term *nonspecific lung abscess* refers to cases in which no likely pathogen is recovered from expectorated sputum; most such cases are presumed to be due to anaerobic bacteria. *Putrid lung abscess* is a term applied to anaerobic bacterial lung abscesses, which are characterized by distinctive foul-smelling breath, sputum, or empyema fluid.

ETIOLOGY

The likely etiologic agent, appropriate diagnostic testing, and appropriate treatment are frequently indicated by the characteristics of the host and the disease process. A variety of microbial pathogens cause lung abscess **(Table 19-2)**. Most nonspecific lung abscesses are presumed to be due to anaerobic bacteria. Mycobacteria, especially *M. tuberculosis*, are a very important cause of pulmonary infections and abscess formation. Fungi and some parasites also cause lung abscess. An acute lung abscess developing in a young, previously healthy patient, especially in conjunction with influenza, is likely to involve *Staphylococcus aureus*; this pathogen generally is seen easily on sputum Gram's stain and culture, and presumptive treatment for methicillin-resistant *S. aureus* is urgent. In an immunocompromised host, suspected pathogens include enteric gram-negative bacilli—especially *Klebsiella pneumoniae*—but also agents that are found almost exclusively in patients with defective cell-mediated immunity, such as *Nocardia asteroides* and *Rhodococcus equi*. Lung abscess acquired in other countries may involve *Burkholderia pseudomallei* or *Paragonimus westermani*.

TABLE 19-2

MICROBIAL PATHOGENS CAUSING CAVITARY LUNG INFECTION

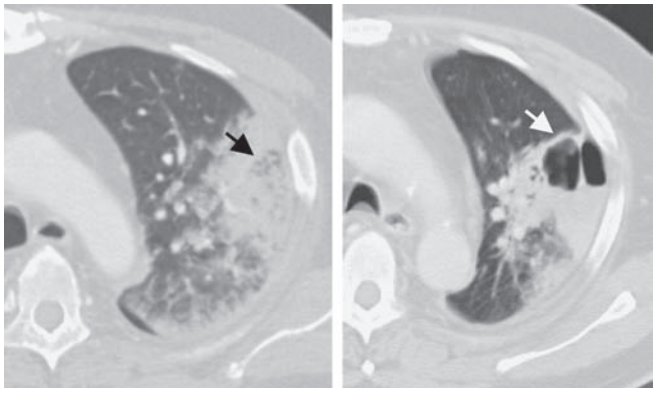
Aspiration-Prone Host
Anaerobic bacteria plus microaerophilic and/or anaerobic streptococci, *Gemella* spp.
Embolic (endovascular) lesions: usually *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Fusobacterium necrophorum*[a]
Endemic fungi: *Histoplasma*, *Blastomyces*, *Coccidioides* spp.
Mycobacteria: *M. tuberculosis*, *M. kansasii*, *M. avium*
Immunocompromised Host
M. tuberculosis, *Nocardia asteroides*, *Rhodococcus equi*, *Legionella* spp., *P. aeruginosa*, Enterobacteriaceae (especially *Klebsiella pneumoniae*), *Aspergillus* spp., *Cryptococcus* spp.
Previously Healthy Host
Bacteria: *S. aureus*,[b] *S. milleri*, *K. pneumoniae*, group A *Streptococcus*; *Gemella*, *Legionella*, and *Actinomyces* spp.
Parasites: *Entamoeba histolytica*, *Paragonimus westermani*, *Strongyloides stercoralis*

[a]Lemierre's disease.
[b]Often in a young patient with influenza.

Multiple pulmonary lesions that are not caused by microbes may resemble lung abscess. These include the lesions of pulmonary infarction, bronchiectasis, necrotizing carcinoma, pulmonary sequestration, vasculitides (e.g., periarteritis nodosa, granulomatosis with polyangiitis, Goodpasture syndrome), and cysts or bullae with fluid collections. In some cases, multiple lung abscesses result from septic emboli, most commonly in association with tricuspid valve endocarditis.

CLINICAL FEATURES

The classic presentation of nonspecific lung abscess is an indolent infection that evolves over several days or weeks, usually in a host who has a predisposition to aspiration. A common feature is periodontal infection with pyorrhea or gingivitis. Anaerobes and aerobic or microaerophilic streptococci that colonize the upper airways are implicated in these lesions. The usual symptoms are fatigue, cough, sputum production, and fever. Chills are uncommon. Many patients have evidence of chronic disease, such as weight loss and anemia. Some patients have putrid-smelling sputum indicative of the presence of anaerobes; the foul odor is presumably due to the organisms' production of short-chain fatty acids, such as butyric or succinic acid. Some patients have



A B

FIGURE 19-2

Representative chest CT demonstrating development of lung abscesses. This patient was immunocompromised due to underlying lymphoma and developed severe *Pseudomonas aeruginosa* pneumonia, as represented by a left lung infiltrate, with concern for central regions of necrosis (**A**, black arrow). Two weeks later, areas of cavitation with air fluid levels were visible in this region and were consistent with the development of lung abscesses (**B**, white arrow). (*Images provided by Dr. Ritu Gill, Division of Chest Radiology, Brigham and Women's Hospital, Boston.*)

pleurisy due to pleural involvement by contiguous spread or by a bronchopleural fistula. The pleurisy may be severe and may be the symptom that prompts medical evaluation. Sequential x-rays or CT scans show the evolution of this lesion from pneumonitis to cavitation, a process that generally requires 7–14 days in experimental animals **(Fig. 19-2)**.

DIAGNOSIS

Lung abscess can usually be detected with standard imaging, including chest x-ray and CT (Fig. 19-2). The latter is clearly preferred for precise definition of the lesion and its location and possibly for detection of underlying lesions. Lymphadenopathy is not associated with bacterial lung abscess; thus this finding suggests an alternative diagnosis.

Microbiologic studies include stains and cultures of expectorated sputum to detect aerobic bacterial pathogens. However, clinical correlations are very important because sputum cultures (especially those that do not satisfy standard cytologic criteria) are unreliable. In appropriate settings, it is important to consider cultures for fungi and mycobacteria. Anaerobic bacteria, the most common causes of primary lung abscess, are not detected in expectorated sputum cultures, and in any case the specimen is subject to anaerobic contamination as it traverses the upper airways. Alternative specimens that may be useful include pleural fluid obtained by thoracentesis in patients who have empyema and quantitative bronchoalveolar lavage (BAL) specimens if they are processed promptly and appropriately for anaerobic bacteria. Many reports describe the use of transtracheal aspiration to bypass the upper airways and obtain a specimen for meaningful anaerobic culture. This procedure, which was used extensively in the 1970s, has largely been abandoned out of concern about adverse consequences and because of a general decline in the pursuit of an etiologic agent in pulmonary infections. Another invasive method for bypassing contamination by the flora of the upper airways is transthoracic needle aspiration under CT guidance; the popularity of this procedure has increased in recent years. In most cases, the etiology of anaerobic lung abscess is clear: the host is prone to aspiration and has an abscess in a dependent pulmonary segment, with no other likely cause. As stated earlier, putrid breath, sputum, or empyema fluid indicates anaerobic infection.

TREATMENT Lung Abscess

ANTIBIOTIC SELECTION Treatment depends on the presumed or established etiology. Infections caused by anaerobic bacteria should usually be treated with clindamycin; the initial IV dosage of 600 mg four times daily can be changed to an oral dosage of 300 mg four times daily once the patient becomes afebrile and improves clinically. The duration of therapy is arbitrary, but many experts recommend continuation of oral treatment until imaging shows that chest lesions have cleared or have left a small, stable scar. A shorter course may be effective. An alternative to clindamycin is any β-lactam/β-lactamase inhibitor combination; parenteral treatment may be followed by orally administered amoxicillin/clavulanate. Carbapenems are also effective against anaerobic bacteria as well as streptococci, but the published data with these drugs in the treatment of anaerobic pulmonary infections are sparse. Penicillin was previously regarded as a preferred drug for these infections, but many oral anaerobes produce β-lactamases, and clindamycin proved superior to penicillin G in a randomized clinical trial. Metronidazole is highly active against virtually all anaerobes but not against aerobic microaerophilic streptococci, which play an important role in mixed infections. In therapeutic trials, metronidazole has done poorly unless combined with a β-lactam or another agent active against aerobic and microaerophilic streptococci.

Persistence of fever beyond 5–7 days or progression of the infiltrate suggests failure of therapy and a need to exclude factors such as obstruction, complicating empyema, and involvement of antibiotic-resistant bacteria. Many patients with uncomplicated lung abscesses and all those with atypical presentations or unresponsive abscesses should undergo bronchoscopy and/or CT to detect a possible associated anatomic lesion, such as a tumor, or a foreign body. Quantitative bacteriologic studies using a protected brush catheter or BAL are much less reliable when done after antibiotic therapy. Postural drainage was previously popular for patients with lung abscess, but aggressive attempts to implement this strategy may result in spillage to other pulmonary segments, leading to airway obstruction and clinical deterioration.

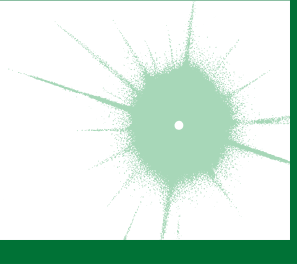
Lung abscess due to *S. aureus* is usually treated with vancomycin at a dosage that targets a trough serum level of 15–20 µg/mL. The main alternative is linezolid. Daptomycin should not be used for pulmonary infections. Lung abscesses caused by aerobic gram-negative bacteria need to be treated according to the results of antibiotic sensitivity tests. Most common among the pathogens involved are *K. pneumoniae* (especially the K1 strain in Taiwan) and *P. aeruginosa* in patients with severe chronic lung disease or compromised immune defenses. Pseudomonal lung abscesses usually require prolonged courses of parenteral antibiotics. Carbapenems or β-lactams are frequently combined with aminoglycosides; oral fluoroquinolones are often effective initially, but resistance is common with prolonged use. Aerosolized colistin and aminoglycosides are sometimes used to augment other therapy, but the efficacy of this approach is variable.

Surgery for lung abscesses was developed at the time penicillin became available in the late 1940s. The relative roles of penicillin and resectional surgery were hotly debated at that time, but by the late 1950s penicillin was favored. Initially the standard choice for most lung abscesses, penicillin was subsequently supplanted by the options summarized earlier. Recent large-scale reviews indicate that, in general, surgery is now reserved for ~10–12% of patients. The major indications for surgery are failure to respond to medical management, suspected neoplasm, and hemorrhage. Failure to respond to antibiotics is usually due to an obstructed bronchus and an extremely large abscess (>6 cm in diameter) or to infection involving relatively resistant bacteria, such as *P. aeruginosa*. The usual procedure is lobectomy. An alternative intervention that is becoming popular is percutaneous drainage under CT guidance. Aspirate samples for assay of possible pathogens should be carefully collected.

RESPONSE TO THERAPY Patients with lung abscess usually show clinical improvement, with decreased fever, within 3–5 days of initiation of antibiotic treatment. Defervescence can be expected within 5–10 days. Patients with fevers persisting for 7–14 days should undergo bronchoscopy or other diagnostic tests to better define anatomic changes and microbiologic findings. Cultures of expectorated sputum are not likely to be helpful at this juncture except for detecting pathogens such as mycobacteria and fungi. The response to therapy apparent on serial chest radiographs is delayed in comparison with the clinical course. In fact, infiltrates usually progress during the first 3 days of treatment in approximately one-half of patients. Pleural involvement is relatively common and may develop in dramatic fashion. The most common causes of failures of medical management include a failure to drain pleural collections, an inappropriate choice of antimicrobial therapy, an obstructed bronchus that prevents drainage, a "giant" abscess, a resistant pathogen, or refractory lesions due to immunocompromise.

CHAPTER 20

INFECTIVE ENDOCARDITIS



Adolf W. Karchmer

The prototypic lesion of infective endocarditis, the *vegetation* **(Fig. 20-1)**, is a mass of platelets, fibrin, microcolonies of microorganisms, and scant inflammatory cells. Infection most commonly involves heart valves (either native or prosthetic), but may also occur on the low-pressure side of a ventricular septal defect, on the mural endocardium where it is damaged by aberrant jets of blood or foreign bodies, or on intracardiac devices themselves. The analogous process involving arteriovenous shunts, arterioarterial shunts (patent ductus arteriosus), or a coarctation of the aorta is called *infective endarteritis*.

Endocarditis may be classified according to the temporal evolution of disease, the site of infection, the cause of infection, or a predisposing risk factor such as injection drug use. While each classification criterion provides therapeutic and prognostic insight, none is sufficient alone. *Acute endocarditis* is a hectically febrile illness that rapidly damages cardiac structures, hematogenously seeds extracardiac sites, and, if untreated, progresses to death within weeks. *Subacute endocarditis* follows an indolent course; causes structural cardiac damage only slowly, if at all; rarely metastasizes; and is gradually progressive

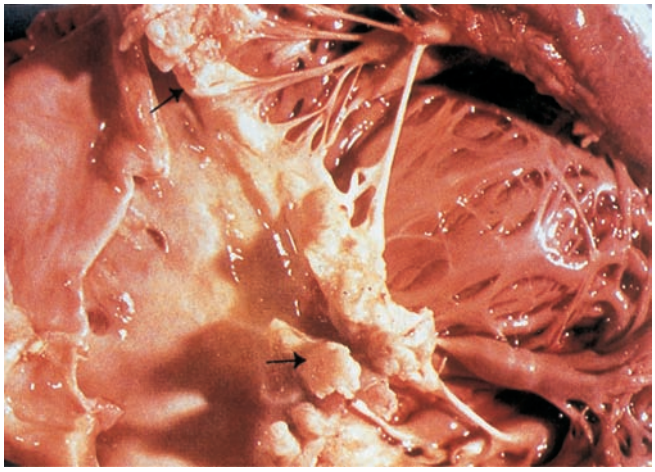


FIGURE 20-1
Vegetations (*arrows*) due to viridans streptococcal endocarditis involving the mitral valve.

unless complicated by a major embolic event or ruptured mycotic aneurysm.

In developed countries, the incidence of endocarditis ranges from 2.6 to 7 cases per 100,000 population per year and has remained relatively stable during recent decades. While congenital heart diseases remain a constant predisposition, predisposing conditions in developed countries have shifted from chronic rheumatic heart disease (which remains a common predisposition in developing countries) to illicit IV drug use, degenerative valve disease, and intracardiac devices. The incidence of endocarditis is notably increased among the elderly. In developed countries, 30–35% of cases of native valve endocarditis (NVE) are associated with health care, and 16–30% of all cases of endocarditis involve prosthetic valves. The risk of prosthesis infection is greatest during the first 6–12 months after valve replacement; gradually declines to a low, stable rate thereafter; and is similar for mechanical and bioprosthetic devices.

ETIOLOGY

Although many species of bacteria and fungi cause sporadic episodes of endocarditis, a few bacterial species cause the majority of cases **(Table 20-1)**. Because of their different portals of entry, the pathogens involved vary somewhat with the clinical types of endocarditis. The oral cavity, skin, and upper respiratory tract are the respective primary portals for the viridans streptococci, staphylococci, and the HACEK organisms: *Haemophilus*, *Aggregatibacter*, *Cardiobacterium*, *Eikenella*, and *Kingella*. (*Haemophilus aphrophilus* and *Actinobacillus actinomycetemcomitans* have been reclassified into the genus *Aggregatibacter*.) *Streptococcus gallolyticus* (formerly *S. bovis*) originates from the gastrointestinal tract, where it is associated with polyps and colonic tumors, and enterococci enter the bloodstream from the genitourinary tract. Health care–associated NVE, commonly caused by *Staphylococcus aureus*, coagulase-negative staphylococci (CoNS), and enterococci, has a nosocomial onset (55%) or a community onset (45%) in patients who have had extensive contact with the health care system over the preceding 90 days. Endocarditis complicates 6–25% of episodes of catheter-associated *S. aureus* bacteremia; the higher rates are detected by careful transesophageal echocardiography (TEE) screening (see "Echocardiography," later in the chapter).

Prosthetic valve endocarditis (PVE) arising within 2 months of valve surgery is generally nosocomial, the result of intraoperative contamination of the prosthesis or a bacteremic postoperative complication. This nosocomial origin is reflected in the primary microbial causes: *S. aureus*, CoNS, facultative gram-negative bacilli, diphtheroids, and fungi. The portals of entry and organisms causing cases beginning >12 months after surgery are similar to those in community-acquired NVE. PVE due to CoNS that presents 2–12 months after surgery often represents delayed-onset nosocomial infection. Regardless of the time of onset after surgery, at least 68–85% of CoNS strains that cause PVE are resistant to methicillin.

Transvenous pacemaker– or implanted defibrillator–associated endocarditis is usually nosocomial. The majority of episodes occur within weeks of implantation or generator change and are caused by *S. aureus* or CoNS, both of which are commonly resistant to methicillin.

Endocarditis occurring among injection drug users, especially that involving the tricuspid valve, is commonly caused by *S. aureus*, many strains of which are resistant to methicillin. Left-sided valve infections in addicts have a more varied etiology. In addition to the usual causes of endocarditis, these cases are caused by *Pseudomonas aeruginosa* and *Candida* species and sporadically by unusual organisms such as *Bacillus*, *Lactobacillus*, and *Corynebacterium* species. Polymicrobial endocarditis occurs among injection drug users. HIV infection in drug users does not significantly influence the causes of endocarditis.

From 5% to 15% of patients with endocarditis have negative blood cultures; in one-third to one-half of these cases, cultures are negative because of prior antibiotic exposure. The remainder of these patients are infected by fastidious organisms, such as nutritionally variant organisms (now designated *Granulicatella* and *Abiotrophia* species), HACEK organisms, *Coxiella burnetii*, and *Bartonella* species. Some fastidious organisms occur in characteristic geographic settings (e.g., *C. burnetii* and *Bartonella* species in Europe, *Brucella* species in the Middle East). *Tropheryma whipplei* causes an indolent, culture-negative, afebrile form of endocarditis.

PATHOGENESIS

The endothelium, unless damaged, is resistant to infection by most bacteria and to thrombus formation. Endothelial injury (e.g., at the site of impact of high-velocity blood jets or on the low-pressure side of a

TABLE 20-1

ORGANISMS CAUSING MAJOR CLINICAL FORMS OF ENDOCARDITIS

	PERCENTAGE OF CASES							
	NATIVE VALVE ENDOCARDITIS		PROSTHETIC VALVE ENDOCARDITIS AT INDICATED TIME OF ONSET (MONTHS) AFTER VALVE SURGERY			ENDOCARDITIS IN INJECTION DRUG USERS		
ORGANISM	COMMUNITY-ACQUIRED (*n* = 1718)	HEALTH CARE–ASSOCIATED (*n* = 788)	<2 (*n* = 144)	2–12 (*n* = 31)	>12 (*n* = 194)	RIGHT-SIDED (*n* = 346)	LEFT-SIDED (*n* = 204)	TOTAL (*n* = 675)[a]
Streptococci[b]	40	9	1	9	31	5	15	12
Pneumococci	2	—	—	—	—	—	—	—
Enterococci	9	13	8	12	11	2	24	9
Staphylococcus aureus	28	53[c]	22	12	18	77	23	57
Coagulase-negative staphylococci	5	12	33	32	11	—	—	—
Fastidious gram-negative coccobacilli (HACEK group)[d]	3	—	—	—	6	—	—	—
Gram-negative bacilli	1	2	13	3	6	5	13	7
Candida spp.	<1	2	8	12	1	—	12	4
Polymicrobial/miscellaneous	3	4	3	6	5	8	10	7
Diphtheroids	—	<1	6	—	3	—	—	0.1
Culture-negative	9	5	5	6	8	3	3	3

[a]The total number of cases is larger than the sum of right- and left-sided cases because the location of infection was not specified in some cases.
[b]Includes viridans streptococci; *Streptococcus gallolyticus*; other non–group A, groupable streptococci; and *Abiotrophia* spp. (nutritionally variant, pyridoxal-requiring streptococci).
[c]Methicillin resistance is common among these *S. aureus* strains.
[d]Includes *Haemophilus* spp., *Aggregatibacter actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella* spp., and *Kingella* spp.
Note: Data are compiled from multiple studies.

cardiac structural lesion) allows either direct infection by virulent organisms or the development of an uninfected platelet-fibrin thrombus—a condition called *nonbacterial thrombotic endocarditis* (NBTE). The thrombus subsequently serves as a site of bacterial attachment during transient bacteremia. The cardiac conditions most commonly resulting in NBTE are mitral regurgitation, aortic stenosis, aortic regurgitation, ventricular septal defects, and complex congenital heart disease. NBTE also arises as a result of a hypercoagulable state; this phenomenon gives rise to the clinical entity of *marantic endocarditis* (uninfected vegetations seen in patients with malignancy and chronic diseases) and to bland vegetations complicating systemic lupus erythematosus and the antiphospholipid antibody syndrome.

Organisms that cause endocarditis generally enter the bloodstream from mucosal surfaces, the skin, or sites of focal infection. Except for more virulent bacteria (e.g., *S. aureus*) that can adhere directly to intact endothelium or exposed subendothelial tissue, microorganisms in the blood adhere at sites of NBTE. If resistant to the bactericidal activity of serum and the microbicidal peptides released locally by platelets, the organisms proliferate and induce platelet deposition and a procoagulant state at the site by eliciting tissue factor from the endothelium or, in the case of *S. aureus*, from monocytes as well. Fibrin deposition combines with platelet aggregation and microorganism proliferation to generate an infected vegetation. The organisms that commonly cause endocarditis have surface adhesin molecules, collectively called microbial surface components recognizing adhesin matrix molecules (MSCRAMMs), that mediate adherence to NBTE sites or injured endothelium. Fibronectin-binding proteins present on many gram-positive bacteria, clumping factor (a fibrinogen- and fibrin-binding surface protein) on *S. aureus*, and glucans or FimA (a member of the family of oral mucosal adhesins) on streptococci facilitate adherence. Fibronectin-binding proteins are required for *S. aureus* invasion of intact endothelium; thus these surface proteins may facilitate infection of previously normal valves. In the absence of host defenses, organisms enmeshed in the growing platelet-fibrin vegetation proliferate to form dense microcolonies. Organisms deep in vegetations are metabolically inactive (nongrowing) and relatively resistant to killing by antimicrobial agents. Proliferating surface organisms are shed into the bloodstream continuously.

The pathophysiologic consequences and clinical manifestations of endocarditis—other than constitutional symptoms, which probably result from cytokine production—arise from damage to intracardiac structures; embolization of vegetation fragments, leading to infection or infarction of remote tissues; hematogenous infection of sites during bacteremia; and tissue injury due to the deposition of circulating immune complexes or immune responses to deposited bacterial antigens.

CLINICAL MANIFESTATIONS

The clinical syndrome of infective endocarditis is highly variable and spans a continuum between acute and subacute presentations. NVE (whether acquired in the community or in association with health care), PVE, and endocarditis due to injection drug use share clinical and laboratory manifestations **(Table 20-2)**. The causative microorganism is primarily responsible for the temporal course of endocarditis. β-Hemolytic streptococci, *S. aureus*, and pneumococci typically result in an acute course, although *S. aureus* occasionally causes subacute disease. Endocarditis caused by *Staphylococcus lugdunensis* (a coagulase-negative species) or by enterococci may present acutely. Subacute endocarditis is typically caused by viridans streptococci, enterococci, CoNS, and the HACEK group. Endocarditis caused by *Bartonella* species, *T. whipplei,* or *C. burnetii* is exceptionally indolent.

The clinical features of endocarditis are nonspecific. However, these symptoms in a febrile patient with valvular abnormalities or a behavior pattern that predisposes to endocarditis (e.g., injection drug use) suggest the diagnosis, as do bacteremia with organisms that frequently cause endocarditis, otherwise-unexplained arterial emboli, and progressive cardiac valvular incompetence. In patients with subacute presentations, fever is typically low-grade and rarely exceeds 39.4°C (103°F); in contrast, temperatures of 39.4°–40°C (103°–104°F) are often noted in acute endocarditis. Fever may be blunted or absent in patients who are elderly or severely debilitated or who have marked cardiac or renal failure.

TABLE 20-2

CLINICAL AND LABORATORY FEATURES OF INFECTIVE ENDOCARDITIS

FEATURE	FREQUENCY, %
Fever	80–90
Chills and sweats	40–75
Anorexia, weight loss, malaise	25–50
Myalgias, arthralgias	15–30
Back pain	7–15
Heart murmur	80–85
New/worsened regurgitant murmur	20–50
Arterial emboli	20–50
Splenomegaly	15–50
Clubbing	10–20
Neurologic manifestations	20–40
Peripheral manifestations (Osler's nodes, subungual hemorrhages, Janeway lesions, Roth's spots)	2–15
Petechiae	10–40
Laboratory manifestations	
Anemia	70–90
Leukocytosis	20–30
Microscopic hematuria	30–50
Elevated erythrocyte sedimentation rate	60–90
Elevated C-reactive protein level	>90
Rheumatoid factor	50
Circulating immune complexes	65–100
Decreased serum complement	5–40

Cardiac manifestations

Although heart murmurs are usually indicative of the predisposing cardiac pathology rather than of endocarditis, valvular damage and ruptured chordae may result in new regurgitant murmurs. In acute endocarditis involving a normal valve, murmurs may be absent initially but ultimately are detected in 85% of cases. Congestive heart failure (CHF) develops in 30–40% of patients; it is usually a consequence of valvular dysfunction but occasionally is due to endocarditis-associated myocarditis or an intracardiac fistula. Heart failure due to aortic valve dysfunction progresses more rapidly than does that due to mitral valve dysfunction. Extension of infection beyond valve leaflets into adjacent annular or myocardial tissue results in perivalvular abscesses, which in turn may cause intracardiac fistulae with new murmurs. Abscesses may burrow from the aortic valve annulus through the epicardium, causing pericarditis, or into the upper ventricular septum, where they may interrupt the conduction system, leading to varying degrees of heart block. Perivalvular abscesses arising from the mitral valve rarely interrupt conduction pathways near the atrioventricular node or in the proximal bundle of His. Emboli to a coronary artery occur in 2% of patients and may result in myocardial infarction.

Noncardiac manifestations

The classic nonsuppurative peripheral manifestations of subacute endocarditis are related to the duration of infection and, with early diagnosis and treatment, have become infrequent. In contrast, septic embolization mimicking some of these lesions (subungual hemorrhage, Osler's nodes) is common in patients with acute *S. aureus* endocarditis **(Fig. 20-2)**. Musculoskeletal pain usually remits promptly with treatment but must be distinguished from focal metastatic infections (e.g., spondylodiscitis), which may complicate 10–15% of cases.

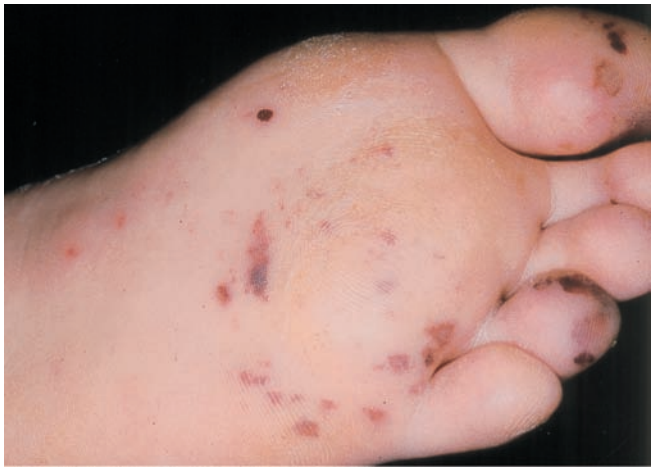


FIGURE 20-2
Septic emboli with hemorrhage and infarction due to acute *Staphylococcus aureus* endocarditis. (*Used with permission of L. Baden.*)

Hematogenously seeded focal infection is most often clinically evident in the skin, spleen, kidneys, skeletal system, and meninges. Arterial emboli are clinically apparent in up to 50% of patients. Endocarditis caused by *S. aureus,* vegetations >10 mm in diameter (as measured by echocardiography), and infection involving the mitral valve are independently associated with an increased risk of embolization. Emboli occurring late during or after effective therapy do not in themselves constitute evidence of failed antimicrobial treatment. Cerebrovascular emboli presenting as strokes or occasionally as encephalopathy complicate 15–35% of cases of endocarditis. One-half of these events precede the diagnosis of endocarditis. The frequency of stroke is 8 per 1000 patient-days during the week prior to diagnosis; the figure falls to 4.8 and 1.7 per 1000 patient-days during the first and second weeks of effective antimicrobial therapy, respectively. This decline exceeds that which can be attributed to change in vegetation size. Only 3% of strokes occur after 1 week of effective therapy. Other neurologic complications include aseptic or purulent meningitis, intracranial hemorrhage due to hemorrhagic infarcts or ruptured mycotic aneurysms, and seizures. (*Mycotic aneurysms* are focal dilations of arteries occurring at points in the artery wall that have been weakened by infection in the vasa vasorum or where septic emboli have lodged.) Microabscesses in brain and meninges occur commonly in *S. aureus* endocarditis; surgically drainable intracerebral abscesses are infrequent.

Immune complex deposition on the glomerular basement membrane causes diffuse hypocomplementemic glomerulonephritis and renal dysfunction, which typically improve with effective antimicrobial therapy. Embolic renal infarcts cause flank pain and hematuria but rarely cause renal dysfunction.

Manifestations of specific predisposing conditions

Almost 50% of endocarditis cases associated with injection drug use are limited to the tricuspid valve and present with fever but with faint or no murmur. In 75% of cases, septic emboli cause cough, pleuritic chest pain, nodular pulmonary infiltrates, or occasionally pyopneumothorax. Infection of the aortic or mitral valves on the left side of the heart presents with the typical clinical features of endocarditis.

Health care–associated endocarditis has typical manifestations if it is not associated with a retained intracardiac device or masked by the symptoms of concurrent comorbid illness. Transvenous pacemaker– or implanted defibrillator–associated endocarditis may be associated with obvious or cryptic generator pocket infection and results in fever, minimal murmur, and pulmonary symptoms due to septic emboli.

Late-onset PVE presents with typical clinical features. In cases arising within 60 days of valve surgery (early onset), typical symptoms may be obscured by comorbidity associated with recent surgery. In both early-onset and more delayed presentations, paravalvular infection is common and often results in partial valve dehiscence, regurgitant murmurs, CHF, or disruption of the conduction system.

DIAGNOSIS

The Duke criteria

The diagnosis of infective endocarditis is established with certainty only when vegetations are examined histologically and microbiologically. Nevertheless, a highly sensitive and specific diagnostic schema—known as the *Duke criteria*—has been developed on the basis of clinical, laboratory, and echocardiographic findings **(Table 20-3)**. Documentation of two major criteria, of one major criterion and three minor criteria, or of five minor criteria allows a clinical diagnosis of definite endocarditis. The diagnosis of endocarditis is rejected if an alternative diagnosis is established, if symptoms resolve and do not recur with ≥4 days of antibiotic therapy, or if surgery or autopsy after ≥4 days of antimicrobial therapy yields no histologic evidence of endocarditis. Illnesses not classified as definite endocarditis or rejected as such are considered cases of possible infective endocarditis when either one major criterion and one minor criterion or three minor criteria are fulfilled. Requiring the identification of clinical features of endocarditis for classification as possible infective endocarditis increases the specificity of the schema without significantly reducing its sensitivity.

The roles of bacteremia and echocardiographic findings in the diagnosis of endocarditis are emphasized in the Duke criteria. The requirement for multiple positive blood cultures over time is consistent with the continuous low-density bacteremia characteristic of endocarditis. Among patients with untreated endocarditis who ultimately have a positive blood culture, 95% of all blood cultures are positive. The diagnostic criteria attach significance to the species of organism isolated from blood cultures. To fulfill a major criterion, the isolation of an organism that causes both endocarditis and bacteremia in the absence of endocarditis (e.g., *S. aureus*, enterococci) must take place repeatedly (i.e., persistent bacteremia) and in the absence of

TABLE 20-3

THE DUKE CRITERIA FOR THE CLINICAL DIAGNOSIS OF INFECTIVE ENDOCARDITIS[a]

Major Criteria

1. Positive blood culture
   - Typical microorganism for infective endocarditis from two separate blood cultures
     - Viridans streptococci, *Streptococcus gallolyticus*, HACEK group, *Staphylococcus aureus*, *or*
     - Community-acquired enterococci in the absence of a primary focus, *or*
   - Persistently positive blood culture, defined as recovery of a microorganism consistent with infective endocarditis from:
     - Blood cultures drawn >12 h apart; *or*
     - All of 3 or a majority of ≥4 separate blood cultures, with first and last drawn at least 1 h apart
   - Single positive blood culture for *Coxiella burnetii* or phase I IgG antibody titer of >1:800
2. Evidence of endocardial involvement
   - Positive echocardiogram[b]
     - Oscillating intracardiac mass on valve or supporting structures or in the path of regurgitant jets or in implanted material, in the absence of an alternative anatomic explanation, *or*
     - Abscess, *or*
     - New partial dehiscence of prosthetic valve, *or*
   - New valvular regurgitation (increase or change in preexisting murmur not sufficient)

Minor Criteria

1. Predisposition: predisposing heart condition or injection drug use
2. Fever ≥38.0°C (≥100.4°F)
3. Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, Janeway lesions
4. Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth's spots, rheumatoid factor
5. Microbiologic evidence: positive blood culture but not meeting major criterion as noted previously[c] or serologic evidence of active infection with organism consistent with infective endocarditis

[a]Definite endocarditis is defined by documentation of two major criteria, of one major criterion and three minor criteria, or of five minor criteria. See text for further details.
[b]Transesophageal echocardiography is recommended for assessing possible prosthetic valve endocarditis or complicated endocarditis.
[c]Excluding single positive cultures for coagulase-negative staphylococci and diphtheroids, which are common culture contaminants, and organisms that do not cause endocarditis frequently, such as gram-negative bacilli.
Note: HACEK, *Haemophilus* spp., *Aggregatibacter actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, *Kingella* spp.
Source: Adapted from JS Li et al: Clin Infect Dis 30:633, 2000, with permission from the University of Chicago Press.

a primary focus of infection. Organisms that rarely cause endocarditis but commonly contaminate blood cultures (e.g., diphtheroids, CoNS) must be isolated repeatedly if their isolation is to serve as a major criterion.

Blood cultures

Isolation of the causative microorganism from blood cultures is critical for diagnosis, determination of antimicrobial susceptibility, and planning of treatment. In the absence of prior antibiotic therapy, three 2-bottle blood culture sets, separated from one another by at least 1 h, should be obtained from different venipuncture sites over 24 h. If the cultures remain negative after 48–72 h, two or three additional blood culture sets should be obtained, and the laboratory should be consulted for advice regarding optimal culture techniques. Pending culture results, empirical antimicrobial therapy should be withheld initially from hemodynamically stable patients with suspected subacute endocarditis, especially those who have received antibiotics within the preceding 2 weeks; thus, if necessary, additional blood culture sets can be obtained without the confounding effect of empirical treatment. Patients with acute endocarditis or with deteriorating hemodynamics who may require urgent surgery should be treated empirically immediately after three sets of blood cultures are obtained over several hours.

Non-blood-culture tests

Serologic tests can be used to implicate causally some organisms that are difficult to recover by blood culture: *Brucella*, *Bartonella*, *Legionella*, *Chlamydia psittaci*, and *C. burnetii*. Pathogens can also be identified in vegetations by culture, microscopic examination with special stains (i.e., the periodic acid–Schiff stain for *T. whipplei*), or direct fluorescence antibody techniques and by the use of polymerase chain reaction (PCR) to recover unique microbial DNA or 16S rRNA that, when sequenced, allows identification of organisms.

Echocardiography

Echocardiography allows anatomic confirmation of infective endocarditis, sizing of vegetations, detection of intracardiac complications, and assessment of cardiac function **(Fig. 20-3)**. Transthoracic echocardiography (TTE) is noninvasive and exceptionally specific; however, it cannot image vegetations <2 mm in diameter, and in 20% of patients it is technically inadequate because of emphysema or body habitus. TTE detects vegetations in only 65% of patients with definite clinical endocarditis. Moreover, TTE is not adequate for evaluating prosthetic valves or detecting intracardiac complications. TEE is safe and detects vegetations in >90% of patients with definite endocarditis; nevertheless, initial studies may be false-negative in 6–18% of endocarditis patients. When endocarditis is likely, a negative TEE result does not exclude the diagnosis but rather warrants repetition of the study in 7–10 days. TEE is the optimal method for the diagnosis of PVE or the detection of myocardial abscess, valve perforation, or intracardiac fistulae.

Experts favor echocardiographic evaluation of all patients with a clinical diagnosis of endocarditis; however, the test should not be used to screen patients with a

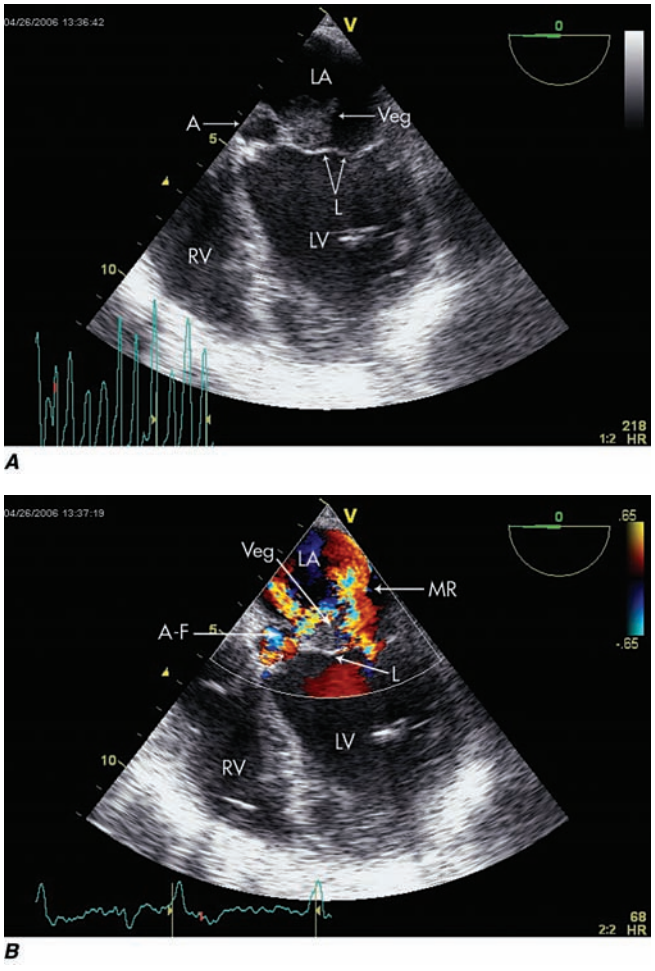


FIGURE 20-3
Imaging of a mitral valve infected with *Staphylococcus aureus* by low-esophageal four-chamber-view transesophageal echocardiography (TEE). ***A.*** Two-dimensional echocardiogram showing a large vegetation with an adjacent echolucent abscess cavity. ***B.*** Color-flow Doppler image showing severe mitral regurgitation through both the abscess-fistula and the central valve orifice. A, abscess; A-F, abscess-fistula; L, valve leaflets; LA, left atrium; LV, left ventricle; MR, mitral central valve regurgitation; RV, right ventricle; veg, vegetation. (*With permission of Andrew Burger, MD.*)

low probability of endocarditis (e.g., patients with unexplained fever). An American Heart Association approach to the use of echocardiography for evaluation of patients with suspected endocarditis is illustrated in **Fig. 20-4**.

Other studies

Many laboratory studies that are not diagnostic—i.e., complete blood count, creatinine determination, liver function tests, chest radiography, and electrocardiography—are nevertheless important in the management of patients with endocarditis. The erythrocyte sedimentation rate, C-reactive protein level, and circulating immune complex titer are commonly increased in endocarditis (Table 20-2). Cardiac catheterization is useful primarily to assess coronary artery patency in older individuals who are to undergo surgery for endocarditis.

TREATMENT Infective Endocarditis

ANTIMICROBIAL THERAPY It is difficult to eradicate bacteria from the vegetation because local host defenses are deficient and because the largely nongrowing, metabolically inactive bacteria are less easily killed by antibiotics. To cure endocarditis, all bacteria in the vegetation must be killed; therefore, therapy must be bactericidal and prolonged. Antibiotics are generally given parenterally to achieve serum concentrations that, through passive diffusion, lead to effective concentrations in the depths of the vegetation. To select effective therapy requires knowledge of the susceptibility of the causative microorganisms. The decision to initiate treatment empirically must balance the need to establish a microbiologic diagnosis against the potential progression of disease or the need for urgent surgery (see "Blood Cultures," earlier). Simultaneous infection at other sites (such as meningitis), allergies, end-organ dysfunction, interactions with concomitant medications, and risks of adverse events must be considered in the selection of therapy.

Although given for several weeks longer, the regimens recommended for the treatment of endocarditis involving prosthetic valves (except for staphylococcal infections) are similar to those used to treat NVE (Table 20-4). Recommended doses and durations of therapy should be adhered to unless alterations are required by end-organ dysfunction or adverse events.

Organism-specific therapies

Streptococci Optimal therapy for streptococcal endocarditis is based on the minimal inhibitory concentration (MIC) of penicillin for the causative isolate (Table 20-4). The 2-week penicillin/gentamicin or ceftriaxone/gentamicin regimens should not be used to treat complicated NVE or PVE. The regimen recommended for relatively penicillin-resistant streptococci is advocated for treatment of group B, C, or G streptococcal endocarditis. Nutritionally variant organisms (*Granulicatella* or *Abiotrophia* species) and *Gemella morbillorum* are treated with the regimen for moderately penicillin-resistant streptococci, as is PVE caused by these organisms or by streptococci with a penicillin MIC of >0.1 μg/mL (Table 20-4).

Enterococci Enterococci are resistant to oxacillin, nafcillin, and the cephalosporins and are only inhibited—not killed—by penicillin, ampicillin, teicoplanin (not available in the United States), and vancomycin. To kill enterococci requires the synergistic interaction of a cell wall–active antibiotic (penicillin, ampicillin, vancomycin, or teicoplanin) that is effective at achievable serum concentrations and an aminoglycoside (gentamicin or streptomycin) to which the isolate does not exhibit high-level resistance. An isolate's resistance to cell wall–active agents or its ability to replicate in the

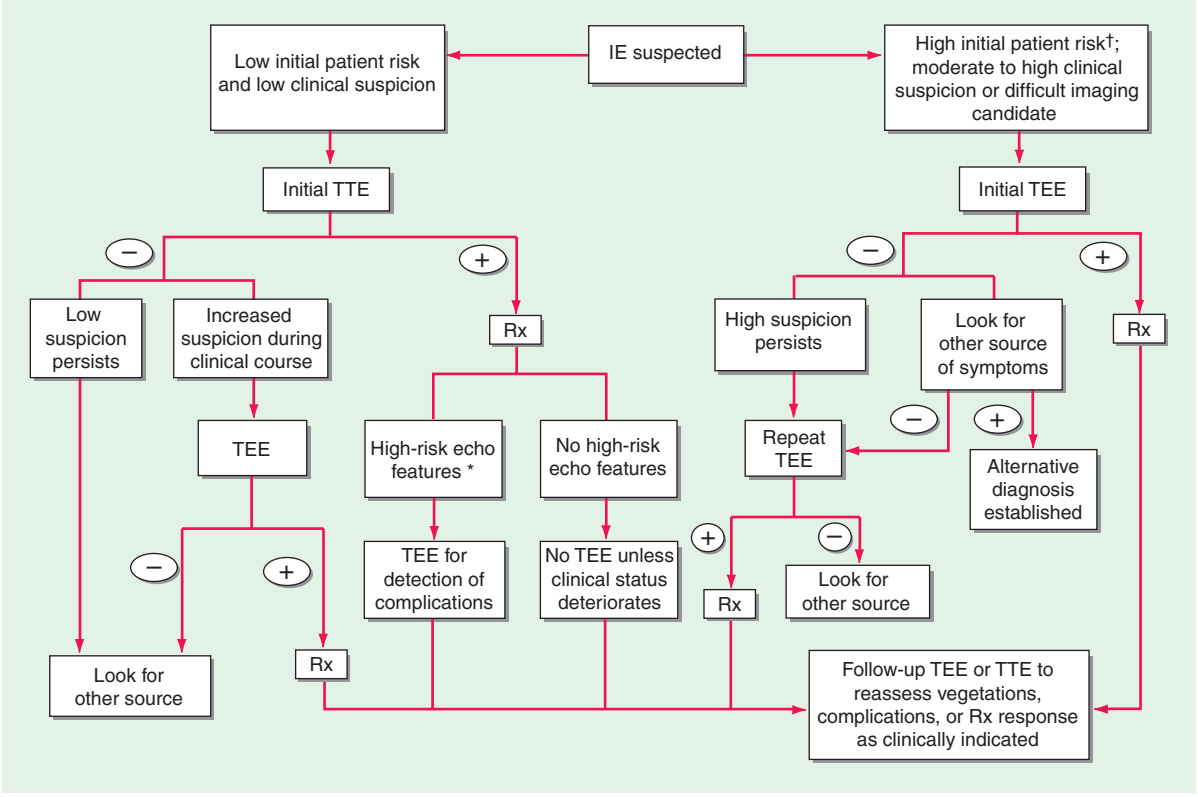


FIGURE 20-4

The diagnostic use of transesophageal and transtracheal echocardiography (TEE and TTE, respectively). †High initial patient risk for endocarditis as listed in Table 20-8 or evidence of intracardiac complications (new regurgitant murmur, new electrocardiographic conduction changes, or congestive heart failure). *High-risk echocardiographic features include large vegetations, valve insufficiency, paravalvular infection, or ventricular dysfunction. Rx indicates initiation of antibiotic therapy. (*Reproduced with permission from Diagnosis and Management of Infective Endocarditis and Its Complications* [*Circulation 98:2936, 1998. © 1998 American Heart Association*].)

presence of gentamicin at ≥500 μg/mL or streptomycin at 1000–2000 μg/mL—a phenomenon called *high-level aminoglycoside resistance*—indicates that the ineffective antimicrobial agent cannot participate in the interaction to produce killing. High-level resistance to gentamicin predicts that tobramycin, netilmicin, amikacin, and kanamycin also will be ineffective. In fact, even when enterococci are not highly resistant to gentamicin, it is difficult to predict the ability of these other aminoglycosides to participate in synergistic killing; consequently, they should not in general be used to treat enterococcal endocarditis. High concentrations of ampicillin plus ceftriaxone or cefotaxime, by expanded binding of penicillin-binding proteins, kill *E. faecalis* in vitro and in animal models of endocarditis.

Enterococci causing endocarditis must be tested for high-level resistance to streptomycin and gentamicin, β-lactamase production, and susceptibility to penicillin and ampicillin (MIC, <8 μg/mL) and to vancomycin (MIC, ≥4 μg/mL). If the isolate produces β-lactamase, ampicillin/sulbactam or vancomycin can be used as the cell wall–active component; if the penicillin/ampicillin MIC is ≥8 μg/mL, vancomycin can be considered; and if the vancomycin MIC is ≥8 μg/mL, penicillin or ampicillin can be considered. In the absence of high-level resistance, gentamicin or streptomycin should be used as the aminoglycoside (Table 20-4). If there is high-level resistance to both these drugs, no aminoglycoside should be given; instead, an 8- to 12-week course of a single cell wall–active agent—or, for *E. faecalis*, high doses of ampicillin combined with ceftriaxone or cefotaxime—is suggested. If this alternative therapy fails or the isolate is resistant to all of the commonly used agents, surgical treatment is advised. The role of newer agents potentially active against multidrug-resistant enterococci [quinupristin/dalfopristin (*E. faecium* only), linezolid, and daptomycin] in the treatment of endocarditis has not been established. Although the dose of gentamicin used to achieve bactericidal synergy in treating enterococcal endocarditis is smaller than that used in standard therapy, nephrotoxicity is not uncommon during treatment for 4–6 weeks. Regimens in which the aminoglycoside component is discontinued at 2–3 weeks because of toxicity have been curative. Thus, discontinuation of the aminoglycoside is recommended when nephrotoxicity develops in patients who have responded satisfactorily to therapy. Alternatively, the ampicillin-ceftriaxone regimen can be used to treat

TABLE 20-4

ANTIBIOTIC TREATMENT FOR INFECTIVE ENDOCARDITIS CAUSED BY COMMON ORGANISMS[a]

ORGANISM	DRUG (DOSE, DURATION)	COMMENTS
Streptococci		
Penicillin-susceptible[b] streptococci, *S. gallolyticus*	• Penicillin G (2–3 mU IV q4h for 4 weeks)	—
	• Ceftriaxone (2 g/d IV as a single dose for 4 weeks)	Can use ceftriaxone in patients with nonimmediate penicillin allergy
	• Vancomycin[c] (15 mg/kg IV q12h for 4 weeks)	Use vancomycin in patients with severe or immediate β-lactam allergy.
	• Penicillin G (2–3 mU IV q4h) or ceftriaxone (2 g IV qd) for 2 weeks *plus* Gentamicin[d] (3 mg/kg qd IV or IM, as a single dose[e] or divided into equal doses q8h for 2 weeks)	Avoid 2-week regimen when risk of aminoglycoside toxicity is increased and in prosthetic valve or complicated endocarditis.
Relatively penicillin-resistant[f] streptococci	• Penicillin G (4 mU IV q4h) or ceftriaxone (2 g IV qd) for 4 weeks *plus* Gentamicin[d] (3 mg/kg qd IV or IM, as a single dose[e] or divided into equal doses q8h for 2 weeks)	Penicillin alone at this dose for 6 weeks or with gentamicin during initial 2 weeks is preferred for prosthetic valve endocarditis caused by streptococci with penicillin MICs of ≤0.1 μg/mL.
	• Vancomycin[c] as noted above for 4 weeks	—
Moderately penicillin-resistant[g] streptococci, nutritionally variant organisms, or *Gemella morbillorum*	• Penicillin G (4–5 mU IV q4h) or ceftriaxone (2 g IV qd) for 6 weeks *plus* Gentamicin[d] (3 mg/kg qd IV or IM as a single dose[e] or divided into equal doses q8h for 6 weeks)	Preferred for prosthetic valve endocarditis caused by streptococci with penicillin MICs of >0.1 μg/mL
	• Vancomycin[c] as noted above for 4 weeks	—
Enterococci[h]		
	• Penicillin G (4–5 mU IV q4h) *plus* Gentamicin[d] (1 mg/kg IV q8h), both for 4–6 weeks	Can use streptomycin (7.5 mg/kg q12h) in lieu of gentamicin if there is not high-level resistance to streptomycin
	• Ampicillin (2 g IV q4h) *plus* Gentamicin[d] (1 mg/kg IV q8h), both for 4–6 weeks	—
	• Vancomycin[c] (15 mg/kg IV q12h) *plus* Gentamicin[d] (1 mg/kg IV q8h), both for 4–6 weeks	Use vancomycin plus gentamicin for penicillin-allergic patients, or desensitize to penicillin.
Staphylococci		
Methicillin-susceptible, infecting native valves (no foreign devices)	• Nafcillin or oxacillin (2 g IV q4h for 4–6 weeks)	Can use penicillin (4 mU q4h) if isolate is penicillin-susceptible (does not produce β-lactamase)
	• Cefazolin (2 g IV q8h for 4–6 weeks)	Can use cefazolin regimen for patients with nonimmediate penicillin allergy
	• Vancomycin[c] (15 mg/kg IV q12h for 4–6 weeks)	Use vancomycin for patients with immediate (urticarial) or severe penicillin allergy
Methicillin-resistant, infecting native valves (no foreign devices)	• Vancomycin[c] (15 mg/kg IV q8–12h for 4–6 weeks)	No role for routine use of rifampin
Methicillin-susceptible, infecting prosthetic valves	• Nafcillin or oxacillin (2 g IV q4h for 6–8 weeks) *plus* Gentamicin[d] (1 mg/kg IM or IV q8h for 2 weeks) *plus* Rifampin[i] (300 mg PO q8h for 6–8 weeks)	Use gentamicin during initial 2 weeks; determine susceptibility to gentamicin before initiating rifampin (see text); if patient is highly allergic to penicillin, use regimen for methicillin-resistant staphylococci; if β-lactam allergy is of the minor, nonimmediate type, cefazolin can be substituted for oxacillin/nafcillin.

(*continued*)

TABLE 20-4

ANTIBIOTIC TREATMENT FOR INFECTIVE ENDOCARDITIS CAUSED BY COMMON ORGANISMS[a] (*CONTINUED*)

ORGANISM	DRUG (DOSE, DURATION)	COMMENTS
Staphylococci (*continued*)		
Methicillin-resistant, infecting prosthetic valves	• Vancomycin[c] (15 mg/kg IV q12h for 6–8 weeks) *plus* Gentamicin[d] (1 mg/kg IM or IV q8h for 2 weeks) *plus* Rifampin[i] (300 mg PO q8h for 6–8 weeks)	Use gentamicin during initial 2 weeks; determine gentamicin susceptibility before initiating rifampin (see text).
HACEK Organisms		
	• Ceftriaxone (2 g/d IV as a single dose for 4 weeks) • Ampicillin/sulbactam (3 g IV q6h for 4 weeks)	Can use another third-generation cephalosporin at comparable dosage —

[a]Doses are for adults with normal renal function. Doses of gentamicin, streptomycin, and vancomycin must be adjusted for reduced renal function. Ideal body weight is used to calculate doses of gentamicin and streptomycin per kilogram (men = 50 kg + 2.3 kg per inch over 5 feet; women = 45.5 kg + 2.3 kg per inch over 5 feet).
[b]MIC, ≤0.1 μg/mL.
[c]Vancomycin dose is based on actual body weight. Adjust for trough level of 10–15 μg/mL for streptococcal and enterococcal infections and 15–20 μg/mL for staphylococcal infections.
[d]Aminoglycosides should not be administered as single daily doses for enterococcal endocarditis and should be introduced as part of the initial treatment. Target peak and trough serum concentrations of divided-dose gentamicin 1 h after a 20- to 30-min infusion or IM injection are ~3.5 μg/mL and ≤1 μg/mL, respectively; target peak and trough serum concentrations of streptomycin (timing as with gentamicin) are 20–35 μg/mL and <10 μg/mL, respectively.
[e]Netilmicin (4 mg/kg qd, as a single dose) can be used in lieu of gentamicin.
[f]MIC, >0.1 μg/mL and <0.5 μg/mL.
[g]MIC, ≥0.5 μg/mL and <8 μg/mL.
[h]Antimicrobial susceptibility must be evaluated; see text.
[i]Rifampin increases warfarin and dicumarol requirements for anticoagulation.

E. faecalis endocarditis if nephrotoxicity develops or is exceptionally threatening.

Staphylococci The regimens used to treat staphylococcal endocarditis (Table 20-4) are based not on coagulase production but rather on the presence or absence of a prosthetic valve or foreign device, the native valve(s) involved, and the susceptibility of the isolate to penicillin, methicillin, and vancomycin. All staphylococci are considered penicillin-resistant until shown not to produce penicillinase. Similarly, methicillin resistance has become so prevalent among staphylococci that therapy should be initiated with a regimen for methicillin-resistant organisms and subsequently revised if the strain proves to be susceptible to methicillin. The addition of 3–5 days of gentamicin (if the isolate is susceptible) to a β-lactam antibiotic to enhance therapy for native mitral or aortic valve endocarditis has been optional. While the addition of gentamicin minimally hastens eradication of bacteremia, it does not improve survival rates, and even abbreviated gentamicin therapy may be associated with nephrotoxicity and thus is not recommended. Gentamicin generally is not added to the vancomycin regimen in this setting.

For treatment of endocarditis caused by methicillin-resistant *S. aureus* (MRSA), vancomycin dosing to achieve trough concentrations of 15–20 μg/mL is recommended, with the recognition that this regimen may be associated with nephrotoxicity. Although resistance to vancomycin among staphylococci is rare, reduced vancomycin susceptibility among MRSA strains is increasingly encountered. Isolates with a vancomycin MIC of 4–16 μg/mL have intermediate susceptibility and are referred to as vancomycin-intermediate *S. aureus* (VISA). Isolates with an MIC of 2 μg/mL may harbor subpopulations with higher MICs. These isolates, called hetero-resistant VISA (hVISA), are not detectable by routine susceptibility testing. Because of the pharmacokinetics/pharmacodynamics of vancomycin, killing of MRSA with a vancomycin MIC of 2 μg/mL is unpredictable even with aggressive vancomycin dosing. Although not approved by the U.S. Food and Drug Administration, daptomycin [6 mg/kg (or, as some experts prefer, 8–10 mg/kg) IV once daily] has been recommended as an alternative to vancomycin, particularly for endocarditis caused by VISA, hVISA, and isolates with a vancomycin MIC of 2 μg/mL. These isolates should be tested to document daptomycin susceptibility. Treatment of endocarditis in which bacteremia persists despite this therapy is beyond the scope of this chapter and requires consultation with an infectious disease specialist. The efficacy of linezolid for left-sided MRSA endocarditis has not been established.

Methicillin-susceptible *S. aureus* endocarditis that is uncomplicated and limited to the tricuspid or pulmonic valve—a condition occurring almost exclusively in injection drug users—can often be treated with a 2-week course that combines oxacillin or nafcillin (but not vancomycin) with gentamicin. Patients with prolonged fever (≥5 days) during therapy or multiple septic pulmonary emboli should receive standard therapy.

Right-sided endocarditis caused by MRSA is treated for 4 weeks with a standard vancomycin regimen or with daptomycin (6 mg/kg as a single daily dose).

Staphylococcal PVE is treated for 6–8 weeks with a multidrug regimen. Rifampin is an essential component because it kills staphylococci that are adherent to foreign material in a biofilm. Two other agents (selected on the basis of susceptibility testing) are combined with rifampin to prevent in vivo emergence of resistance. Because many staphylococci (particularly MRSA and *S. epidermidis*) are resistant to gentamicin, susceptibility to gentamicin or an alternative agent should be established before rifampin treatment is begun. If the isolate is resistant to gentamicin, then another aminoglycoside, a fluoroquinolone (chosen on the basis of susceptibility), or another active agent should be substituted for gentamicin.

Other organisms In the absence of meningitis, endocarditis caused by *S. pneumoniae* with a penicillin MIC of ≥1 μg/mL can be treated with IV penicillin (4 million units every 4 h), ceftriaxone (2 g/d as a single dose), or cefotaxime (at a comparable dosage). Infection caused by pneumococcal strains with a penicillin MIC of ≥2 μg/mL should be treated with vancomycin. Until the strain's susceptibility to penicillin is established, therapy should consist of vancomycin plus ceftriaxone, especially if concurrent meningitis is suspected. *P. aeruginosa* endocarditis is treated with an antipseudomonal penicillin (ticarcillin or piperacillin) and high doses of tobramycin (8 mg/kg per day in three divided doses). Endocarditis caused by Enterobacteriaceae is treated with a potent β-lactam antibiotic plus an aminoglycoside. Corynebacterial endocarditis is treated with penicillin plus an aminoglycoside (if the organism is susceptible to the aminoglycoside) or with vancomycin, which is highly bactericidal for most strains. Therapy for *Candida* endocarditis consists of amphotericin B plus flucytosine and early surgery; long-term (if not indefinite) suppression with an oral azole is advised. Caspofungin treatment of *Candida* endocarditis has been effective in sporadic cases; nevertheless, the role of echinocandins in this setting has not been established.

Empirical therapy In the design and execution of therapy without culture data (i.e., before culture results are known or when cultures are negative), clinical clues (e.g., site of infection, patient's predispositions) as well as epidemiologic clues to etiology must be considered. Thus, empirical therapy for acute endocarditis in an injection drug user should cover MRSA and gram-negative bacilli. Treatment with vancomycin plus gentamicin, initiated immediately after blood is obtained for cultures, covers these as well as many other potential causes. Similarly, treatment of health care–associated endocarditis must cover MRSA. In the treatment of culture-negative episodes, marantic endocarditis must be excluded and fastidious organisms sought by serologic testing. In the absence of prior antibiotic therapy, it is unlikely that *S. aureus*, CoNS, or enterococcal infection will present with negative blood cultures; thus, in this situation, recommended empirical therapy targets not these organisms but rather nutritionally variant organisms, the HACEK group, and *Bartonella* species. Pending the availability of diagnostic data, blood culture–negative subacute NVE is treated either with ampicillin-sulbactam (12 g every 24 h) or with ceftriaxone plus gentamicin; doxycycline (100 mg twice daily) is added for *Bartonella* coverage. Vancomycin, gentamicin, cefepime, and rifampin should be used if prosthetic valves in place for ≥1 year are involved. Empirical therapy for infected prosthetic valves in place for >1 year is similar to that for culture-negative PVE. If negative cultures have been confounded by prior antibiotic administration, broader empirical therapy may be indicated, with particular attention to pathogens likely to be inhibited by the specific prior therapy.

Outpatient antimicrobial therapy Fully compliant patients who have sterile blood cultures, no fever, and no clinical or echocardiographic findings that suggest an impending complication may complete therapy as outpatients. Careful follow-up and a stable home setting are necessary, as are predictable IV access and use of antimicrobial agents that are stable in solution.

Monitoring antimicrobial therapy The serum bactericidal titer—the highest dilution of the patient's serum during therapy that kills 99.9% of the standard inoculum of the infecting organism—is no longer recommended for assessment of standard regimens. However, in the treatment of endocarditis caused by unusual organisms, this measurement may provide a patient-specific assessment of in vivo antibiotic effect. Serum concentrations of aminoglycosides and vancomycin should be monitored.

Antibiotic toxicities, including allergic reactions, occur in 25–40% of patients and commonly arise during the third week of therapy. Blood tests to detect renal, hepatic, and hematologic toxicity should be performed periodically.

Blood cultures should be repeated daily until sterile, rechecked if there is recrudescent fever, and performed again 4–6 weeks after therapy to document cure. Blood cultures become sterile within 2 days after the start of appropriate therapy when infection is caused by viridans streptococci, enterococci, or HACEK organisms. In *S. aureus* endocarditis, β-lactam therapy results in sterile cultures in 3–5 days, whereas with MRSA endocarditis positive cultures may persist for 7–9 days with vancomycin treatment. MRSA bacteremia persisting despite an adequate dosage of vancomycin may indicate infection due to a strain with reduced vancomycin susceptibility and therefore may point to a need for alternative therapy. When fever persists for 7 days despite appropriate antibiotic therapy, patients should be evaluated for paravalvular abscess, extracardiac abscesses (spleen, kidney), or complications (embolic events). Recrudescent fever raises the question of these complications but also of drug reactions or complications of hospitalization. Vegetations become smaller with effective therapy; however, 3 months after cure, 50% are unchanged and 25% are slightly larger.

SURGICAL TREATMENT Intracardiac and central nervous system complications of endocarditis are important causes of morbidity and death. In some cases, effective treatment for these complications requires surgery. The indications for cardiac surgical treatment of endocarditis (Table 20-5) have been derived from observational studies and expert opinion. The strength of individual indications varies; thus, the risks and benefits as well as the timing of surgery must be individualized (Table 20-6). From 25% to 40% of patients with left-sided endocarditis undergo cardiac surgery during active infection, with slightly higher surgery rates with PVE than with NVE. Clinical events resulting from intracardiac complications, which are most reliably detected by TEE, justify most surgery. In the absence of randomized trials to evaluate a survival benefit for surgical intervention, the effect of surgery has been assessed in studies comparing populations of medically and surgically treated patients matched for the necessity of surgery (indication), with adjustments for predictors of death (comorbidity) and time of the surgical intervention. Although study results vary, surgery for currently advised indications appears to convey a significant survival benefit (27–55%) that becomes apparent only with follow-up for ≥6 months after the intervention. During the initial weeks after surgery, mortality risk is actually increased (disease- plus surgery-related mortality). With less demanding surgical indications, this combined mortality risk may erode potential long-term benefits.

TABLE 20-5

INDICATIONS FOR CARDIAC SURGICAL INTERVENTION IN PATIENTS WITH ENDOCARDITIS

Surgery required for optimal outcome
Moderate to severe congestive heart failure due to valve dysfunction
Partially dehisced unstable prosthetic valve
Persistent bacteremia despite optimal antimicrobial therapy
Lack of effective microbicidal therapy (e.g., fungal or *Brucella* endocarditis)
S. aureus prosthetic valve endocarditis with an intracardiac complication
Relapse of prosthetic valve endocarditis after optimal antimicrobial therapy
Surgery to be strongly considered for improved outcome[a]
Perivalvular extension of infection
Poorly responsive *S. aureus* endocarditis involving the aortic or mitral valve
Large (>10-mm diameter) hypermobile vegetations with increased risk of embolism
Persistent unexplained fever (≥10 days) in culture-negative native valve endocarditis
Poorly responsive or relapsed endocarditis due to highly antibiotic-resistant enterococci or gram-negative bacilli

[a]Surgery must be carefully considered; findings are often combined with other indications to prompt surgery.

Benefit is greatest for NVE complicated by heart failure or myocardial abscess and is less clear for PVE; this difference may reflect sample size in the relevant studies.

Congestive heart failure Moderate to severe refractory CHF caused by new or worsening valve dysfunction is the major indication for cardiac surgical treatment of endocarditis. At 6 months of follow-up, patients with left-sided endocarditis and moderate to severe heart failure due to valve dysfunction who are treated only medically have a 50% mortality rate; the figure is 15% among matched patients who undergo surgery. The survival benefit with surgery is seen in both NVE and PVE. Surgery can relieve functional stenosis due to large vegetations or restore competence to damaged regurgitant valves by repair or replacement.

Perivalvular infection This complication, which is most common with aortic valve infection, occurs in 10–15% of native valve and 45–60% of prosthetic valve infections. It is suggested by persistent unexplained fever during appropriate therapy, new electrocardiographic conduction disturbances, and pericarditis. TEE with color Doppler is the test of choice to detect perivalvular abscesses (sensitivity, ≥85%). For optimal outcome, surgery is required, especially when fever persists, fistulae develop, prostheses are dehisced and unstable, and invasive infection relapses after appropriate treatment. Cardiac rhythm must be monitored since high-grade heart block may require insertion of a pacemaker.

Uncontrolled infection Continued positive blood cultures or otherwise-unexplained persistent fevers (in patients with either blood culture–positive or –negative endocarditis) despite optimal antibiotic therapy may reflect uncontrolled infection and may warrant surgery. Surgical treatment is also advised for endocarditis caused by organisms for which experience indicates that effective antimicrobial therapy is lacking (e.g., yeasts, fungi, *P. aeruginosa*, other highly resistant gram-negative bacilli, *Brucella* species, and probably *C. burnetii*).

S. aureus endocarditis The mortality rate for *S. aureus* PVE exceeds 50% with medical treatment but is reduced to 25% with surgical treatment. In patients with intracardiac complications associated with *S. aureus* PVE, surgical treatment reduces the mortality rate twentyfold. Surgical treatment should be considered for patients with *S. aureus* native aortic or mitral valve infection who have TTE-demonstrable vegetations and remain septic during the initial week of therapy. Isolated tricuspid valve endocarditis, even with persistent fever, rarely requires surgery.

Prevention of systemic emboli Death and persisting morbidity due to emboli are largely limited to patients suffering occlusion of cerebral or coronary arteries. Echocardiographic determination of vegetation size and anatomy, although predictive of patients at high risk of systemic emboli, does not identify those patients in whom the benefits of surgery to prevent

TABLE 20-6

TIMING OF CARDIAC SURGICAL INTERVENTION IN PATIENTS WITH ENDOCARDITIS

	INDICATION FOR SURGICAL INTERVENTION	
TIMING	**STRONG SUPPORTING EVIDENCE**	**CONFLICTING EVIDENCE, BUT MAJORITY OF OPINIONS FAVOR SURGERY**
Emergent (same day)	Acute aortic regurgitation plus preclosure of mitral valve Sinus of Valsalva abscess ruptured into right heart Rupture into pericardial sac	
Urgent (within 1–2 days)	Valve obstruction by vegetation Unstable (dehisced) prosthesis Acute aortic or mitral regurgitation with heart failure (New York Heart Association class III or IV) Septal perforation Perivalvular extension of infection with/without new electrocardiographic conduction system changes Lack of effective antibiotic therapy	Major embolus plus persisting large vegetation (>10 mm in diameter)
Elective (earlier usually preferred)	Progressive paravalvular prosthetic regurgitation Valve dysfunction plus persisting infection after ≥7–10 days of antimicrobial therapy Fungal (mold) endocarditis	Staphylococcal PVE Early PVE (≤2 months after valve surgery) Fungal endocarditis (*Candida* spp.) Antibiotic-resistant organisms

Note: PVE, prosthetic valve endocarditis.
Source: Adapted from L Olaison, G Pettersson: Infect Dis Clin North Am 16:453, 2002.

emboli clearly exceed the risks of the surgical procedure. Net benefits from surgery to prevent emboli are most likely when other surgical benefits can be achieved simultaneously—e.g., repair of a moderately dysfunctional valve or debridement of a paravalvular abscess. Only 3.5% of patients undergo surgery solely to prevent systemic emboli. Valve repair avoiding insertion of a prosthesis makes the benefit-to-risk ratio of surgery to address vegetations more favorable.

Timing of cardiac surgery In general, when indications for surgical treatment of infective endocarditis are identified, surgery should not be delayed simply to permit additional antibiotic therapy, since this course of action increases the risk of death (Table 20-6). After 14 days of recommended antibiotic therapy, excised valves are culture-negative in 99% and 50% of patients with streptococcal and *S. aureus* endocarditis, respectively. Recrudescent endocarditis on a new implanted prosthetic valve follows surgery for active NVE and PVE in 2% and 6–15% of patients, respectively. These frequencies do not justify the risk of adverse outcome with delayed surgery, particularly in patients with severe heart failure, valve dysfunction, and staphylococcal infections. Delay is justified only when infection is controlled and CHF is resolved with medical therapy.

Among patients who have experienced a neurologic complication of endocarditis, further neurologic deterioration can occur as a consequence of cardiac surgery. The risk of neurologic deterioration is related to the type of neurologic complication and the interval between the complication and surgery. Whenever feasible, cardiac surgery should be delayed for 2–3 weeks after a nonhemorrhagic embolic infarction and for 4 weeks after a cerebral hemorrhage. A ruptured mycotic aneurysm should be treated before cardiac surgery.

Antibiotic therapy after cardiac surgery Bacteria visible in Gram-stained preparations of excised valves do not necessarily indicate a failure of antibiotic therapy. Organisms have been detected on Gram's stain—or their DNA has been detected by PCR—in excised valves from 45% of patients who have successfully completed the recommended therapy for endocarditis. In only 7% of these patients are the organisms, most of which are unusual and antibiotic resistant, cultured from the valve. Despite the detection of organisms or their DNA, relapse of endocarditis after surgery is uncommon. Thus, when valve cultures are negative in uncomplicated NVE caused by susceptible organisms, the duration of preoperative plus postoperative treatment should equal the total duration of recommended therapy, with ~2 weeks of treatment administered after surgery. For endocarditis complicated by paravalvular abscess, partially treated PVE, or cases with culture-positive valves, a full course of therapy should be given postoperatively.

Extracardiac complications Splenic abscess develops in 3–5% of patients with endocarditis. Effective therapy requires either image-guided percutaneous

drainage or splenectomy. Mycotic aneurysms occur in 2–15% of endocarditis patients; one-half of these cases involve the cerebral arteries and present as headaches, focal neurologic symptoms, or hemorrhage. Cerebral aneurysms should be monitored by angiography. Some will resolve with effective antimicrobial therapy, but those that persist, enlarge, or leak should be treated surgically if possible. Extracerebral aneurysms present as local pain, a mass, local ischemia, or bleeding; these aneurysms are treated by resection.

OUTCOME

Older age, severe comorbid conditions and diabetes, delayed diagnosis, involvement of prosthetic valves or the aortic valve, an invasive (*S. aureus*) or antibiotic-resistant (*P. aeruginosa*, yeast) pathogen, intracardiac and major neurologic complications, and an association with health care adversely affect outcome. Death and poor outcome often are related not to failure of antibiotic therapy but rather to the interactions of comorbidities and endocarditis-related end-organ complications. Overall survival rates for patients with NVE caused by viridans streptococci, HACEK organisms, or enterococci (susceptible to synergistic therapy) are 85–90%. For *S. aureus* NVE in patients who do not inject drugs, survival rates are 55–70%, whereas 85–90% of injection drug users survive this infection. PVE beginning within 2 months of valve replacement results in mortality rates of 40–50%, whereas rates are only 10–20% in later-onset cases.

PREVENTION

In the past, in an effort to prevent endocarditis (long a goal in clinical practice), expert committees have supported systemic antibiotic administration prior to many bacteremia-inducing procedures. In the absence of human trials, a reappraisal of the indirect evidence on antibiotic prophylaxis for endocarditis by the American Heart Association has culminated in guidelines that reverse prior recommendations and restrict prophylactic antibiotic use. At best, the benefit of antibiotic prophylaxis is minimal. Most endocarditis cases do not follow a procedure. In case-control studies, dental treatments—widely considered as predisposing to endocarditis—occur no more frequently before endocarditis than in matched controls. Furthermore, the frequency and magnitude of bacteremia associated with dental procedures and routine daily activities (e.g., tooth brushing and flossing) are similar. Because dental procedures are infrequent, exposure of cardiac structures to bacteremic oral-cavity organisms is notably greater from routine daily activities than from dental care. The relation of gastrointestinal and genitourinary procedures to subsequent endocarditis is more tenuous than that of dental procedures. In addition, cost-effectiveness and cost-benefit estimates suggest that antibiotic prophylaxis represents a poor use of resources.

Studies in animal models suggest that antibiotic prophylaxis may be effective. Thus, it is possible that rare cases of endocarditis are prevented. Weighing the potential benefits, potential adverse events, and costs associated with antibiotic prophylaxis, the American Heart Association and the European Society of Cardiology now recommend prophylactic antibiotics **(Table 20-7)** only for those patients at highest risk for severe morbidity or death from endocarditis **(Table 20-8)**. Maintaining good dental hygiene is essential. Prophylaxis is recommended only when there is manipulation of gingival tissue or the periapical region of the teeth or perforation

TABLE 20-7

ANTIBIOTIC REGIMENS FOR PROPHYLAXIS OF ENDOCARDITIS IN ADULTS WITH HIGH-RISK CARDIAC LESIONS[a,b]

A. Standard oral regimen
   1. Amoxicillin: 2 g PO 1 h before procedure
B. Inability to take oral medication
   1. Ampicillin: 2 g IV or IM within 1 h before procedure
C. Penicillin allergy
   1. Clarithromycin or azithromycin: 500 mg PO 1 h before procedure
   2. Cephalexin[c]: 2 g PO 1 h before procedure
   3. Clindamycin: 600 mg PO 1 h before procedure
D. Penicillin allergy, inability to take oral medication
   1. Cefazolin[c] or ceftriaxone[c]: 1 g IV or IM 30 min before procedure
   2. Clindamycin: 600 mg IV or IM 1 h before procedure

[a]Dosing for children: for amoxicillin, ampicillin, cephalexin, or cefadroxil, use 50 mg/kg PO; cefazolin, 25 mg/kg IV; clindamycin, 20 mg/kg PO, 25 mg/kg IV; clarithromycin, 15 mg/kg PO; and vancomycin, 20 mg/kg IV.
[b]For high-risk lesions, see Table 20-8. Prophylaxis is not advised for other lesions.
[c]Do not use cephalosporins in patients with immediate hypersensitivity (urticaria, angioedema, anaphylaxis) to penicillin.
Source: W Wilson et al: Circulation 116:1736, 2007, published online 4/19/2007.

TABLE 20-8

HIGH-RISK CARDIAC LESIONS FOR WHICH ENDOCARDITIS PROPHYLAXIS IS ADVISED BEFORE DENTAL PROCEDURES

Prosthetic heart valves
Prior endocarditis
Unrepaired cyanotic congenital heart disease, including palliative shunts or conduits
Completely repaired congenital heart defects during the 6 months after repair
Incompletely repaired congenital heart disease with residual defects adjacent to prosthetic material
Valvulopathy developing after cardiac transplantation

Source: W Wilson et al: Circulation 116:1736, 2007, published online 4/19/2007.

of the oral mucosa (including surgery on the respiratory tract). Prophylaxis is not advised for patients undergoing gastrointestinal or genitourinary tract procedures. High-risk patients should be treated before or when they undergo procedures on an infected genitourinary tract or on infected skin and soft tissue. The British Society for Antimicrobial Chemotherapy continues to recommend prophylaxis for at-risk patients undergoing selected gastrointestinal and genitourinary procedures. In contrast, the National Institute for Health and Clinical Excellence in the United Kingdom found no convincing evidence that antibiotic prophylaxis was cost effective and advised discontinuation of the practice (see *www.nice.org.uk/guidance/CG64*).

CHAPTER 21

PERICARDIAL DISEASE

Eugene Braunwald

NORMAL FUNCTIONS OF THE PERICARDIUM

The normal pericardium is a double-layered sac; the visceral pericardium is a serous membrane that is separated by a small quantity (15–50 mL) of fluid, an ultrafiltrate of plasma, from the fibrous parietal pericardium. The normal pericardium, by exerting a restraining force, prevents sudden dilation of the cardiac chambers, especially the right atrium and ventricle, during exercise and with hypervolemia. It also restricts the anatomic position of the heart, minimizes friction between the heart and surrounding structures, prevents displacement of the heart and kinking of the great vessels, and probably retards the spread of infections from the lungs and pleural cavities to the heart. Nevertheless, total absence of the pericardium, either congenital or after surgery, does not produce obvious clinical disease. In partial left pericardial defects, the main pulmonary artery and left atrium may bulge through the defect; very rarely, herniation and subsequent strangulation of the left atrium may cause sudden death.

ACUTE PERICARDITIS

Acute pericarditis, by far the most common pathologic process involving the pericardium, may be classified both clinically and etiologically **(Table 21-1)**. There are four principal diagnostic features:

1. *Chest pain* is an important but not invariable symptom in various forms of acute pericarditis; it is usually present in the acute infectious types and in many of the forms presumed to be related to hypersensitivity or autoimmunity. Pain is often absent in slowly developing tuberculous, postirradiation, neoplastic, and uremic pericarditis. The pain of acute pericarditis is often severe, retrosternal and left precordial, and referred to the neck, arms, or left shoulder. Often the pain is pleuritic, consequent to accompanying pleural inflammation (i.e., sharp and aggravated by inspiration and coughing), but sometimes it is a steady, constricting pain that radiates into either arm or both arms and resembles that of myocardial ischemia; therefore, confusion with acute myocardial infarction (AMI) is common. Characteristically, however, pericardial pain may be relieved by sitting up and leaning forward and is intensified by lying supine. The differentiation of AMI from acute pericarditis becomes perplexing when, with acute pericarditis, serum biomarkers of myocardial damage such as creatine kinase and troponin rise, presumably because of concomitant involvement of the epicardium in the inflammatory process (an epi-myocarditis) with resulting myocyte necrosis. However, these elevations, if they occur, are quite modest given the extensive electrocardiographic ST-segment elevation in pericarditis. This dissociation is useful in differentiating between these conditions.
2. A *pericardial friction rub* is audible in about 85% of these patients, may have up to three components per cardiac cycle, is high-pitched, and is described as rasping, scratching, or grating; it can be elicited sometimes when the diaphragm of the stethoscope is applied

TABLE 21-1

CLASSIFICATION OF PERICARDITIS

Clinical Classification

I. Acute pericarditis (<6 weeks)
   A. Fibrinous
   B. Effusive (serous or sanguineous)
II. Subacute pericarditis (6 weeks to 6 months)
   A. Effusive-constrictive
   B. Constrictive
III. Chronic pericarditis (>6 months)
   A. Constrictive
   B. Effusive
   C. Adhesive (nonconstrictive)

Etiologic Classification

I. Infectious pericarditis
   A. Viral (coxsackieviruses A and B, echovirus, mumps virus, adenovirus, hepatitis virus, HIV)
   B. Pyogenic (pneumococcus, *Streptococcus, Staphylococcus, Neisseria, Legionella*)
   C. Tuberculous
   D. Fungal (histoplasmosis, coccidioidomycosis, candidiasis, blastomycosis)
   E. Other infections (syphilitic, protozoal, parasitic)
II. Noninfectious pericarditis
   A. Acute myocardial infarction
   B. Uremia
   C. Neoplasia
      1. Primary tumors (benign or malignant, mesothelioma)
      2. Tumors metastatic to pericardium (lung and breast cancer, lymphoma, leukemia)
   D. Myxedema
   E. Cholesterol
   F. Chylopericardium
   G. Trauma
      1. Penetrating chest wall
      2. Nonpenetrating
   H. Aortic dissection (with leakage into pericardial sac)
   I. Postirradiation
   J. Familial Mediterranean fever
   K. Familial pericarditis
      1. Mulibrey nanism[a]
   L. Acute idiopathic
   M. Whipple's disease
   N. Sarcoidosis
III. Pericarditis presumably related to hypersensitivity or autoimmunity
   A. Rheumatic fever
   B. Collagen vascular disease (systemic lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis, scleroderma, acute rheumatic fever, granulomatosis with polyangiitis
   C. Drug-induced (e.g., procainamide, hydralazine, phenytoin, isoniazide, minoxidil, anticoagulants, methysergide)
   D. Post-cardiac injury
      1. Postmyocardial infarction (Dressler's syndrome)
      2. Postpericardiotomy
      3. Posttraumatic

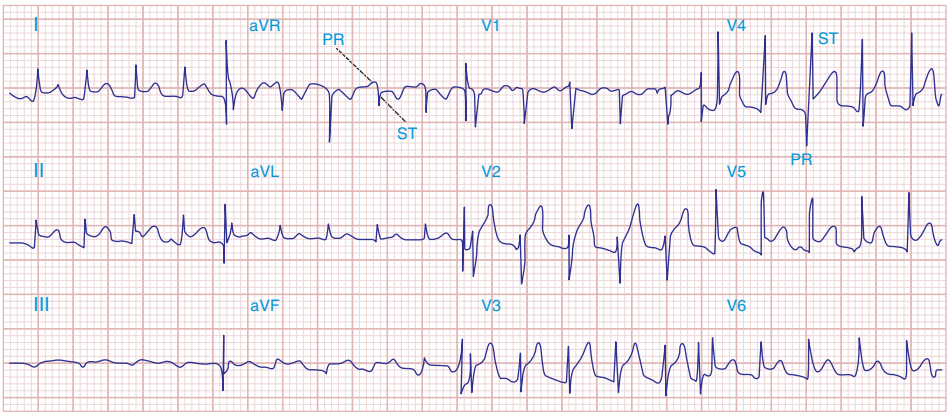
[a]An autosomal recessive syndrome characterized by growth failure, muscle hypotonia, hepatomegaly, ocular changes, enlarged cerebral ventricles, mental retardation, ventricular hypertrophy, and chronic constrictive pericarditis.

firmly to the chest wall at the left lower sternal border. It is heard most frequently at end expiration with the patient upright and leaning forward. The rub is often inconstant, and the loud to-and-fro leathery sound may disappear within a few hours, possibly to reappear on the next day. A pericardial rub is heard throughout the respiratory cycle, whereas a pleural rub disappears when respiration is suspended.

3. The *electrocardiogram* (ECG) in acute pericarditis without massive effusion usually displays changes secondary to acute subepicardial inflammation **(Fig. 21-1)**. It typically evolves through four stages. In stage 1, there is widespread elevation of the ST segments, often with upward concavity, involving two or three standard limb leads and V_2 to V_6, with reciprocal depressions only in aVR and sometimes V_1, as well as depression of the PR segment below the TP segment reflecting atrial involvement. Usually there are no significant changes in QRS complexes. In stage 2, after several days, the ST segments return to normal, and only then, or even later, do the T waves become inverted (stage 3). Ultimately, weeks or months after the onset of acute pericarditis, the ECG returns to normal in stage 4. In contrast, in AMI, ST elevations are convex, and reciprocal depression is usually more prominent; QRS changes occur, particularly the development of Q waves, as well as notching and loss of R-wave amplitude, and T-wave inversions are usually seen within hours *before* the ST segments have become isoelectric. Sequential ECGs are useful in distinguishing acute pericarditis from AMI. In the latter, elevated ST segments return to normal within hours.

   Early repolarization is a normal variant and may also be associated with widespread ST-segment elevation, most prominent in left precordial leads. However, in this condition the T waves are usually tall and the ST/T ratio is <0.25; importantly, this ratio is higher in acute pericarditis.

4. *Pericardial effusion* is usually associated with pain and/or the ECG changes mentioned above, as well as with an enlargement of the cardiac silhouette. Pericardial effusion is especially important clinically when it develops within a relatively short time as it may lead to cardiac tamponade (see later in chapter). Differentiation from cardiac enlargement may be difficult on physical examination, but heart sounds may be fainter with pericardial effusion. The friction rub may disappear, and the apex impulse may vanish, but sometimes it remains palpable, albeit medial to the left border of cardiac dullness. The base of the left lung may be compressed by pericardial fluid, producing *Ewart's sign*, a patch of dullness and increased fremitus (and egophony) beneath the angle of the left scapula. The chest roentgenogram may show a "water bottle" configuration of the cardiac silhouette **(Fig. 21-2)** but may be normal.



1.

FIGURE 21-1
Acute pericarditis often produces diffuse ST-segment elevations (in this case in leads I, II, aVF, and V_2 to V_6) due to a ventricular current of injury. Note also the characteristic PR-segment deviation (opposite in polarity to the ST segment) due to a concomitant atrial injury current.

Diagnosis

Echocardiography is the most widely used imaging technique since it is sensitive, specific, simple, and noninvasive; may be performed at the bedside; and can identify accompanying cardiac tamponade (see next) **(Fig. 21-3)**. The presence of pericardial fluid is recorded by two-dimensional transthoracic echocardiography as a relatively echo-free space between the posterior pericardium and left ventricular epicardium in patients with small effusions and as a space between the anterior right ventricle and the parietal pericardium just beneath the anterior chest wall in those with larger effusions. In the latter, the heart may swing freely within the pericardial sac. When severe, the extent of this motion alternates and may be associated with electrical alternans. Echocardiography allows localization and estimation of the quantity of pericardial fluid.

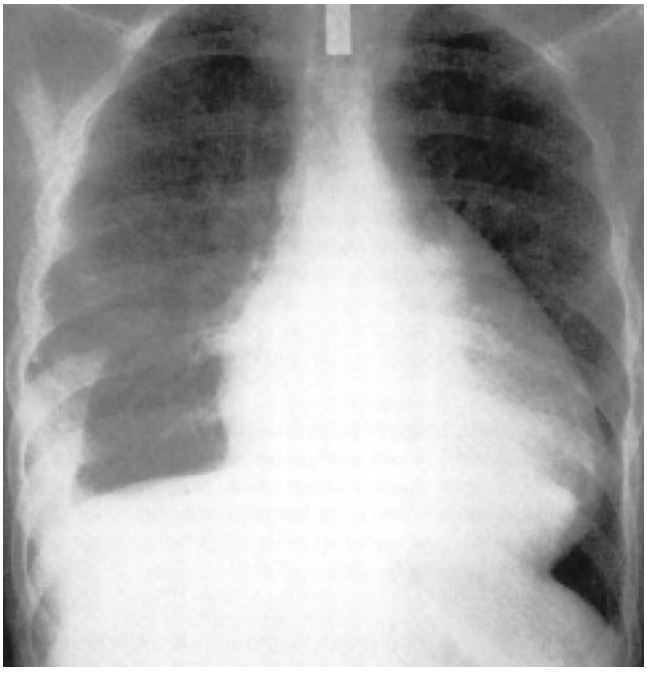


FIGURE 21-2
Chest radiogram from a patient with a pericardial effusion showing typical "water bottle" heart. There is also a right pleural effusion. (*From SS Kabbani, M LeWinter, in MH Crawford et al [eds]: Cardiology. London, Mosby, 2001.*)

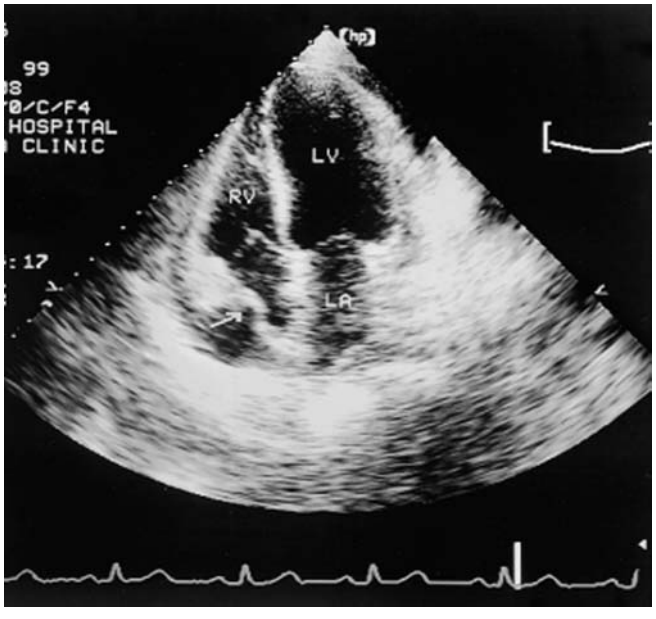


FIGURE 21-3
Apical four-chamber echocardiogram recorded in a patient with a moderate pericardial effusion and evidence of hemodynamic compromise. The frame is recorded in early ventricular systole, immediately after atrial contraction. Note that the right atrial wall is indented inward and its curvature is frankly reversed (*arrow*), implying elevated intrapericardial pressure above right atrial pressure. LA, left atrium; LV, left ventricle; RV, right ventricle. (*From WF Armstrong: Echocardiography, in DP Zipes et al [eds]: Braunwald's Heart Disease, 7th ed. Philadelphia, Elsevier, 2005.*)

The diagnosis of pericardial fluid or thickening may be confirmed by computed tomography (CT) or magnetic resonance imaging (MRI) **(Fig. 21-4)**. These techniques may be superior to echocardiography in detecting loculated pericardial effusions, pericardial thickening, and the presence of pericardial masses.

CARDIAC TAMPONADE

The accumulation of fluid in the pericardial space in a quantity sufficient to cause serious obstruction to the inflow of blood to the ventricles results in cardiac tamponade. This complication may be fatal if it is not recognized and treated promptly. The three most common causes of tamponade are neoplastic disease, idiopathic pericarditis, and renal failure. Tamponade may also result from bleeding into the pericardial space after cardiac operations, trauma, and treatment of patients with acute pericarditis with anticoagulants.

The three principal features of tamponade (*Beck's triad*) are hypotension, soft or absent heart sounds, and jugular venous distention with a prominent *x* descent but an absent *y* descent. There are both limitation of ventricular filling and reduction of cardiac output. The quantity of fluid necessary to produce this critical state may be as small as 200 mL when the fluid develops rapidly or >2000 mL in slowly developing effusions when the pericardium has had the opportunity to stretch and adapt to an increasing volume. Tamponade may also develop more slowly, and in these circumstances the clinical manifestations may resemble those of heart failure, including dyspnea, orthopnea, and hepatic engorgement. A high index of suspicion for cardiac tamponade is required since in many instances no obvious cause for pericardial disease is apparent, and it should be considered in any patient with otherwise unexplained enlargement of the cardiac silhouette, hypotension, and elevation of jugular venous pressure. There may be reduction in amplitude of the QRS complexes, and *electrical alternans* of the P, QRS, or T waves should raise the suspicion of cardiac tamponade.

Table 21-2 lists the features that distinguish acute cardiac tamponade from constrictive pericarditis.

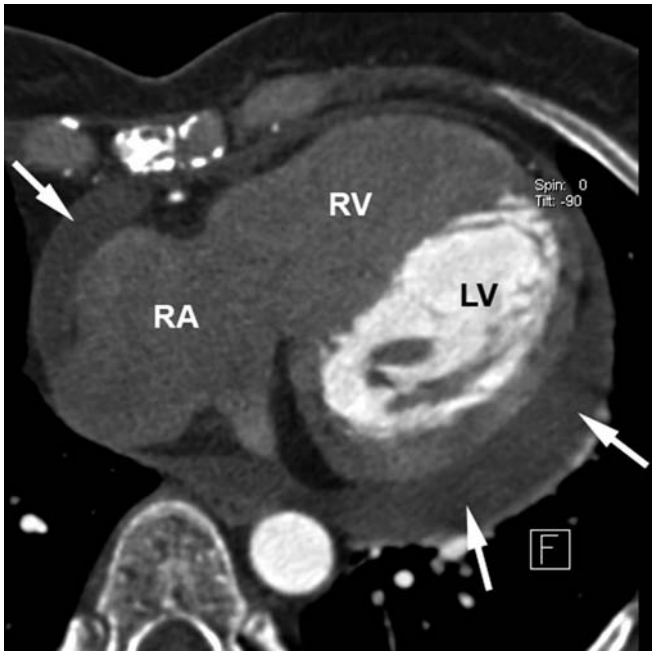


FIGURE 21-4
Chronic pericardial effusion in a 54-year-old female patient with Hodgkin's disease seen in contrast-enhanced 64-slice CT. The arrows point at the pericardial effusion (LV, left ventricle; RV, right ventricle; RA, right atrium). Due to the timing of the scan relative to contrast injection, only the blood in the left ventricle is contrast-enhanced—hence, the low attenuation in the right-sided chambers. (*From Achenbach S, Daniel WG: Computed Tomography of the Heart, in P Libby et al [eds]: Braunwald's Heart Disease, 8th ed. Philadelphia, Elsevier, 2008.*)

Paradoxical pulse

This important clue to the presence of cardiac tamponade consists of a greater than normal (10 mmHg) inspiratory decline in systolic arterial pressure. When severe, it may be detected by palpating weakness or disappearance of the arterial pulse during inspiration, but usually sphygmomanometric measurement of systolic pressure during slow respiration is required.

Since both ventricles share a tight incompressible covering, i.e., the pericardial sac, the inspiratory enlargement of the right ventricle in cardiac tamponade compresses and reduces left ventricular volume; leftward bulging of the interventricular septum further reduces the left ventricular cavity as the right ventricle enlarges during inspiration. Thus, in cardiac tamponade the normal inspiratory augmentation of right ventricular volume causes an exaggerated reciprocal reduction in left ventricular volume. Also, respiratory distress increases the fluctuations in intrathoracic pressure, which exaggerates the mechanism just described. Right ventricular infarction may resemble cardiac tamponade with hypotension, elevated jugular venous pressure, an absent *y* descent in the jugular venous pulse, and, occasionally, pulsus paradoxus. The differences between these two conditions are shown in Table 21-2.

Paradoxical pulse occurs not only in cardiac tamponade but also in approximately one-third of patients with constrictive pericarditis (see below). This physical finding is not pathognomonic of pericardial disease because it may be observed in some cases of hypovolemic shock, acute and chronic obstructive airway disease, and pulmonary embolus.

Low-pressure tamponade refers to mild tamponade in which the intrapericardial pressure is increased from its slightly subatmospheric levels to +5 to +10 mmHg; in some instances, hypovolemia coexists. As a consequence, the central venous pressure is normal or only slightly elevated, whereas arterial pressure is unaffected and there is no paradoxical pulse. These patients are asymptomatic or complain of mild weakness and dyspnea. The diagnosis is aided by echocardiography, and both hemodynamic and clinical manifestations improve after pericardiocentesis.

TABLE 21-2

FEATURES THAT DISTINGUISH CARDIAC TAMPONADE FROM CONSTRICTIVE PERICARDITIS AND SIMILAR CLINICAL DISORDERS

CHARACTERISTIC	TAMPONADE	CONSTRICTIVE PERICARDITIS	RESTRICTIVE CARDIOMYOPATHY	RVMI
Clinical				
Pulsus paradoxus	Common	Usually absent	Rare	Rare
Jugular veins				
Prominent *y* descent	Absent	Usually present	Rare	Rare
Prominent *x* descent	Present	Usually present	Present	Rare
Kussmaul's sign	Absent	Present	Present	Present
Third heart sound	Absent	Absent	Rare	May be present
Pericardial knock	Absent	Often present	Absent	Absent
Electrocardiography				
Low ECG voltage	May be present	May be present	May be present	Absent
Electrical alternans	May be present	Absent	Absent	Absent
Echocardiography				
Thickened pericardium	Absent	Present	Absent	Absent
Pericardial calcification	Absent	Often present	Absent	Absent
Pericardial effusion	Present	Absent	Absent	Absent
RV size	Usually small	Usually normal	Usually normal	Enlarged
Myocardial thickness	Normal	Normal	Usually increased	Normal
Right atrial collapse and RVDC	Present	Absent	Absent	Absent
Increased early filling, ↑ mitral flow velocity	Absent	Present	Present	May be present
Exaggerated respiratory variation in flow velocity	Present	Present	Absent	Absent
CT/MRI				
Thickened/calcific pericardium	Absent	Present	Absent	Absent
Cardiac catheterization				
Equalization of diastolic pressures	Usually present	Usually present	Usually absent	Absent or present
Cardiac biopsy helpful?	No	No	Sometimes	No

Abbreviations: ECG, electrocardiograph; RV, right ventricle; RVDC, right ventricular diastolic collapse; RVMI, right ventricular myocardial infarction.
Source: From GM Brockington et al: Cardiol Clin 8:645, 1990, with permission.

Diagnosis

Since immediate treatment of cardiac tamponade may be lifesaving, prompt measures to establish the diagnosis by echocardiography should be undertaken (Fig. 21-3). When pericardial effusion causes tamponade, Doppler ultrasound shows that tricuspid and pulmonic valve flow velocities increase markedly during inspiration, whereas pulmonic vein, mitral, and aortic flow velocities diminish. Often the right ventricular cavity is reduced in diameter, and there is late diastolic inward motion (collapse) of the right ventricular free wall and the right atrium. Transesophageal echocardiography may be necessary to diagnose a loculated or hemorrhagic effusion responsible for cardiac tamponade.

TREATMENT Cardiac Tamponade

Patients with acute pericarditis should be observed frequently for the development of an effusion; if a large effusion is present, the patient should be hospitalized and pericardiocentesis carried out or the patient should be watched closely for signs of tamponade. Arterial and venous pressures and heart rate should be monitored or followed carefully, and serial echocardiograms obtained.

PERICARDIOCENTESIS If manifestations of tamponade appear, echocardiographically or fluoroscopically guided pericardiocentesis using an apical, parasternal, or, most commonly, subxiphoid approach must be carried out at once as reduction of the elevated intrapericardial pressure may be lifesaving. Intravenous saline may be administered as the patient is being readied for the procedure, but the pericardiocentesis must not be delayed. If possible, intrapericardial pressure should be measured before fluid is withdrawn, and the pericardial cavity should be drained as completely as possible. A small, multiholed catheter advanced over the needle inserted into the pericardial cavity may be left in place to allow draining of the pericardial space if fluid reaccumulates. Surgical drainage through a limited (subxiphoid) thoracotomy may be required in recurrent tamponade, when it

is necessary to remove loculated effusions, and/or when it is necessary to obtain tissue for diagnosis.

Pericardial fluid obtained from an effusion often has the physical characteristics of an exudate. Bloody fluid is most commonly due to neoplasm in the United States and tuberculosis in developing nations but may also be found in the effusion of acute rheumatic fever, postcardiac injury, and post-myocardial infarction, as well as in the pericarditis associated with renal failure or dialysis. Transudative pericardial effusions may occur in heart failure.

The pericardial fluid should be analyzed for red and white blood cells, and cytologic studies for cancer, microscopic studies, and cultures should be obtained. The presence of DNA of *Mycobacterium tuberculosis* determined by polymerase chain reaction or an elevated adenosine deaminase activity (>30 U/L) strongly supports the diagnosis of tuberculous pericarditis (Chap. 70).

VIRAL OR IDIOPATHIC ACUTE PERICARDITIS

In many instances, acute pericarditis occurs in association with illnesses of known or presumed viral origin and probably is caused by the same agent. Commonly, there is an antecedent infection of the respiratory tract, and viral isolation and serologic studies are negative. In some cases, coxsackievirus A or B virus, influenza virus, echovirus, mumps virus, herpes simplex virus, varicella-zoster virus, adenovirus, cytomegalovirus, Epstein-Barr virus, or HIV has been isolated from pericardial fluid and/or appropriate elevations in viral antibody titers have been noted. Pericardial effusion is a common cardiac manifestation of HIV; it is usually secondary to infection (often mycobacterial) or neoplasm, most frequently lymphoma. Most frequently, a viral causation cannot be established; the term *idiopathic acute pericarditis* is then appropriate. Viral or idiopathic acute pericarditis occurs at all ages but is more common in young adults and is often associated with pleural effusions and pneumonitis. The almost simultaneous development of fever and precordial pain, often 10 to 12 days after a presumed viral illness, constitutes an important feature in the differentiation of acute pericarditis from AMI, in which chest pain precedes fever. The constitutional symptoms are usually mild to moderate, and a pericardial friction rub is often audible. The disease ordinarily runs its course in a few days to 4 weeks. The ST-segment alterations in the ECG usually disappear after 1 or more weeks, but the abnormal T waves may persist for several years and be a source of confusion in persons without a clear history of pericarditis.

Pleuritis and pneumonitis frequently accompany pericarditis. Accumulation of some pericardial fluid is common, and both tamponade and constrictive pericarditis are possible complications. Recurrent (relapsing) pericarditis occurs in about one-fourth of patients with acute idiopathic pericarditis. In a smaller number, there are multiple recurrences.

TREATMENT Idiopathic Acute Pericarditis

In acute idiopathic pericarditis there is no specific therapy, but bed rest and anti-inflammatory treatment with aspirin (2–4 g/d) may be given. If this is ineffective, one of the nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen (400–600 mg tid), indomethacin (25–50 mg tid), or colchicine (0.6 mg bid), is often effective. Glucocorticoids (e.g., prednisone, 40–80 mg daily) usually suppress the clinical manifestations of the acute illness and may be useful in patients in whom purulent bacterial pericarditis has been excluded and in patients with pericarditis secondary to connective tissue disorders and renal failure (see later). Anticoagulants should be avoided since their use could cause bleeding into the pericardial cavity and tamponade.

After the patient has been asymptomatic and afebrile for about a week, the dose of the NSAID may be tapered gradually. Colchicine may prevent recurrences, but pericardiectomy may be necessary to terminate the illness when recurrences are multiple, frequent, and disabling; continue beyond 2 years; and are not controlled by glucocorticoids.

Postcardiac injury syndrome

Acute pericarditis may appear in a variety of circumstances that have one common feature: previous injury to the myocardium with blood in the pericardial cavity. The syndrome may develop after a cardiac operation (postpericardiotomy syndrome), after blunt or penetrating cardiac trauma, or after perforation of the heart with a catheter. Rarely, it follows AMI.

The clinical picture mimics acute viral or idiopathic pericarditis. The principal symptom is the pain of acute pericarditis, which usually develops 1 to 4 weeks after the cardiac injury (1 to 3 days after AMI) but sometimes appears only after an interval of months. Recurrences are common and may occur up to 2 years or more after the injury. Pericarditis, fever with temperature up to 39°C (102.2°F), pleuritis, and pneumonitis are the outstanding features, and the bout of illness usually subsides in 1 or 2 weeks. The pericarditis may be of the fibrinous variety, or it may be a pericardial effusion, which is often serosanguineous but rarely causes tamponade. Leukocytosis, an increased sedimentation rate, and ECG changes typical of acute pericarditis may also occur.

This syndrome is probably the result of a hypersensitivity reaction to antigen that originates from injured myocardial tissue and/or pericardium. Circulating myocardial antisarcolemmal and antifibrillar autoantibodies occur frequently, but their precise role in the development of this syndrome has not been defined. Viral infection may also play an etiologic role, since antiviral antibodies are often elevated in patients who develop this syndrome after cardiac surgery.

Often no treatment is necessary aside from aspirin and analgesics. When the illness is followed by a series of disabling recurrences, therapy with an NSAID, colchicine, or a glucocorticoid is usually effective.

Differential diagnosis

Since there is no specific test for *acute idiopathic pericarditis*, the diagnosis is one of exclusion. Consequently, all other disorders that may be associated with acute fibrinous pericarditis must be considered. A common diagnostic error is mistaking acute viral or idiopathic pericarditis for AMI and vice versa. When acute fibrinous pericarditis is associated with AMI, it is characterized by fever, pain, and a friction rub in the first 4 days after the development of the infarct. ECG abnormalities (such as the appearance of Q waves, brief ST-segment elevations with reciprocal changes, and earlier T-wave changes in AMI) and the extent of the elevations of myocardial enzymes are helpful in differentiating pericarditis from AMI.

Pericarditis secondary to postcardiac injury is differentiated from acute idiopathic pericarditis chiefly by timing. If it occurs within a few days or weeks of an AMI, a chest blow, a cardiac perforation, or a cardiac operation, it may be justified to conclude that the two are probably related.

It is important to distinguish *pericarditis due to collagen vascular disease* from acute idiopathic pericarditis. Most important in the differential diagnosis is the pericarditis due to systemic lupus erythematosus (SLE) or drug-induced (procainamide or hydralazine) lupus. When pericarditis occurs in the absence of any obvious underlying disorder, the diagnosis of SLE may be suggested by a rise in the titer of antinuclear antibodies. Acute pericarditis is an occasional complication of *rheumatoid arthritis*, *scleroderma*, and *polyarteritis nodosa*, and other evidence of these diseases is usually obvious. Asymptomatic pericardial effusion is also common in these disorders. The pericarditis of *acute rheumatic fever* is generally associated with evidence of severe pancarditis and with cardiac murmurs (Chap. 41).

Pyogenic (purulent) pericarditis is usually secondary to cardiothoracic operations, by extension of infection from the lungs or pleural cavities, from rupture of the esophagus into the pericardial sac, or from rupture of a ring abscess in a patient with infective endocarditis, or it can occur if septicemia complicates aseptic pericarditis. It is usually accompanied by fever, chills, septicemia, and evidence of infection elsewhere and generally has a poor prognosis. The diagnosis is made by examination of the pericardial fluid. Acute pericarditis may also complicate the viral, pyogenic, mycobacterial, and fungal infections that occur with HIV infection.

Pericarditis of renal failure occurs in up to one-third of patients with chronic uremia *(uremic pericarditis)*, is also seen in patients undergoing chronic dialysis with normal levels of blood urea and creatinine, and is termed *dialysis-associated pericarditis*. These two forms of pericarditis may be fibrinous and are generally associated with an effusion that may be sanguineous. A pericardial friction rub is common, but pain is usually absent or mild. Treatment with an NSAID and intensification of dialysis are usually adequate. Occasionally, tamponade occurs and pericardiocentesis is required. When the pericarditis of renal failure is recurrent or persistent, a pericardial window should be created or pericardiectomy may be necessary.

Pericarditis due to *neoplastic diseases* results from extension or invasion of metastatic tumors (most commonly carcinoma of the lung and breast, malignant melanoma, lymphoma, and leukemia) to the pericardium; pain, atrial arrhythmias, and tamponade are complications that occur occasionally. Diagnosis is made by pericardial fluid cytology or pericardial biopsy. *Mediastinal irradiation* for neoplasm may cause acute pericarditis and/or chronic constrictive pericarditis. Unusual causes of acute pericarditis include syphilis, fungal infection (histoplasmosis, blastomycosis, aspergillosis, and candidiasis), and parasitic infestation (amebiasis, toxoplasmosis, echinococcosis, trichinosis).

CHRONIC PERICARDIAL EFFUSIONS

Chronic pericardial effusions are sometimes encountered in patients without an antecedent history of acute pericarditis. They may cause few symptoms per se, and their presence may be detected by finding an enlarged cardiac silhouette on chest roentgenogram. Tuberculosis is a common cause (Chap. 70).

Other causes

Myxedema may be responsible for chronic pericardial effusion that is sometimes massive but rarely, if ever, causes cardiac tamponade. The cardiac silhouette is markedly enlarged, and an echocardiogram distinguishes cardiomegaly from pericardial effusion. The diagnosis of myxedema can be confirmed by tests for thyroid function. Myxedematous pericardial effusion responds to thyroid hormone replacement.

Neoplasms, systemic lupus erythematosus (SLE), rheumatoid arthritis, mycotic infections, radiation therapy to the chest, pyogenic infections, and chylopericardium may also cause chronic pericardial effusion and should be considered and specifically sought in such patients.

Aspiration and analysis of the pericardial fluid are often helpful in diagnosis. Grossly sanguineous pericardial fluid results most commonly from a neoplasm, tuberculosis, renal failure, or slow leakage from an aortic aneurysm. Pericardiocentesis may resolve large effusions, but pericardiectomy may be required with recurrence. Intrapericardial instillation of sclerosing agents or antineoplastic agents may be used to prevent reaccumulation of fluid.

CHRONIC CONSTRICTIVE PERICARDITIS

This disorder results when the healing of an acute fibrinous or serofibrinous pericarditis or the resorption of a chronic pericardial effusion is followed by obliteration of the pericardial cavity with the formation of granulation tissue. The latter gradually contracts and forms a firm scar, which may be calcified, encasing the

heart and interfering with filling of the ventricles. In developing nations where the condition is prevalent, a high percentage of cases are of tuberculous origin, but this is now an uncommon cause in North America. Chronic constrictive pericarditis may follow acute or relapsing viral or idiopathic pericarditis, trauma with organized blood clot, cardiac surgery of any type, mediastinal irradiation, purulent infection, histoplasmosis, neoplastic disease (especially breast cancer, lung cancer, and lymphoma), rheumatoid arthritis, SLE, and chronic renal failure with uremia treated by chronic dialysis. In many patients the cause of the pericardial disease is undetermined, and in them an asymptomatic or forgotten bout of viral pericarditis, acute or idiopathic, may have been the inciting event.

The basic physiologic abnormality in patients with chronic constrictive pericarditis is the inability of the ventricles to fill because of the limitations imposed by the rigid, thickened pericardium. In constrictive pericarditis, ventricular filling is unimpeded during early diastole but is reduced abruptly when the elastic limit of the pericardium is reached, whereas in cardiac tamponade, ventricular filling is impeded throughout diastole. In both conditions, ventricular end-diastolic and stroke volumes are reduced and the end-diastolic pressures in both ventricles and the mean pressures in the atria, pulmonary veins, and systemic veins are all elevated to similar levels (i.e., within 5 mmHg of one another). Despite these hemodynamic changes, myocardial function may be normal or only slightly impaired in chronic constrictive pericarditis. However, the fibrotic process may extend into the myocardium and cause myocardial scarring and atrophy, and venous congestion may then be due to the combined effects of the pericardial and myocardial lesions.

In constrictive pericarditis, the right and left atrial pressure pulses display an M-shaped contour, with prominent *x* and *y* descents. The *y* descent, which is absent or diminished in cardiac tamponade, is the most prominent deflection in constrictive pericarditis; it reflects rapid early filling of the ventricles. The *y* descent is interrupted by a rapid rise in atrial pressure during early diastole, when ventricular filling is impeded by the constricting pericardium. These characteristic changes are transmitted to the jugular veins, where they may be recognized by inspection. In constrictive pericarditis, the ventricular pressure pulses in both ventricles exhibit characteristic "square root" signs during diastole. These hemodynamic changes, although characteristic, are not pathognomonic of constrictive pericarditis and may also be observed in cardiomyopathies characterized by restriction of ventricular filling (Table 21-2).

Clinical and laboratory findings

Weakness, fatigue, weight gain, increased abdominal girth, abdominal discomfort, a protuberant abdomen, and edema are common. The patient often appears chronically ill, and in advanced cases there are anasarca, skeletal muscle wasting, and cachexia. Exertional dyspnea is common, and orthopnea may occur, although it is usually not severe. Acute left ventricular failure (acute pulmonary edema) is very uncommon. The cervical veins are distended and may remain so even after intensive diuretic treatment, and venous pressure may fail to decline during inspiration (*Kussmaul's sign*). The latter is common in chronic pericarditis but may also occur in tricuspid stenosis, right ventricular infarction, and restrictive cardiomyopathy.

The pulse pressure is normal or reduced. In about one-third of cases, a paradoxical pulse can be detected. Congestive hepatomegaly is pronounced and may impair hepatic function and cause jaundice; ascites is common and is usually more prominent than dependent edema. The apical pulse is reduced and may retract in systole (*Broadbent's sign*). The heart sounds may be distant; an early third heart sound (i.e., a pericardial knock, occurring at the cardiac apex 0.09–0.12 s after aortic valve closure) is often conspicuous; it occurs with the abrupt cessation of ventricular filling. A systolic murmur of tricuspid regurgitation may be present.

The *ECG* frequently displays low voltage of the QRS complexes and diffuse flattening or inversion of the T waves. Atrial fibrillation is present in about one-third of patients. The *chest roentgenogram* shows a normal or slightly enlarged heart; pericardial calcification is most common in tuberculous pericarditis. Pericardial calcification may, however, occur in the absence of constriction.

In as much as the usual physical signs of cardiac disease (murmurs, cardiac enlargement) may be inconspicuous or absent in chronic constrictive pericarditis, hepatic enlargement and dysfunction associated with jaundice and intractable ascites may lead to a mistaken diagnosis of hepatic cirrhosis. This error can be avoided if the neck veins are inspected carefully in patients with ascites and hepatomegaly. Given a clinical picture resembling hepatic cirrhosis, but with the added feature of distended neck veins, a careful search for thickening of the pericardium by imaging should be carried out and may disclose this curable or remediable form of heart disease.

The transthoracic *echocardiogram* typically shows pericardial thickening, dilation of the inferior vena cava and hepatic veins, and a sharp halt in ventricular filling in early diastole, with normal ventricular systolic function and flattening of the left ventricular posterior wall. Atrial enlargement may be seen, especially in patients with long-standing constrictive physiology. There is a distinctive pattern of transvalvular flow velocity on Doppler flow-velocity echocardiography. During inspiration there is an exaggerated reduction in blood flow velocity in the pulmonary veins and across the mitral valve and a leftward shift of the ventricular septum; the opposite occurs during expiration. Diastolic flow velocity in the vena cavae into the right atrium and across the tricuspid valve increases in an exaggerated manner during inspiration and declines during expiration **(Fig.21-5)**. However, echocardiography cannot definitively exclude the diagnosis of constrictive pericarditis.

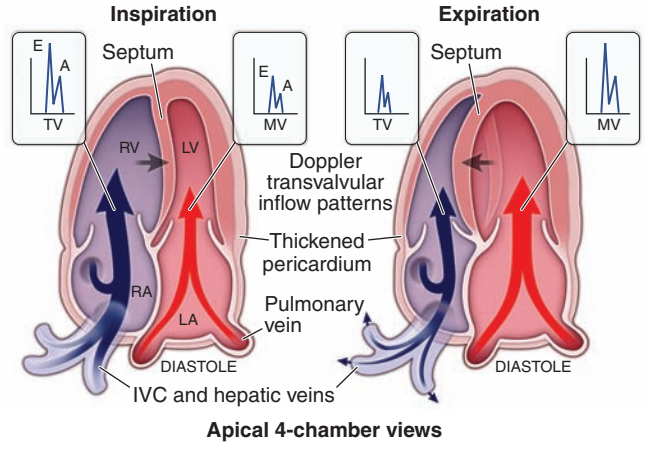


FIGURE 21-5
Constrictive pericarditis. Doppler schema of respirophasic changes in mitral and tricuspid inflow. Reciprocal patterns of ventricular filling are assessed on pulsed Doppler examination of mitral valve (MV) and tricuspid valve (TV) inflow. (*Courtesy of Bernard E. Bulwer, MD; with permission.*)

MRI and CT scanning **(Fig. 21-6)** are more accurate than echocardiography in establishing or excluding the presence of a thickened pericardium. Pericardial thickening and even pericardial calcification, however, are not synonymous with constrictive pericarditis since they may occur without seriously impairing ventricular filling.

Differential diagnosis

Like chronic constrictive pericarditis, cor pulmonale may be associated with severe systemic venous hypertension but little pulmonary congestion; the heart is usually not enlarged, and a paradoxical pulse may be present. However, in cor pulmonale, advanced parenchymal pulmonary disease is usually obvious and venous pressure *falls* during inspiration (i.e., Kussmaul's sign is negative). *Tricuspid stenosis* may also simulate chronic constrictive pericarditis; congestive hepatomegaly, splenomegaly, ascites, and venous distention may be equally prominent. However, in tricuspid stenosis, a characteristic murmur as well as the murmur of accompanying mitral stenosis is usually present.

Because constrictive pericarditis can be corrected surgically, it is important to distinguish chronic constrictive pericarditis from restrictive cardiomyopathy, which has a similar physiologic abnormality (i.e., restriction of ventricular filling). In many patients with restrictive cardiomyopathy the ventricular wall is thickened as shown on echocardiographic examination (Table 21-2). The features favoring the diagnosis of restrictive cardiomyopathy over chronic constrictive pericarditis include a well-defined apex beat, cardiac enlargement, and pronounced orthopnea with attacks of acute left ventricular failure, left ventricular hypertrophy, gallop sounds (in place of a pericardial knock), bundle branch block, and, in some cases, abnormal Q waves on the ECG. The typical echocardiographic features of constrictive pericarditis (see above) are useful in the differential diagnosis in chronic constrictive pericarditis (Fig. 21-5). CT imaging (usually with contrast) and MRI are key in distinguishing between restrictive cardiomyopathy and chronic constrictive pericarditis. In the former, the ventricular walls are hypertrophied, whereas in the latter, the pericardium is thickened and sometimes calcified. When a patient has progressive, disabling, and unresponsive congestive heart failure and displays any of the features of constrictive heart disease, Doppler echocardiography to record respiratory effects on transvalvular flow and an MRI or CT scan should be obtained to detect or exclude constrictive pericarditis, since the latter is usually curable.

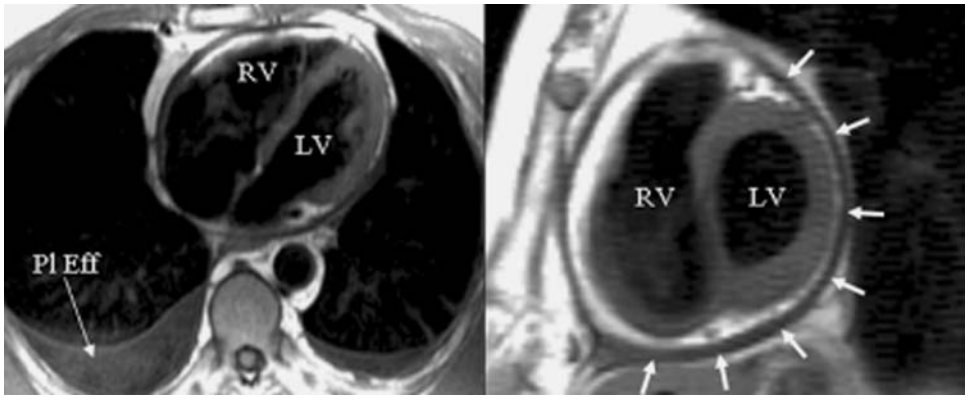


FIGURE 21-6
Cardiovascular magnetic resonance in a patient with constrictive pericarditis. On the right is a basal short-axis view of the ventricles showing a thickened pericardium encasing the heart (*arrows*). On the left is a transaxial view, again showing the thickened pericardium, particularly over the right heart, but also a pleural effusion (Pl Eff). LV, left ventricle; RV, right ventricle. (*From D Pennell: Cardiovascular Magnetic Resonance, in P Libby et al [eds]: Braunwald's Heart Disease, 8th ed. Philadelphia, Elsevier, 2005.*)

TREATMENT Constrictive Pericarditis

Pericardial resection is the only definitive treatment of constrictive pericarditis and should be as complete as possible. Dietary sodium restriction and diuretics are useful during preoperative preparation. Coronary arteriography should be carried out preoperatively in patients older than 50 years of age to exclude unsuspected coronary artery disease. The benefits derived from cardiac decortication are usually progressive over a period of months. The risk of this operation depends on the extent of penetration of the myocardium by the fibrotic and calcific process, the severity of myocardial atrophy, the extent of secondary impairment of hepatic and/or renal function, and the patient's general condition. Operative mortality is in the range of 5 to 10%; the patients with the most severe disease are at highest risk. Therefore, surgical treatment should, if possible, be carried out relatively early in the course.

Subacute effusive-constrictive pericarditis

This form of pericardial disease is characterized by the combination of a tense effusion in the pericardial space and constriction of the heart by thickened pericardium. It shares a number of features both with chronic pericardial effusion producing cardiac compression and with pericardial constriction. It may be caused by tuberculosis (see next), multiple attacks of acute idiopathic pericarditis, radiation, traumatic pericarditis, renal failure, scleroderma, and neoplasms. The heart is generally enlarged, and a paradoxical pulse and a prominent *x* descent (without a prominent *y* descent) are present in the atrial and jugular venous pressure pulses. After pericardiocentesis, the physiologic findings may change from those of cardiac tamponade to those of pericardial constriction. Furthermore, the intrapericardial pressure and the central venous pressure may decline, but not to normal. The diagnosis can be established by pericardiocentesis followed by pericardial biopsy. Wide excision of both the visceral and parietal pericardium is usually effective therapy.

Tuberculous pericardial disease

This chronic infection is a common cause of chronic pericardial effusion, although less so in the United States than in Africa, Asia, the Middle East, and other parts of the developing world where active tuberculosis is endemic (Chap. 70). The clinical picture is that of a chronic, systemic illness in a patient with pericardial effusion. It is important to consider this diagnosis in a patient with known tuberculosis, with HIV, and with fever, chest pain, weight loss, and enlargement of the cardiac silhouette of undetermined origin. If the etiology of chronic pericardial effusion remains obscure despite detailed analysis of the pericardial fluid (see earlier), a pericardial biopsy, preferably by a limited thoracotomy, should be performed. If definitive evidence is still lacking but the specimen shows granulomas with caseation, antituberculous chemotherapy (Chap. 70) is indicated.

If the biopsy specimen shows a thickened pericardium, pericardiectomy should be carried out to prevent the development of constriction. Tubercular cardiac constriction should be treated surgically while the patient is receiving antituberculous chemotherapy.

OTHER DISORDERS OF THE PERICARDIUM

Pericardial cysts appear as rounded or lobulated deformities of the cardiac silhouette, most commonly at the right cardiophrenic angle. They do not cause symptoms, and their major clinical significance lies in the possibility of confusion with a tumor, ventricular aneurysm, or massive cardiomegaly. *Tumors* involving the pericardium are most commonly secondary to malignant neoplasms originating in or invading the mediastinum, including carcinoma of the bronchus and breast, lymphoma, and melanoma. The most common *primary* malignant tumor is the mesothelioma. The usual clinical picture of malignant pericardial tumor is an insidiously developing, often bloody pericardial effusion. Surgical exploration is required to establish a definitive diagnosis and to carry out definitive or, more commonly, palliative treatment.

CHAPTER 22

INFECTIONS OF THE SKIN, MUSCLES, AND SOFT TISSUES

Dennis L. Stevens

ANATOMIC RELATIONSHIPS: CLUES TO THE DIAGNOSIS OF SOFT TISSUE INFECTIONS

Skin and soft tissue infections have been common human afflictions for centuries. However, between 2000 and 2004, hospital admissions for skin and soft tissue infections rose by 27%, a remarkable increase that was attributable largely to the emergence of the USA300 clone of methicillin-resistant *Staphylococcus aureus* (MRSA). This chapter provides an anatomic approach to understanding the types of soft tissue infections and the diverse microbes responsible.

Protection against infection of the epidermis depends on the mechanical barrier afforded by the stratum corneum, since the epidermis itself is devoid of blood vessels (Fig. 22-1). Disruption of this layer by burns or bites, abrasions, foreign bodies, primary dermatologic disorders (e.g., herpes simplex, varicella, ecthyma gangrenosum), surgery, or vascular or pressure ulcer allows penetration of bacteria to the deeper structures. Similarly, the hair follicle can serve as a portal either for components of the normal flora (e.g., *Staphylococcus*) or for extrinsic bacteria (e.g., *Pseudomonas* in hot-tub folliculitis). Intracellular infection of the squamous epithelium with vesicle formation may arise from cutaneous inoculation, as in infection with herpes simplex virus (HSV) type 1; from the dermal capillary plexus, as in varicella and infections due to other viruses associated with viremia; or from cutaneous nerve roots, as in herpes zoster. Bacteria infecting the epidermis, such as *Streptococcus pyogenes*, may be translocated laterally to deeper structures via lymphatics, an event that results in the rapid superficial spread of erysipelas. Later, engorgement or obstruction of lymphatics causes flaccid edema of the epidermis, another characteristic of erysipelas.

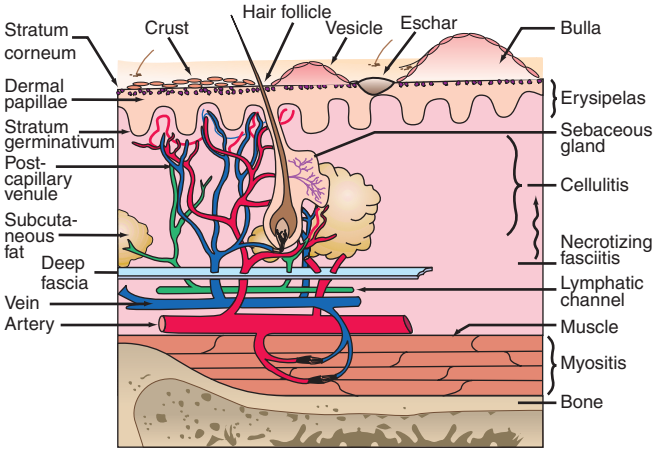


FIGURE 22-1
Structural components of the skin and soft tissue, superficial infections, and infections of the deeper structures. The rich capillary network beneath the dermal papillae plays a key role in the localization of infection and in the development of the acute inflammatory reaction.

The rich plexus of capillaries beneath the dermal papillae provides nutrition to the stratum germinativum, and physiologic responses of this plexus produce important clinical signs and symptoms. For example, infective vasculitis of the plexus results in petechiae, Osler's nodes, Janeway lesions, and palpable purpura, which, if present, are important clues to the existence of endocarditis (Chap. 20). In addition, metastatic infection within this plexus can result in cutaneous manifestations of disseminated fungal infection (Chap. 110), gonococcal infection (Chap. 49), *Salmonella* infection (Chap. 58), *Pseudomonas* infection (i.e., ecthyma gangrenosum; Chap. 57), meningococcemia (Chap. 48), and staphylococcal infection (Chap. 38). The plexus also provides bacteria with access to the circulation, thereby facilitating local spread or bacteremia. The postcapillary venules of this plexus are a major site of polymorphonuclear leukocyte sequestration, diapedesis, and chemotaxis to the site of cutaneous infection.

Exaggeration of these physiologic mechanisms by excessive levels of cytokines or bacterial toxins causes leukostasis, venous occlusion, and pitting edema. Edema

with purple bullae, ecchymosis, and cutaneous anesthesia suggests loss of vascular integrity and necessitates exploration of the deeper structures for evidence of necrotizing fasciitis or myonecrosis. An early diagnosis requires a high level of suspicion in instances of unexplained fever and of pain and tenderness in the soft tissue, even in the absence of acute cutaneous inflammation.

Table 22-1 indicates the chapters in which the infections described below are discussed in greater detail. Many of these infections are illustrated in the chapters cited or in Chap. 11 (Atlas of Rashes Associated with Fever).

INFECTIONS ASSOCIATED WITH VESICLES

(Table 22-1) Vesicle formation due to infection is caused by viral proliferation within the epidermis. In varicella and variola, viremia precedes the onset of a diffuse centripetal rash that progresses from macules to vesicles, then to pustules, and finally to scabs over the course of 1–2 weeks. Vesicles of varicella have a "dewdrop" appearance and develop in crops randomly about the trunk, extremities, and face over 3–4 days. Herpes zoster occurs in a single dermatome; the appearance of vesicles is preceded by pain for several days. Zoster may occur in persons of any age but is most common among immunosuppressed individuals and elderly patients, whereas most cases of varicella occur in young children. Vesicles due to HSV are found on or around the lips (HSV-1) or genitals (HSV-2), but may appear on the head and neck of young wrestlers (herpes gladiatorum) or on the digits of health care workers (herpetic whitlow). Recurrent herpes labialis (HSV-1) and herpes genitalis commonly follow primary infection. Coxsackievirus A16 characteristically causes vesicles on the hands, feet, and mouth of children. Orf is caused by a DNA virus related to smallpox virus and infects the fingers of individuals who work around goats and sheep. Molluscum contagiosum virus induces flaccid vesicles on the skin of healthy and immunocompromised individuals. Although variola (smallpox) in nature was eradicated as of 1977, recent terrorist events have renewed interest in this devastating infection (Chap. 7). Viremia beginning after an incubation period of 12 days is followed by a diffuse maculopapular rash, with rapid evolution to vesicles, pustules, and then scabs. Secondary cases can occur among close contacts.

Rickettsialpox begins after mite-bite inoculation of *Rickettsia akari* into the skin. A papule with a central vesicle evolves to form a 1- to 2.5-cm painless crusted black eschar with an erythematous halo and proximal adenopathy. While more common in the northeastern United States and the Ukraine in 1940–1950, rickettsialpox has recently been described in Ohio, Arizona, and Utah. Blistering dactylitis is a painful, vesicular, localized *S. aureus* or group A streptococcal infection of the pulps of the distal digits of the hands.

INFECTIONS ASSOCIATED WITH BULLAE

(Table 22-1) Staphylococcal scalded-skin syndrome (SSSS) in neonates is caused by a toxin (exfoliatin) from phage group II *S. aureus*. SSSS must be distinguished from toxic epidermal necrolysis (TEN), which occurs primarily in adults, is drug-induced, and is associated with a higher mortality rate. Punch biopsy with frozen section is useful in making this distinction since the cleavage plane is the stratum corneum in SSSS and the stratum germinativum in TEN (Fig. 22-1). Intravenous γ-globulin is a promising treatment for TEN. Necrotizing fasciitis and gas gangrene also induce bulla formation (see "Necrotizing Fasciitis," later in chapter). Halophilic vibrio infection can be as aggressive and fulminant as necrotizing fasciitis; a helpful clue in its diagnosis is a history of exposure to waters of the Gulf of Mexico or the Atlantic seaboard or (in a patient with cirrhosis) the ingestion of raw seafood. The etiologic organism (*Vibrio vulnificus*) is highly susceptible to tetracycline.

INFECTIONS ASSOCIATED WITH CRUSTED LESIONS

(Table 22-1) Impetigo contagiosa is caused by *S. pyogenes*, and bullous impetigo is due to *S. aureus*. Both skin lesions may have an early bullous stage but then appear as thick crusts with a golden-brown color. Epidemics of impetigo caused by MRSA have been reported. Streptococcal lesions are most common among children 2–5 years of age, and epidemics may occur in settings of poor hygiene, particularly among children in lower socioeconomic settings in tropical climates. It is important to recognize impetigo contagiosa because of its relationship to poststreptococcal glomerulonephritis. Rheumatic fever is not a complication of skin infection caused by *S. pyogenes*. Superficial dermatophyte infection (ringworm) can occur on any skin surface, and skin scrapings with KOH staining are diagnostic. Primary infections with dimorphic fungi such as *Blastomyces dermatitidis* and *Sporothrix schenckii* can initially present as crusted skin lesions resembling ringworm. Disseminated infection with *Coccidioides immitis* can also involve the skin, and biopsy and culture should be performed on crusted lesions in patients from endemic areas. Crusted nodular lesions caused by *Mycobacterium chelonei* have been described in HIV-seropositive patients. Treatment with clarithromycin looks promising.

FOLLICULITIS

(Table 22-1) Hair follicles serve as portals for a number of bacteria, although *S. aureus* is the most common cause of localized folliculitis. Sebaceous glands empty into hair follicles and ducts and, if these portals are blocked, form sebaceous cysts that may resemble staphylococcal abscesses or may become secondarily infected. Infection of sweat glands (hidradenitis suppurativa) can also mimic infection of hair follicles, particularly in the axillae. Chronic folliculitis is uncommon except in acne vulgaris, where constituents of the normal flora (e.g., *Propionibacterium acnes*) may play a role.

Diffuse folliculitis occurs in two settings. Hot-tub folliculitis is caused by *Pseudomonas aeruginosa* in waters that

TABLE 22-1

SKIN AND SOFT TISSUE INFECTIONS

LESION, CLINICAL SYNDROME	INFECTIOUS AGENT	CHAPTER(S)
Vesicles		
Smallpox	Variola virus	7
Chickenpox	Varicella-zoster virus	85
Shingles (herpes zoster)	Varicella-zoster virus	85
Cold sores, herpetic whitlow, herpes gladiatorum	Herpes simplex virus	84
Hand-foot-and-mouth disease	Coxsackievirus A16	97
Orf	Parapoxvirus	88
Molluscum contagiosum	Pox-like virus	88
Rickettsialpox	*Rickettsia akari*	79
Blistering distal dactylitis	*Staphylococcus aureus* or *Streptococcus pyogenes*	38, 39
Bullae		
Staphylococcal scalded-skin syndrome	*S. aureus*	38
Necrotizing fasciitis	*S. pyogenes, Clostridium* spp., mixed aerobes and anaerobes	39, 46, 69
Gas gangrene	*Clostridium* spp.	46
Halophilic vibrio	*Vibrio vulnificus*	61
Crusted lesions		
Bullous impetigo/ecthyma	*S. aureus*	38
Impetigo contagiosa	*S. pyogenes*	39
Ringworm	Superficial dermatophyte fungi	113
Sporotrichosis	*Sporothrix schenckii*	113
Histoplasmosis	*Histoplasma capsulatum*	106
Coccidioidomycosis	*Coccidioides immitis*	107
Blastomycosis	*Blastomyces dermatitidis*	108
Cutaneous leishmaniasis	*Leishmania* spp.	122
Cutaneous tuberculosis	*Mycobacterium tuberculosis*	70
Nocardiosis	*Nocardia asteroides*	67
Folliculitis		
Furunculosis	*S. aureus*	38
Hot-tub folliculitis	*Pseudomonas aeruginosa*	57
Swimmer's itch	*Schistosoma* spp.	129
Acne vulgaris	*Propionibacterium acnes*	
Papular and nodular lesions		
Fish-tank or swimming-pool granuloma	*Mycobacterium marinum*	72
Creeping eruption (cutaneous larva migrans)	*Ancylostoma braziliense*	126
Dracunculiasis	*Dracunculus medinensis*	128
Cercarial dermatitis	*Schistosoma mansoni*	129
Verruca vulgaris	Human papillomaviruses 1, 2, 4	90
Condylomata acuminata (anogenital warts)	Human papillomaviruses 6, 11, 16, 18	90
Onchocerciasis nodule	*Onchocerca volvulus*	128
Cutaneous myiasis	*Dermatobia hominis*	132
Verruca peruana	*Bartonella bacilliformis*	65
Cat-scratch disease	*Bartonella henselae*	65
Lepromatous leprosy	*Mycobacterium leprae*	71
Secondary syphilis (papulosquamous and nodular lesions, condylomata lata)	*Treponema pallidum*	74
Tertiary syphilis (nodular gummatous lesions)	*T. pallidum*	74
Ulcers with or without eschars		
Anthrax	*Bacillus anthracis*	7
Ulceroglandular tularemia	*Francisella tularensis*	63, 7
Bubonic plague	*Yersinia pestis*	64, 7
Buruli ulcer	*Mycobacterium ulcerans*	72
Leprosy	*M. leprae*	71

(*continued*)

TABLE 22-1

SKIN AND SOFT TISSUE INFECTIONS (*CONTINUED*)

LESION, CLINICAL SYNDROME	INFECTIOUS AGENT	CHAPTER(S)
Cutaneous tuberculosis	*M. tuberculosis*	70
Chancroid	*Haemophilus ducreyi*	50
Primary syphilis	*T. pallidum*	74
Erysipelas	*S. pyogenes*	39
Cellulitis	*Staphylococcus* spp., *Streptococcus* spp., various other bacteria	Various
Necrotizing fasciitis		
Streptococcal gangrene	*S. pyogenes*	39
Fournier's gangrene	Mixed aerobic and anaerobic bacteria	69
Staphylococcal necrotizing fasciitis	Methicillin-resistant *S. aureus*	38
Myositis and myonecrosis		
Pyomyositis	*S. aureus*	38
Streptococcal necrotizing myositis	*S. pyogenes*	39
Gas gangrene	*Clostridium* spp.	46
Nonclostridial (crepitant) myositis	Mixed aerobic and anaerobic bacteria	69
Synergistic nonclostridial anaerobic myonecrosis	Mixed aerobic and anaerobic bacteria	69

are insufficiently chlorinated and maintained at temperatures of 37–40°C. Infection is usually self-limited, although bacteremia and shock have been reported. Swimmer's itch occurs when a skin surface is exposed to water infested with freshwater avian schistosomes. Warm water temperatures and alkaline pH are suitable for mollusks that serve as intermediate hosts between birds and humans. Free-swimming schistosomal cercariae readily penetrate human hair follicles or pores, but quickly die and elicit a brisk allergic reaction, causing intense itching and erythema.

PAPULAR AND NODULAR LESIONS

(Table 22-1) Raised lesions of the skin occur in many different forms. *Mycobacterium marinum* infections of the skin may present as cellulitis or as raised erythematous nodules. Erythematous papules are early manifestations of cat-scratch disease (with lesions developing at the primary site of inoculation of *Bartonella henselae*) and bacillary angiomatosis (also caused by *B. henselae*). Raised serpiginous or linear eruptions are characteristic of cutaneous larva migrans, which is caused by burrowing larvae of dog or cat hookworms (*Ancylostoma braziliense*) and which humans acquire through contact with soil that has been contaminated with dog or cat feces. Similar burrowing raised lesions are present in dracunculiasis caused by migration of the adult female nematode *Dracunculus medinensis*. Nodules caused by *Onchocerca volvulus* measure 1–10 cm in diameter and occur mostly in persons bitten by *Simulium* flies in Africa. The nodules contain the adult worm encased in fibrous tissue. Migration of microfilariae into the eyes may result in blindness. Verruga peruana is caused by *Bartonella bacilliformis*, which is transmitted to humans by the sandfly *Phlebotomus*. This condition can take the form of single gigantic lesions (several centimeters in diameter) or multiple small lesions (several millimeters in diameter). Numerous subcutaneous nodules may also be present in cysticercosis caused by larvae of *Taenia solium*. Multiple erythematous papules develop in schistosomiasis; each represents a cercarial invasion site. Skin nodules as well as thickened subcutaneous tissue are prominent features of lepromatous leprosy. Large nodules or gummas are features of tertiary syphilis, whereas flat papulosquamous lesions are characteristic of secondary syphilis. Human papillomavirus may cause singular warts (verruca vulgaris) or multiple warts in the anogenital area (condylomata acuminata). The latter are major problems in HIV-infected individuals.

ULCERS WITH OR WITHOUT ESCHARS

(Table 22-1) Cutaneous anthrax begins as a pruritic papule, which develops within days into an ulcer with surrounding vesicles and edema and then into an enlarging ulcer with a black eschar. Cutaneous anthrax may cause chronic nonhealing ulcers with an overlying dirty-gray membrane, although lesions may also mimic psoriasis, eczema, or impetigo. Ulceroglandular tularemia may have associated ulcerated skin lesions with painful regional adenopathy. Although buboes are the major cutaneous manifestation of plague, ulcers with eschars, papules, or pustules are also present in 25% of cases.

Mycobacterium ulcerans typically causes chronic skin ulcers on the extremities of individuals living in the tropics. *Mycobacterium leprae* may be associated with cutaneous ulcerations in patients with lepromatous leprosy related to Lucio's phenomenon, in which

immune-mediated destruction of tissue bearing high concentrations of *M. leprae* bacilli occurs, usually several months after initiation of effective therapy. *Mycobacterium tuberculosis* may also cause ulcerations, papules, or erythematous macular lesions of the skin in both normal and immunocompromised patients.

Decubitus ulcers are due to tissue hypoxemia secondary to pressure-induced vascular insufficiency and may become secondarily infected with components of the skin and gastrointestinal flora, including anaerobes. Ulcerative lesions on the anterior shins may be due to pyoderma gangrenosum, which must be distinguished from similar lesions of infectious etiology by histologic evaluation of biopsy sites. Ulcerated lesions on the genitals may be either painful (chancroid) or painless (primary syphilis).

ERYSIPELAS

(Table 22-1) Erysipelas is due to *S. pyogenes* and is characterized by an abrupt onset of fiery-red swelling of the face or extremities. The distinctive features of erysipelas are well-defined indurated margins, particularly along the nasolabial fold; rapid progression; and intense pain. Flaccid bullae may develop during the second or third day of illness, but extension to deeper soft tissues is rare. Treatment with penicillin is effective; swelling may progress despite appropriate treatment, although fever, pain, and the intense red color diminish. Desquamation of the involved skin occurs 5–10 days into the illness. Infants and elderly adults are most commonly afflicted, and the severity of systemic toxicity varies.

CELLULITIS

(Table 22-1) Cellulitis is an acute inflammatory condition of the skin that is characterized by localized pain, erythema, swelling, and heat. It may be caused by indigenous flora colonizing the skin and appendages (e.g., *S. aureus* and *S. pyogenes*) or by a wide variety of exogenous bacteria. Because the exogenous bacteria involved in cellulitis occupy unique niches in nature, a thorough history (including epidemiologic data) provides important clues to etiology. When there is drainage, an open wound, or an obvious portal of entry, Gram's stain and culture provide a definitive diagnosis. In the absence of these findings, the bacterial etiology of cellulitis is difficult to establish, and in some cases staphylococcal and streptococcal cellulitis may have similar features. Even with needle aspiration of the leading edge or a punch biopsy of the cellulitis tissue itself, cultures are positive in only 20% of cases. This observation suggests that relatively low numbers of bacteria may cause cellulitis and that the expanding area of erythema within the skin may be a direct effect of extracellular toxins or of the soluble mediators of inflammation elicited by the host.

Bacteria may gain access to the epidermis through cracks in the skin, abrasions, cuts, burns, insect bites, surgical incisions, and IV catheters. Cellulitis caused by *S. aureus* spreads from a central localized infection, such as an abscess, folliculitis, or an infected foreign body (e.g., a splinter, a prosthetic device, or an IV catheter). MRSA is rapidly replacing methicillin-sensitive *S. aureus* (MSSA) as a cause of cellulitis in both inpatient and outpatient settings. Cellulitis caused by MSSA or MRSA is usually associated with a focal infection, such as a furuncle, a carbuncle, a surgical wound, or an abscess. In contrast, cellulitis due to *S. pyogenes* is a more rapidly spreading, diffuse process that is frequently associated with lymphangitis and fever. Recurrent streptococcal cellulitis of the lower extremities may be caused by organisms of group A, C, or G in association with chronic venous stasis or with saphenous venectomy for coronary artery bypass surgery. Streptococci also cause recurrent cellulitis among patients with chronic lymphedema resulting from elephantiasis, lymph node dissection, or Milroy's disease. Recurrent staphylococcal cutaneous infections are more common among individuals who have eosinophilia and elevated serum levels of IgE (Job's syndrome) and among nasal carriers of staphylococci. Cellulitis caused by *Streptococcus agalactiae* (group B *Streptococcus*) occurs primarily in elderly patients and those with diabetes mellitus or peripheral vascular disease. *Haemophilus influenzae* typically causes periorbital cellulitis in children in association with sinusitis, otitis media, or epiglottitis. It is unclear whether this form of cellulitis will (like meningitis) become less common as a result of the impressive efficacy of the *H. influenzae* type b vaccine.

Many other bacteria also cause cellulitis. It is fortunate that these organisms occur in such characteristic settings that a good history provides useful clues to the diagnosis. Cellulitis associated with cat bites and, to a lesser degree, with dog bites is commonly caused by *Pasteurella multocida*, although in the latter case *Staphylococcus intermedius* and *Capnocytophaga canimorsus* (formerly DF-2) must also be considered. Sites of cellulitis and abscesses associated with dog bites and human bites also contain a variety of anaerobic organisms, including *Fusobacterium*, *Bacteroides*, aerobic and anaerobic streptococci, and *Eikenella corrodens*. *Pasteurella* is notoriously resistant to dicloxacillin and nafcillin but is sensitive to all other β-lactam antimicrobial agents as well as to quinolones, tetracycline, and erythromycin. Ampicillin/clavulanate, ampicillin/sulbactam, and cefoxitin are good choices for the treatment of animal or human bite infections. *Aeromonas hydrophila* causes aggressive cellulitis in tissues surrounding lacerations sustained in freshwater (lakes, rivers, and streams). This organism remains sensitive to aminoglycosides, fluoroquinolones, chloramphenicol, trimethoprim-sulfamethoxazole, and third-generation cephalosporins; it is resistant to ampicillin, however.

P. aeruginosa causes three types of soft tissue infection: ecthyma gangrenosum in neutropenic patients, hot-tub folliculitis, and cellulitis following penetrating injury. Most commonly, *P. aeruginosa* is introduced into the deep tissues when a person steps on a nail. Treatment includes surgical inspection and drainage, particularly if the injury also involves bone or joint capsule. Choices for empirical treatment while antimicrobial susceptibility data are awaited include an aminoglycoside,

a third-generation cephalosporin (ceftazidime, cefoperazone, or cefotaxime), a semisynthetic penicillin (ticarcillin, mezlocillin, or piperacillin), or a fluoroquinolone (although drugs of the last class are not indicated for the treatment of children <13 years old).

Gram-negative bacillary cellulitis, including that due to *P. aeruginosa*, is most common among hospitalized, immunocompromised hosts. Cultures and sensitivity tests are critically important in this setting because of multidrug resistance (Chap. 57).

The gram-positive aerobic rod *Erysipelothrix rhusiopathiae* is most often associated with fish and domestic swine and causes cellulitis primarily in bone renderers and fishmongers. *E. rhusiopathiae* remains susceptible to most β-lactam antibiotics (including penicillin), erythromycin, clindamycin, tetracycline, and cephalosporins, but is resistant to sulfonamides, chloramphenicol, and vancomycin. Its resistance to vancomycin, which is unusual among gram-positive bacteria, is of potential clinical significance since this agent is sometimes used in empirical therapy for skin infection. Fish food containing the water flea *Daphnia* is sometimes contaminated with *M. marinum*, which can cause cellulitis or granulomas on skin surfaces exposed to the water in aquariums or injured in swimming pools. Rifampin plus ethambutol has been an effective therapeutic combination in some cases, although no comprehensive studies have been undertaken. In addition, some strains of *M. marinum* are susceptible to tetracycline or to trimethoprim-sulfamethoxazole.

NECROTIZING FASCIITIS

(Table 22-1) Necrotizing fasciitis, formerly called streptococcal gangrene, may be associated with group A *Streptococcus* or mixed aerobic-anaerobic bacteria or may occur as part of gas gangrene caused by *Clostridium perfringens*. Strains of MRSA that produce the Panton-Valentine leukocidin (PVL) toxin have been reported to cause necrotizing fasciitis. Early diagnosis may be difficult when pain or unexplained fever is the only presenting manifestation. Swelling then develops and is followed by brawny edema and tenderness. With progression, dark-red induration of the epidermis appears, along with bullae filled with blue or purple fluid. Later the skin becomes friable and takes on a bluish, maroon, or black color. By this stage, thrombosis of blood vessels in the dermal papillae (Fig. 22-1) is extensive. Extension of infection to the level of the deep fascia causes this tissue to take on a brownish-gray appearance. Rapid spread occurs along fascial planes, through venous channels and lymphatics. Patients in the later stages are toxic and frequently manifest shock and multiorgan failure.

Necrotizing fasciitis caused by mixed aerobic-anaerobic bacteria begins with a breach in the integrity of a mucous membrane barrier, such as the mucosa of the gastrointestinal or genitourinary tract. The portal can be a malignancy, a diverticulum, a hemorrhoid, an anal fissure, or a urethral tear. Other predisposing factors include peripheral vascular disease, diabetes mellitus, surgery, and penetrating injury to the abdomen. Leakage into the perineal area results in a syndrome called *Fournier's gangrene*, characterized by massive swelling of the scrotum and penis with extension into the perineum or the abdominal wall and legs.

Necrotizing fasciitis caused by *S. pyogenes* has increased in frequency and severity since 1985. There are two distinct clinical presentations: those with no portal of entry and those with a defined portal of entry. Infections in the first category often begin deep at the site of a nonpenetrating minor trauma, such as a bruise or a muscle strain. Seeding of the site via transient bacteremia is likely, although most patients deny antecedent streptococcal infection. The affected patients present with only severe pain and fever. Late in the course, the classic signs of necrotizing fasciitis, such as purple (violaceous) bullae, skin sloughing, and progressive toxicity, develop. In infections of the second type, *S. pyogenes* may reach the deep fascia from a site of cutaneous infection or penetrating trauma. These patients have early signs of superficial skin infection with progression to necrotizing fasciitis. In either case, toxicity is severe, and renal impairment may precede the development of shock. In 20–40% of cases, myositis occurs concomitantly, and, as in gas gangrene (see below), serum creatine phosphokinase levels may be markedly elevated. Necrotizing fasciitis due to mixed aerobic-anaerobic bacteria may be associated with gas in deep tissue, but gas usually is not present when the cause is *S. pyogenes* or MRSA. Prompt surgical exploration down to the deep fascia and muscle is essential. Necrotic tissue must be surgically removed, and Gram's staining and culture of excised tissue are useful in establishing whether group A streptococci, mixed aerobic-anaerobic bacteria, MRSA, or *Clostridium* species are present (see "Treatment," later in chapter).

MYOSITIS AND MYONECROSIS

(Table 22-1) Muscle involvement can occur with viral infection (e.g., influenza, dengue, or coxsackievirus B infection) or parasitic invasion (e.g., trichinellosis, cysticercosis, or toxoplasmosis). Although myalgia can occur in most of these infections, severe muscle pain is the hallmark of pleurodynia (coxsackievirus B), trichinellosis, and bacterial infection. Acute rhabdomyolysis predictably occurs with clostridial and streptococcal myositis but may also be associated with influenza virus, echovirus, coxsackievirus, Epstein-Barr virus, and *Legionella* infections.

Pyomyositis is usually due to *S. aureus*, is common in tropical areas, and generally has no known portal of entry. Cases of pyomyositis caused by MRSA producing the PVL toxin have been described among children in the United States. Muscle infection begins at the exact site of blunt trauma or muscle strain. Infection remains localized, and shock does not develop unless organisms produce toxic shock syndrome toxin 1 or certain enterotoxins and the patient lacks antibodies to the toxin produced by the infecting organisms. In contrast, *S. pyogenes* may induce primary myositis (referred to as *streptococcal necrotizing myositis*) in association with severe systemic toxicity. Myonecrosis occurs

concomitantly with necrotizing fasciitis in ~50% of cases. Both are part of the streptococcal toxic shock syndrome.

Gas gangrene usually follows severe penetrating injuries that result in interruption of the blood supply and introduction of soil into wounds. Such cases of traumatic gangrene are usually caused by the clostridial species *C. perfringens*, *C. septicum*, and *C. histolyticum*. Rarely, latent or recurrent gangrene can occur years after penetrating trauma; dormant spores that reside at the site of previous injury are most likely responsible. Spontaneous nontraumatic gangrene among patients with neutropenia, gastrointestinal malignancy, diverticulosis, or recent radiation therapy to the abdomen is caused by several clostridial species, of which *C. septicum* is the most commonly involved. The tolerance of this anaerobe to oxygen probably explains why it can initiate infection spontaneously in normal tissue anywhere in the body.

Gas gangrene of the uterus, especially that due to *C. sordellii,* historically occurred as a consequence of illegal or self-induced abortion and nowadays also follows spontaneous abortion, vaginal delivery, and cesarean section. *C. sordellii* has also been implicated in medically induced abortion. Postpartum *C. sordellii* infections in young, previously healthy women present as a unique clinical picture: little or no fever, lack of a purulent discharge, refractory hypotension, extensive peripheral edema and effusions, hemoconcentration, and a markedly elevated white blood cell count. The infection is almost uniformly fatal, with death ensuing rapidly.

Synergistic nonclostridial anaerobic myonecrosis, also known as necrotizing cutaneous myositis and synergistic necrotizing cellulitis, is a variant of necrotizing fasciitis caused by mixed aerobic and anaerobic bacteria with the exclusion of clostridial organisms (see "Necrotizing Fasciitis," earlier).

DIAGNOSIS

This chapter has emphasized the physical appearance and location of lesions within the soft tissues as important diagnostic clues. The temporal progression of the lesions as well as the patient's travel history, animal exposure or bite history, age, underlying disease status, and lifestyle are also crucial considerations in narrowing the differential diagnosis. However, even the astute clinician may find it challenging to diagnose all infections of the soft tissues by history and inspection alone. Soft tissue radiography, computed tomography **(Fig. 22-2)**, and magnetic resonance imaging may be useful in determining the depth of infection and should be performed when the patient has rapidly progressing lesions or evidence of a systemic inflammatory response syndrome. These tests are particularly valuable for defining a localized abscess or detecting gas in tissue. Unfortunately, they may reveal only soft tissue swelling and, thus, are not specific for fulminant infections such as necrotizing fasciitis or myonecrosis caused by group A *Streptococcus* (Fig. 22-2), where gas is not found in lesions.

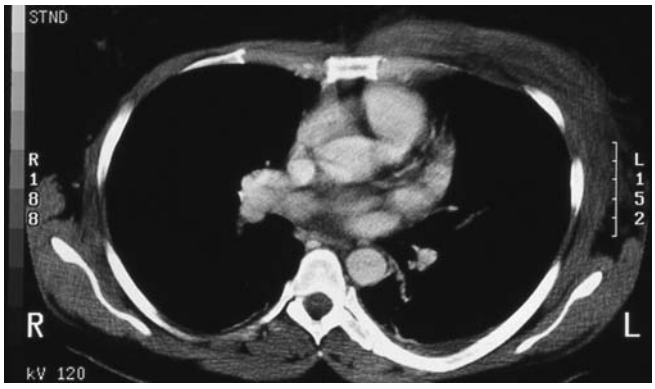


FIGURE 22-2
Computed tomography showing edema and inflammation of the left chest wall in a patient with necrotizing fasciitis and myonecrosis caused by group A *Streptococcus*.

Aspiration of the leading edge or punch biopsy with frozen section may be helpful if the results of imaging tests are positive, but false-negative results occur in ~80% of cases. There is some evidence that aspiration alone may be superior to injection and aspiration with normal saline. Frozen sections are especially useful in distinguishing SSSS from TEN and are quite valuable in cases of necrotizing fasciitis. Open surgical inspection, with debridement as indicated, is clearly the best way to determine the extent and severity of infection and to obtain material for Gram's staining and culture. Such an aggressive approach is important and may be lifesaving if undertaken early in the course of fulminant infections where there is evidence of systemic toxicity.

TREATMENT Infections of the Skin, Muscles, and Soft Tissues

A full description of the treatment of all the clinical entities described herein is beyond the scope of this chapter. As a guide to the clinician in selecting appropriate treatment, the antimicrobial agents useful in the most common and the most fulminant cutaneous infections are listed in Table 22-2.

Furuncles, carbuncles, and abscesses caused by MRSA and MSSA are common, and their treatment depends upon the size of the lesion. Furuncles <2.5 cm in diameter are usually treated with moist heat. Those that are larger (4.5 cm of erythema and induration) require surgical drainage, and the occurrence of these larger lesions in association with fever, chills, or leukocytosis requires both drainage and antibiotic treatment. A study in children demonstrated that surgical drainage of abscesses (mean diameter, 3.8 cm) was as effective when used alone as when combined with trimethoprim-sulfamethoxazole treatment. However, the rate of recurrence of new lesions was lower in the group undergoing both drainage and antibiotic treatment.

TABLE 22-2

TREATMENT OF COMMON INFECTIONS OF THE SKIN

DIAGNOSIS/CONDITION	PRIMARY TREATMENT	ALTERNATIVE TREATMENT	SEE ALSO CHAP(S).
Animal bite (prophylaxis or early infection)[a]	Amoxicillin/clavulanate, 875/22 mg PO bid	Doxycycline, 100 mg PO bid	35
Animal bite[a] (established infection)	Ampicillin/sulbactam, 1.5–3 g IV q6h	Clindamycin, 600–900 mg IV q8h, *plus* Ciprofloxacin, 400 mg IV q12h, *or* Cefoxitin, 2 g IV q6h	35
Bacillary angiomatosis	Erythromycin, 500 mg PO qid	Doxycycline, 100 mg PO bid	65
Herpes simplex (primary genital)	Acyclovir, 400 mg PO tid for 10 days	Famciclovir, 250 mg PO tid for 5–10 days, *or* Valacyclovir, 1000 mg PO bid for 10 days	84
Herpes zoster (immuno-competent host >50 years of age)	Acyclovir, 800 mg PO 5 times daily for 7–10 days	Famciclovir, 500 mg PO tid for 7–10 days, *or* Valacyclovir, 1000 mg PO tid for 7 days	85
Cellulitis (staphylococcal or streptococcal[b,c])	Nafcillin or oxacillin, 2 g IV q4–6h	Cefazolin, 1–2 g q8h, *or* Ampicillin/sulbactam, 1.5–3 g IV q6h, *or* Erythromycin, 0.5–1 g IV q6h, *or* Clindamycin, 600–900 mg IV q8h	38, 39
MRSA skin infection[d]	Vancomycin, 1 g IV q12h	Linezolid, 600 mg IV q12h	38
Necrotizing fasciitis (group A streptococcal[b])	Clindamycin, 600–900 mg IV q6–8h, *plus* Penicillin G, 4 million units IV q4h	Clindamycin, 600–900 mg IV q6–8h, *plus* Cephalosporin (first- or second-generation)	39
Necrotizing fasciitis (mixed aerobes and anaerobes)	Ampicillin, 2 g IV q4h, *plus* Clindamycin, 600–900 mg IV q6–8h, *plus* Ciprofloxacin, 400 mg IV q6–8h	Vancomycin, 1 g IV q6h, *plus* Metronidazole, 500 mg IV q6h, *plus* Ciprofloxacin, 400 mg IV q6–8h	69
Gas gangrene	Clindamycin, 600–900 mg IV q6–8h, *plus* Penicillin G, 4 million units IV q4–6h	Clindamycin, 600–900 mg IV q6–8h, *plus* Cefoxitin, 2 g IV q6h	46

[a]*Pasteurella multocida*, a species commonly associated with both dog and cat bites, is resistant to cephalexin, dicloxacillin, clindamycin, and erythromycin. *Eikenella corrodens*, a bacterium commonly associated with human bites, is resistant to clindamycin, penicillinase-resistant penicillins, and metronidazole but is sensitive to trimethoprim-sulfamethoxazole and fluoroquinolones.

[b]The frequency of erythromycin resistance in group A *Streptococcus* is currently ~5% in the United States but has reached 70–100% in some other countries. Most, but not all, erythromycin-resistant group A streptococci are susceptible to clindamycin. Approximately 90–95% of *Staphylococcus aureus* strains are sensitive to clindamycin.

[c]Severe hospital-acquired *S. aureus* infections or community-acquired *S. aureus* infections that are not responding to the ß-lactam antibiotics recommended in this table may be caused by methicillin-resistant strains, requiring a switch to vancomycin or linezolid.

[d]Some strains of methicillin-resistant *S. aureus* (MRSA) remain sensitive to tetracycline and trimethoprim-sulfamethoxazole. Daptomycin (4 mg/kg IV q24h) or tigecycline (100-mg loading dose followed by 50 mg IV q12h) are alternative treatments for MRSA.

Early and aggressive surgical exploration is essential in cases of suspected necrotizing fasciitis, myositis, or gangrene in order to (1) visualize the deep structures, (2) remove necrotic tissue, (3) reduce compartment pressure, and (4) obtain suitable material for Gram's staining and for aerobic and anaerobic cultures. Appropriate empirical antibiotic treatment for mixed aerobic-anaerobic infections could consist of ampicillin/sulbactam, cefoxitin, or the following combination: (1) clindamycin (600–900 mg intravenously every 8 h) or metronidazole (500 mg every 6 h) plus (2) ampicillin or ampicillin/sulbactam (1.5–3 g intravenously every 6 h) plus (3) gentamicin (1–1.5 mg/kg every 8 h). Group A streptococcal and clostridial infection of the fascia and/or muscle carries a mortality rate of 20–50% with penicillin treatment. In experimental models of streptococcal and

clostridial necrotizing fasciitis/myositis, clindamycin has exhibited markedly superior efficacy, but no comparative clinical trials have been performed. A retrospective study of children with invasive group A streptococcal infection demonstrated higher survival rates with clindamycin treatment than with β-lactam antibiotic therapy. Hyperbaric oxygen treatment may also be useful in gas gangrene due to clostridial species. Antibiotic treatment should be continued until all signs of systemic toxicity have resolved, all devitalized tissue has been removed, and granulation tissue has developed (Chaps. 39, 46, and 69).

In summary, infections of the skin and soft tissues are diverse in presentation and severity and offer a great challenge to the clinician. This chapter provides an approach to diagnosis and understanding of the pathophysiologic mechanisms involved in these infections. More in-depth information is found in chapters on specific infections.

CHAPTER 23

OSTEOMYELITIS

Alan D. Tice

Osteomyelitis, an infection of bone that leads to tissue destruction and often to debility, can be caused by a wide variety of bacteria (including mycobacteria) and fungi and may be associated with viral infections. Its management must be individualized and depends on numerous factors, including the causative organism, the specific bone involved, vascular supply, nerve function, foreign bodies, recent injury, the physiologic status of the host, and associated comorbidities. The spectrum of the disease can range from extensive (e.g., tibial and vertebral osteomyelitis) to localized (e.g., bone invasion associated with a tooth abscess). Two major classification systems for osteomyelitis are used in making decisions about medical therapy and surgery. Lee and Waldvogel categorized cases as acute or chronic, hematogenous or contiguous, and with or without vascular compromise. The Cierny and Mader classification system for long-bone osteomyelitis encompasses the location and extent of the infection as well as a number of other factors.

ETIOLOGY (TABLE 23-1)

The foremost bacterial cause of osteomyelitis is *Staphylococcus aureus*. Gram-negative organisms such as *Pseudomonas aeruginosa* and *Escherichia coli*, coagulase-negative staphylococci, enterococci, and propionibacteria may also be involved. *Mycobacterium tuberculosis* is a common cause of osteomyelitis in countries with limited medical resources; other mycobacterial species that infect bone include *M. marinum*, *M. chelonei*, and *M. fortuitum*. Fungal etiologies include *Candida*, *Coccidioides*, *Histoplasma*, and *Aspergillus* species. Noninfectious pathogenic mechanisms that may cause disease mimicking osteomyelitis include avascular necrosis, rheumatoid diseases, neuropathy with chronic trauma, gout, and malignancies.

The precipitating event(s) for osteomyelitis vary greatly. The prosthetic joint implants and stabilization devices that are increasingly being used in orthopedic surgery are associated with complex infections. Trauma is also a common cause of infection, especially when a wound is involved and there is contamination of bone or surrounding tissue along with significant tissue damage or destruction. Even in the absence of an open wound or a compound fracture, damaged tissue and extravasated blood may slow the circulation, establishing a favorable medium for the growth of bacteria that may reach the area through low-level bacteremia from the peripheral venous circulation or from distal lymphatic channels. Bacteremia—whether due to endocarditis or due to seeding from other sites of infection (e.g., abscesses, boils, or vascular devices)—is also a frequent etiologic factor in osteomyelitis. Studies of *S. aureus* bacteremia indicate a rate of metastatic osteomyelitis approaching 28% if there is a prosthetic joint in place; *S. aureus* bacteremia can be complicated by the involvement of methicillin-resistant strains (MRSA), which are progressively replacing strains that are more susceptible to antibiotics. The overlapping circulations of the urinary tract and the spine may be

TABLE 23-1

MICROORGANISMS THAT CAUSE OSTEOMYELITIS

ORGANISM	COMMENT
Frequently Encountered Bacteria	
Staphylococcus aureus	Most likely bacterial pathogen Aggressive, invasive Often metastatic foci with bacteremia Consider surgery early
Staphylococci other than *S. aureus* (coagulase-negative)	Usually associated with foreign material or implants Biofilm production
Streptococci	May spread rapidly through soft tissues
Enterobacteriaceae (*Escherichia coli*, *Klebsiella*, others)	Considerable variation in antibiotic susceptibility Increasing antibiotic resistance with overuse May become resistant to antibiotics during therapy
Pseudomonas aeruginosa	Increasingly resistant to antibiotics Frequent successor to other bacteria when initial therapy fails May be related to contamination
Unusual Organisms	
Anaerobic bacteria	Usually mixed with aerobic bacteria May be synergistic Survival dependent on devitalized tissue
Bartonella henselae	Associated with cat scratches and probably with fleas
Brucella species	Prominent in developing countries, especially with unpasteurized milk
Fungi	*Candida* the most likely genus Considerable variation in susceptibility, depending on species Surgery may be helpful if infection is invasive.
Mycobacterium tuberculosis	May involve any bone Vertebral osteomyelitis common in some countries
Mycobacteria other than *M. tuberculosis*	Need special culture media to recover
Viruses	Associated with some viral infections, including varicella and variola

a source of vertebral osteomyelitis due to urinary tract pathogens such as *E. coli* and *Klebsiella*. Additional predisposing factors include a poor arterial and venous supply, which may limit perfusion to bone to the point of an inadequate response and poor healing, even in patients with normal function. Host factors such as diabetes and its consequences contribute significantly to the development of osteomyelitis through impaired immunity with hyperglycemia, loss of sensation, vascular disease, and renal failure.

EPIDEMIOLOGY

In the United States, acute osteomyelitis affects ~0.1–1.8% of the otherwise healthy adult population. After a foot puncture, 30–40% of adults with diabetes develop osteomyelitis. In this country, there has been a major change in the profile of certain bacterial pathogens, with the emergence of MRSA strains over the last decade. MRSA has become a source of great concern in hospitals, especially after surgery. The morbidity and economic consequences appear to be greater for MRSA osteomyelitis than for osteomyelitis caused by methicillin-sensitive *S. aureus* strains. However, it is not clear that these poorer outcomes for MRSA are due to new or more destructive virulence factors. Rather, they may simply be the result of a delay in effective antimicrobial treatment.

The types and etiologies of osteomyelitis vary by region and with time. The United States has seen a rise in infections related to the increasing use of orthopedic surgery for correction of deformities and implantation of screws, pins, rods, plates, and prosthetic joints. With the aging of populations and the epidemics of obesity and diabetes in some countries, the frequency of these predisposing factors continues to increase, requiring adaptations in treatment approaches. Any type of instrumentation may lead to infection in a small proportion of cases. Osteomyelitis attributable to orthopedic devices and surgical interventions is considerably less common in countries with limited medical resources, where tuberculosis may be the dominant infection and brucellosis is not unusual. In many of these areas, agricultural injuries, industrial accidents, and war wounds are much more common than in wealthy countries, and the pathogens causing infection reflect those injuries. Osteomyelitis is more common in situations where wounds cannot promptly be debrided and repaired, microbiology laboratories are not readily available, and effective antimicrobial agents are in short supply.

PATHOGENESIS

The most common predisposing factor for osteomyelitis is an area of bone or contiguous surrounding tissue that is abnormal in terms of viability, blood supply, sensation, or edema. The damaged tissue not only compromises healthy circulation to the area but may slow the flow of venous blood and lymph, thereby providing nutrients to bacteria and fueling ongoing damage. Host factors such as poor nutrition and immunosuppression may also be relevant. Diabetes in adults poses the most significant risk. Diabetic neuropathy adds to the progression of osteomyelitis as the patient may be unaware of infection as it spreads into the bone; the consequences include thousands of amputations each year. Additional sources of immunosuppression, such as chemotherapy and treatment with glucocorticoids or tumor necrosis factor (TNF) inhibitors, also inhibit normal defense mechanisms and thus predispose to more frequent and serious infections whose symptoms are diminished because of reduced inflammatory responses.

The bacteria involved in osteomyelitis perpetuate themselves by elaborating toxins that further damage tissues, including bone. *S. aureus* is particularly adept in this respect; it colonizes the nasal area in about one-third of healthy individuals and can produce a wide variety of cytokines, enzymes, and toxins that destroy tissue and affect neutrophil response. Some *S. aureus* bacteria survive uptake into the phagocytic vacuoles of macrophages and continue to cause disease and recrudescence by persistently eluding the usual defense mechanisms. This capacity for "hibernation" and persistence may allow *S. aureus* to remain dormant for decades before infection erupts at the sites of old injuries (e.g., shrapnel or other penetrating wounds).

Coagulase-negative staphylococci are generally not as virulent as *S. aureus* but have been found to persist by producing a biofilm that protects them from the host and apparently allows them to exist for many years on prosthetic joints, with minimal symptoms. The extent to which other organisms use biofilm to their advantage is unclear, but biofilm production probably plays a significant role in osteomyelitis, especially the chronic forms.

Multiple bacteria may be recovered from cultures, especially when there is an entry wound. Decisions about which ones to target in antibiotic therapy are often difficult. Common skin-dwelling and colonizing microbes usually do not need to be treated, and overtreatment in fact results in unnecessary toxicity and increases antimicrobial resistance among the organisms that survive. Anaerobic bacteria can often be recovered and may play a synergistic role with usual or unusual pathogens; specific therapy is sometimes beneficial in these situations.

The intrinsic factors of organisms that are responsible for persistence and bone destruction have not yet been identified. However, there is probably strain-to-strain variation in virulence factors produced by particular clones, with some strains consequently much more virulent than others. The prevention of biofilm production merits investigation in this regard.

APPROACH TO THE PATIENT

Osteomyelitis

The best approach to the care of a patient with significant osteomyelitis is to assemble a team of providers who can work together in considering the microbiology of the infection and make sound decisions about antibiotic therapy and surgery. The most effective program will include evaluation and management of antibiotics, microbiology, pharmacology, glucose levels, vascular disease, neuropathy, and renal function, with close follow-up by a knowledgeable physician who is interested in leading the team in coordinating care.

When osteomyelitis is suspected, a careful, methodical approach is needed (see "Clinical Manifestations and Diagnosis," next). Patients should be educated about the significance of an infection that involves bone, especially if risk factors cannot be eliminated. Blood tests, cultures, standard radiography, scans, biopsies, and surgery may all be necessary for a clear diagnosis and full delineation of the pathogen. Collection of this baseline information can be very important in both early and late decision-making.

Initial evaluations for osteomyelitis must be aggressive, as the infection can progress rapidly in the absence of antibiotic therapy effective against the wide variety of potential pathogens. Inadequacies in cultures, surgery, or temporizing measures may greatly exacerbate the damage caused by the infection. Hospitalization may be indicated for rapid multispecialty evaluation, imaging, and stabilization of complex infections such as with a diabetic foot. Outpatient therapy may not be adequate for the teamwork and interventions needed. Early admission and procedures may actually shorten the length of hospital stay.

The physician should inform the patient about the value of all the necessary evaluations, the implications of surgery, and the possibility of a prolonged course of IV antibiotic therapy, whether in the hospital or at home. A patient's fear of amputation can lead to inordinate delays in seeking treatment that allow the infection to progress. Moreover, it is not unusual for a patient to refuse surgery and amputation even though such treatments will clearly increase the likelihood of a functional lifestyle. Therefore, it is best to prepare patients early on if there may be negative outcomes such as amputation and perhaps to set criteria and timelines for success or failure of therapy and interventions.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Diagnosis of acute osteomyelitis within the first few weeks of onset is important and is usually relatively easy. If the diagnosis is missed, however, the symptoms may become chronic, with slow progression or a dormant phase of several years.

A thorough history and physical examination are the mainstays of evaluation for osteomyelitis. A clear pattern of pain, swelling, and possibly drainage after surgery or injury should raise suspicion, but such indicators may not all be present, even in a patient with neuropathy, compromised circulation, chronic edema, organ failure, diabetes, or other predisposing factors. Direct questions about previous injuries, infections, surgeries, or hardware implantation—even decades earlier—can yield information critical in guiding empirical antibiotic therapy and surgery. A history of injury is particularly important, even if the skin was not broken and there were no clinical signs of bacteremia. It is not unusual for a soft tissue injury to serve as a nidus of secondary bone infection, presumably seeded by low-level bacteremia and often occurring without symptoms. Other sources of seeding may include boils, abscesses, cellulitis, or injection sites. A careful examination is essential in identifying additional predisposing factors and assessing the role of comorbidities such as neuropathy, arterial disease, venous insufficiency, and chronic trauma that can lead to severe accumulation of callus in insensate feet.

Careful consideration and assessment of disorders that may mimic or accompany osteomyelitis are essential. Arthritis, gout, ischemia, neuropathies, and recent surgery may be diagnosed when osteomyelitis is the real cause of symptoms or a cofactor. For example, chronic back pain may be attributed to degenerative arthritis, but there can be a substantial loss of neurologic function if the pain is actually due to diskitis with vertebral osteomyelitis.

Correctly diagnosing osteomyelitis early has crucial implications for later function, disability, treatment cost, and risk of a fatal outcome. A variety of tools must be used to definitively diagnose or conclusively rule out an infection. A standard x-ray is a good starting point that can reveal a variety of abnormalities **(Fig. 23-1*A*)** and may eliminate the need for further imaging studies. Bone loss, sequestra, periosteal elevation or swelling (which can develop early on), and shadows around foreign bodies are hallmarks of bone infection. However, these findings may also be found with other disorders, such as tumors, trauma, avascular necrosis, and gout. Standard two-dimensional images can be of limited value in assessing complex bones. The value of radiology may be limited by the time required for an infection to become apparent; actual dissolution or resorption of bone due to infection may not be apparent for several weeks or more.

Depending on the results of the initial x-ray, further investigations with invasive techniques may be appropriate. Collection of pus by needle aspiration through a clean area from a closed pocket not only documents bone infection but also permits recovery and evaluation of the pathogen(s). A culture of a wound swab may be of some value but is clearly less reliable in identifying the real culprit(s), which may be present in the bone but absent from its surface. Biopsy provides more accurate microbiologic information than needle aspiration and supplies tissue for pathology studies, which may be helpful. Some organisms that usually are not recovered (in a timely fashion or at all) by standard cultures may be rendered visible with special staining of tissue samples. Unfortunately, the size of the needle used for needle biopsy may not be appropriate for small bones of the hands or feet. Open surgical exploration, biopsy, and drainage, which can provide high-quality tissue samples for culture and pathology and offer a view of the infected bone and surrounding area, should also be considered. Necrotic tissue can be removed and circulation assessed with one procedure. Polymerase chain reaction and other sequencing technologies are increasingly being used to detect and identify specific organisms—and even to determine their susceptibilities—within hours instead of days or weeks. Information on specific strains of unusual organisms may be of value, especially in difficult cases.

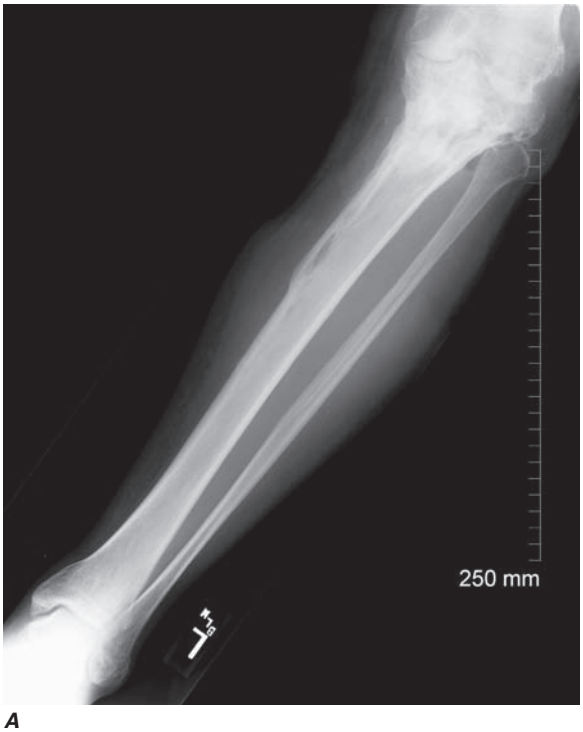
Laboratory tests are useful in assessing osteomyelitis but usually do not yield specific information relevant to etiology or severity. Leukocytosis may be noted in acute infection but is less likely in chronic infection, which may also be associated with anemia. Determination of the erythrocyte sedimentation rate (ESR) is a simple, inexpensive aid to diagnosis; it serves as an indicator of response with *S. aureus* infections but is not as useful for gram-negative infections because the cytokines and inflammatory elements that result in elevations are different for gram-positive (*S. aureus*) than for gram-negative infections. C-reactive protein (CRP) measurement may be helpful, especially in the evaluation of children, but may not be as useful as an ESR determination in some cases. CRP changes occur earlier in response to bacterial infection. Both ESR and CRP determinations have significant limitations in multifactorial diseases, with elevated values reflecting conditions other than osteomyelitis. Additional laboratory tests for diseases associated with bone loss that may mimic or complicate osteomyelitis should include measurement of glucose levels and tests for renal failure, gout, vasculitis, and rheumatoid diseases.

Additional imaging studies may be of value if the diagnosis remains unclear. CT can delineate bone more clearly than standard radiography and offers three-dimensional displays that can be extremely useful in detecting abnormalities and devising a surgical approach. MRI (Fig. 23-1*B–D*) provides high-quality images of the soft tissue around the bone abnormality and may be essential in diagnosing an epidural abscess related to vertebral osteomyelitis. Technetium and leukocyte isotope scans offer insight into the activity of the disease process and the affected site(s). Although these additional screening tools may be helpful in evaluation and decision-making, they may not be cost-effective.

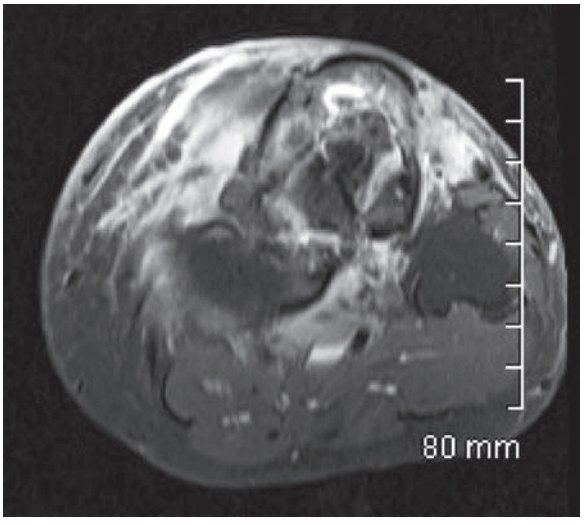
TREATMENT Osteomyelitis

Therapy for osteomyelitis is challenging because of the variety of causative organisms, the usual comorbidities, the need for a prolonged course and IV administration, the common physical limitations of the patient, and high costs. An aggressive therapeutic approach is warranted given the dire consequences of failure of medical therapy, which can include loss of limbs. The sooner the infection is diagnosed and treated, the better the outcome and the less damage done during delays in intervention. Antibiotic therapy should be used aggressively to stop disease progression and should be designed to avoid the development of resistant organisms. Early surgical intervention (e.g., debridement) can confirm the infection, identify and characterize the etiologic agent(s), and remove dead or devitalized tissue that may be providing bacteria with nutrients and allowing them to spread. A variety of antibiotics are available for most of the likely pathogens **(Table 23-2)**, although the most common pathogen—*S. aureus*—continues to evolve mechanisms to elude these drugs. MRSA strains represent an increasing problem in both the hospital and the community. Staphylococci and Enterobacteriaceae resistant to even more antibiotics than MRSA appear to be evolving.

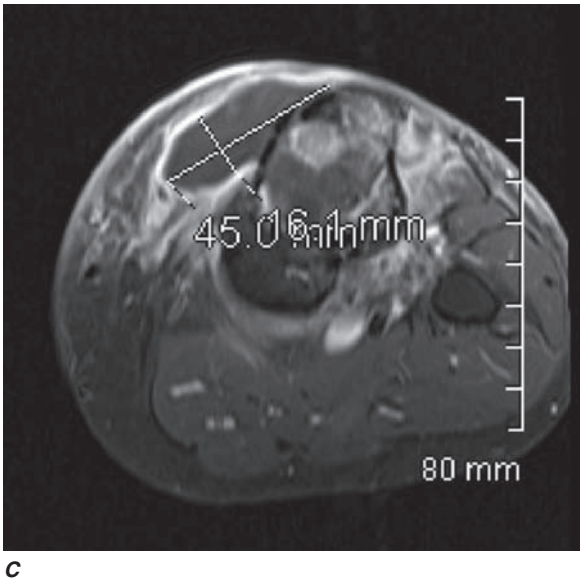
The most common targets for empirical antibiotic therapy are staphylococci, which are carried asymptomatically in and around the nares by nearly one-third of



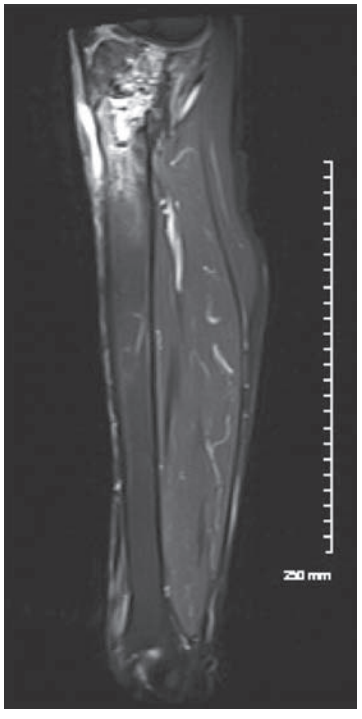
A



B



C



D

FIGURE 23-1

(***A***) Standard radiology image indicates infection with sclerosis of the proximal tibia and periosteal elevation and obvious bone destruction with an apparent cavity and the suggestion of a sequestrum in the proximal medial tibia. (***B, C***) Magnetic resonance images more clearly visualize the bone and soft tissue anatomy, confirming an extensive infection with destruction within the proximal tibia that has extended into the surrounding soft tissues and the joint as well as a ring of calcification most consistent with an abscess. (***D***) A longitudinal MRI shows the extent of longitudinal bone destruction and soft tissue involvement with contrast enhancement that suggests viable marrow from the middle to the distal tibial shaft.

healthy people. The common β-lactam antibiotics provide excellent results against methicillin-sensitive *S. aureus* strains. Oxacillin and nafcillin are first-line agents but may elicit more adverse reactions than cephalosporins. Cefazolin is a reasonable alternative in the hospital, but ceftriaxone is preferred as an outpatient drug because it can be given (by the IV or IM route) only once a day.

MRSA strains have been controlled with vancomycin for many years, but this drug appears to be losing its effectiveness against these microbes. New antibiotics have been designed to fill this need, although their efficacy has not been documented. In an outpatient setting, vancomycin does not appear to be as effective against methicillin-susceptible staphylococcal osteomyelitis as

TABLE 23-2

ANTIBIOTICS FOR THE TREATMENT OF OSTEOMYELITIS

ORGANISM	ANTIMICROBIAL AGENT	DOSING	COMMENTS
Methicillin-susceptible *Staphylococcus aureus*	Oxacillin or nafcillin	2 g IV q6h	May be more active than cephalosporins More difficult than cephalosporins to administer for long periods
	Cephalosporins	Cefazolin: 2 g IV q8h Ceftriaxone: 1–2 g IV q24h	Ceftriaxone advantageous with OPAT
	Clindamycin[a]	600–900 mg IV q8h	Not well studied for osteomyelitis Oral form possible (300–600 mg q8h) Resistance significant and increasing Toxicity different from that of β-lactam antibiotics
Methicillin-resistant *S. aureus*	Vancomycin	15 mg/kg IV q12h	Strains with an MIC of ≥2 μg/mL may not respond well.
	Daptomycin[a]	4–6 mg/kg IV q24h	Promising, but concern about adverse effects with prolonged therapy
	Linezolid[a]	600 mg IV or PO q12h	Effectiveness and adverse effects with prolonged therapy unclear Bacteriostatic
Streptococci	Penicillin	5 mU IV q6h or 20 mU/d by continuous infusion	Not all streptococci are susceptible. Ceftriaxone (1 g/d IV or IM) and ampicillin (12 g/d IV) are alternatives.
Enterococci	Penicillin plus gentamicin	As above 5 mg/kg daily IV	If strain is susceptible
	Vancomycin	As above	If strain is susceptible
Enterobacteriaceae (*E. coli*, *Klebsiella*, other)	Ceftriaxone or another cephalosporin	As above	If strain is susceptible
	Ciprofloxacin	400 mg IV q8–12h	500–750 mg q8–12h if strain is susceptible
Pseudomonas aeruginosa	Ciprofloxacin	As above	Resistance may develop during therapy; if strain is resistant, drugs to consider include cefepime and ceftazidime.

[a]Not approved for use in osteomyelitis by the U.S. Food and Drug Administration.
Abbreviations: MIC, minimal inhibitory concentration; OPAT, outpatient parenteral antimicrobial therapy.

oxacillin or ceftriaxone. Publications about the value of daptomycin for osteomyelitis are encouraging. Tigecycline is active against MRSA but is only bacteriostatic and does not yet have a well-established outcomes record. Telavancin may also be of value against vancomycin-resistant staphylococci but has not yet been adequately tested for bone infections.

Additional antimicrobial agents for use against staphylococcal infections include linezolid, which offers the advantage of both oral and IV formulations but is bacteriostatic and has not yet been well studied. Moreover, its use—although apparently less expensive than that of other parenteral drugs—is limited by its cost. Clindamycin can also be used as both an IV and an oral agent, although antimicrobial resistance is a growing problem. Rifampin, a potential adjunct to other antistaphylococcal agents, is highly active in vitro and can penetrate phagocytic vacuoles to reach staphylococci therein. Unfortunately, resistance develops rapidly if rifampin is used alone, and clinical outcomes are not always as good as anticipated. Other agents, such as aminoglycosides, folic acid inhibitors, and macrolides, may play a limited role; they generally are neither as effective nor as toxic as other available agents.

Fluoroquinolone antibiotics offer both IV and oral therapy options and are often included in the standard recommendation for treatment of many susceptible strains of Enterobacteriaceae and *Pseudomonas* species. Drugs of this class do, however, have some limitations in terms of emerging resistance (even during therapy) and may exert some adverse neuromuscular effects (e.g., tendon rupture and impaired healing) that may be particularly relevant to the prolonged courses of antibiotics usually needed to cure the infection. In general, fluoroquinolones should not be used to treat *S. aureus* infections because of these limitations and the availability of better-studied antibiotics.

The optimal route and duration of therapy for osteomyelitis remain controversial. The usual recommendations stem from a 1970 study in which cases of osteomyelitis were characterized and outcomes were

evaluated in relation to the duration of IV therapy. Better outcomes appeared to be related to a course of ≥4 weeks in some types of infection. Even though the characteristics of the bacteria and the available antibiotics were quite different at that time, a 4- to 6-week course of IV therapy remains the standard and is the usual recommended minimum. This recommendation has been challenged in pediatric studies in light of increasing evidence that oral agents and shorter courses may be adequate. Because some of the active agents reach comparable levels when given by mouth, a switch from the recommended IV administration to oral therapy may be appropriate in some situations. The proper duration of antimicrobial therapy depends on a variety of factors, including the infecting organism, the bone involved, surgical procedures, and drug tolerance and safety. Prolonged courses may be justified by extensive disease, immunocompromise, poor clinical response, and vertebral osteomyelitis. Whether a bone infection has truly been cured becomes clear only over time; relapse is not uncommon and may occur years later, especially in patients with ongoing risk factors and comorbidities. The literature suggests that a 6-month follow-up period is adequate to determine the success of treatment. Patients should be followed for at least that long, even though antibiotics have been discontinued. The possibility of relapses and the potential for their prevention should not be overlooked.

Surgery is an important tool in the treatment of osteomyelitis, offering the benefits of direct observation, prompt removal of all devitalized tissue and bone, and drainage of the infection site. Nevertheless, it is not without risk, and loss of bone or other tissue may adversely affect function. In addition, because bone may regenerate to some degree when infection is eradicated, surgery is not always needed. Surgical approaches vary with the bone involved and the extent of disease. The Cierny-Mader classification system is helpful when three-dimensional imaging is done, and MRI may help determine the viability of bone or marrow. Residual dead spaces are a source of concern and may require tissue flaps and closure. Local antibiotics and impregnated cement or beads may be of value but not should not replace IV antibiotic therapy without further study. If surgery is performed and most or all of the infected bone is removed, a full 4- to 6-week course of IV therapy probably is not necessary. However, the precise duration that is required is not clear and most likely depends primarily on the other factors involved in individual cases. One week of IV therapy after surgery may be justified to ensure pathogen eradication and healing.

Outpatient parenteral antibiotic therapy (OPAT) is a valuable means of providing the long course of IV antibiotics that is considered the standard of care and has been proven efficacious over decades. Despite potential risks outside the hospital that patients and their providers must consider, OPAT is safe and effective when properly managed and administered. This approach is conducive to a better quality of life in a familiar setting, is considered safer because of the lack of exposure to hospital-related infections (which affect ~1 patient in every 20 admitted), is much less expensive than treatment administered in the hospital, and generally facilitates recovery, often allowing the patient to return to work or resume other day-to-day activities during the treatment course.

COMPLICATIONS

The complications of osteomyelitis are numerous and are most commonly related to loss of full function of the bone or supporting tissues. Fractures are more likely with progressive disease. Local spread and dissemination of infection are also possible. Misdiagnosis is particularly likely when another disease is complicating the infection. In rare instances, chronic inflammation and infection may lead to malignant transformation into squamous cell carcinoma or sarcoma.

PROGNOSIS

The outcomes of osteomyelitis vary tremendously depending on the bone involved, the predisposing factors, the underlying diseases, and the treatment provided. Standard guidelines cannot be applied uniformly; e.g., a case of mandible infection arising from a tooth abscess may be cured with an extraction alone, whereas a case of vertebral osteomyelitis may require a prolonged course of IV therapy as it cannot be approached surgically without neurologic sequelae. For large bones, the 4- to 6-week course of IV therapy still seems reasonable, although recent studies suggest that with some new antimicrobial agents a shorter course of IV therapy, possibly with an early switch to oral therapy, may be sufficient. Determining the outcome even of long-bone osteomyelitis is complicated by uncertainty as to the duration of follow-up needed. The actual outcome in terms of debility and limb salvage may be as dependent on underlying and complicating factors and care as it is on antibiotic therapy.

PREVENTION

Osteomyelitis can be prevented in some instances by better infection-control measures, especially before surgery. Both mupirocin and chlorhexidine are of proven value in preventing operative infections, which are an increasing cause of bone infections associated with implanted material. Prompt treatment of bacteremia and elimination of sources of infection (e.g., boils or folliculitis) before surgery and in other situations may prevent infections. Aggressive surgical management of injuries may also help avoid the constellation of factors that lead to bone infections.

Awareness of persistent sites of infection and reasonable attempts at eradication may promote prevention. Many persistent infections that do not initially impair function or cause pain are ignored by patients; an example is provided by the classic problem of diabetic foot infections, with ulcers that burrow into the soles of insensate feet and often reach bones. Likewise, sacral ulcers are often overlooked or ignored both by physicians and by patients with neurologic impairment. Attempts to eradicate or close entry wounds are critical and should be undertaken early on.

CHAPTER 24

INFECTIOUS ARTHRITIS

Lawrence C. Madoff

Although *Staphylococcus aureus*, *Neisseria gonorrhoeae*, and other bacteria are the most common causes of infectious arthritis, various mycobacteria, spirochetes, fungi, and viruses also infect joints **(Table 24-1)**. Since acute bacterial infection can destroy articular cartilage rapidly, all inflamed joints must be evaluated without delay to exclude noninfectious processes and determine appropriate antimicrobial therapy and drainage procedures. For more detailed information on infectious arthritis caused by specific organisms, the reader is referred to the chapters on those organisms.

Acute bacterial infection typically involves a single joint or a few joints. Subacute or chronic monarthritis or oligoarthritis suggests mycobacterial or fungal infection; episodic inflammation is seen in syphilis, Lyme disease, and the reactive arthritis that follows enteric infections and chlamydial urethritis. Acute polyarticular inflammation occurs as an immunologic reaction during the course of endocarditis, rheumatic fever, disseminated neisserial infection, and acute hepatitis B. Bacteria and viruses occasionally infect multiple joints, the former most commonly in persons with rheumatoid arthritis.

APPROACH TO THE PATIENT

Infectious Arthritis

Aspiration of synovial fluid—an essential element in the evaluation of potentially infected joints—can be performed without difficulty in most cases by the insertion of

TABLE 24-1

DIFFERENTIAL DIAGNOSIS OF ARTHRITIS SYNDROMES

ACUTE MONARTICULAR ARTHRITIS	CHRONIC MONARTICULAR ARTHRITIS	POLYARTICULAR ARTHRITIS
Staphylococcus aureus	*Mycobacterium tuberculosis*	*Neisseria meningitidis*
Streptococcus pneumoniae	Nontuberculous mycobacteria	*N. gonorrhoeae*
β-Hemolytic streptococci	*Borrelia burgdorferi*	Nongonococcal bacterial arthritis
Gram-negative bacilli	*Treponema pallidum*	Bacterial endocarditis
Neisseria gonorrhoeae	*Candida* species	*Candida* species
Candida species	*Sporothrix schenckii*	Poncet's disease (tuberculous rheumatism)
Crystal-induced arthritis	*Coccidioides immitis*	Hepatitis B virus
Fracture	*Blastomyces dermatitidis*	Parvovirus B19
Hemarthrosis	*Aspergillus* species	HIV
Foreign body	*Cryptococcus neoformans*	Human T-lymphotropic virus type I
Osteoarthritis	*Nocardia* species	Rubella virus
Ischemic necrosis	*Brucella* species	Arthropod-borne viruses
Monarticular rheumatoid arthritis	Legg-Calvé-Perthes disease	Sickle cell disease flare
	Osteoarthritis	Reactive arthritis
		Serum sickness
		Acute rheumatic fever
		Inflammatory bowel disease
		Systemic lupus erythematosus
		Rheumatoid arthritis/Still's disease
		Other vasculitides
		Sarcoidosis

a large-bore needle into the site of maximal fluctuance or tenderness or by the route of easiest access. Ultrasonography or fluoroscopy may be used to guide aspiration of difficult-to-localize effusions of the hip and, occasionally, the shoulder and other joints. Normal synovial fluid contains <180 cells (predominantly mononuclear cells) per microliter. Synovial cell counts averaging 100,000/μL (range, 25,000–250,000/μL), with >90% neutrophils, are characteristic of acute bacterial infections. Crystal-induced, rheumatoid, and other noninfectious inflammatory arthritides usually are associated with <30,000–50,000 cells/μL; cell counts of 10,000–30,000/μL, with 50–70% neutrophils and the remainder lymphocytes, are common in mycobacterial and fungal infections. Definitive diagnosis of an infectious process relies on identification of the pathogen in stained smears of synovial fluid, isolation of the pathogen from cultures of synovial fluid and blood, or detection of microbial nucleic acids and proteins by nucleic acid amplification (NAA)–based assays and immunologic techniques.

ACUTE BACTERIAL ARTHRITIS

Pathogenesis

Bacteria enter the joint from the bloodstream; from a contiguous site of infection in bone or soft tissue; or by direct inoculation during surgery, injection, animal or human bite, or trauma. In hematogenous infection, bacteria escape from synovial capillaries, which have no limiting basement membrane, and within hours provoke neutrophilic infiltration of the synovium. Neutrophils and bacteria enter the joint space; later, bacteria adhere to articular cartilage. Degradation of cartilage begins within 48 h as a result of increased intraarticular pressure, release of proteases and cytokines from chondrocytes and synovial macrophages, and invasion of the cartilage by bacteria and inflammatory cells. Histologic studies reveal bacteria lining the synovium and cartilage as well as abscesses extending into the synovium, cartilage, and—in severe cases—subchondral bone. Synovial proliferation results in the formation of a pannus over the cartilage, and thrombosis of inflamed synovial vessels develops. Bacterial factors that appear important in the pathogenesis of infective arthritis include various surface-associated adhesins in *S. aureus* that permit adherence to cartilage and endotoxins that promote chondrocyte-mediated breakdown of cartilage.

Microbiology

The hematogenous route of infection is the most common route in all age groups, and nearly every bacterial pathogen is capable of causing septic arthritis. In infants, group B streptococci, gram-negative enteric bacilli, and *S. aureus* are the most common pathogens. Since the advent of the *Haemophilus influenzae* vaccine, the predominant causes among children <5 years of age have been *S. aureus*, *Streptococcus pyogenes* (group A *Streptococcus*), and (in some centers) *Kingella kingae*. Among young adults and adolescents, *N. gonorrhoeae* is the most commonly implicated organism. *S. aureus* accounts for most nongonococcal isolates in adults of all ages; gram-negative bacilli, pneumococci, and β-hemolytic streptococci—particularly groups A and B but also groups C, G, and F—are involved in up to one-third of cases in older adults, especially those with underlying comorbid illnesses.

Infections after surgical procedures or penetrating injuries are due most often to *S. aureus* and occasionally to other gram-positive bacteria or gram-negative bacilli. Infections with coagulase-negative staphylococci are unusual except after the implantation of prosthetic joints or arthroscopy. Anaerobic organisms, often in association with aerobic or facultative bacteria, are found after human bites and when decubitus ulcers or intraabdominal abscesses spread into adjacent joints. Polymicrobial infections complicate traumatic injuries with extensive contamination. Bites and scratches from cats and other animals may introduce *Pasteurella multocida* into joints, and bites from humans may introduce *Eikenella corrodens* or other components of the oral flora.

Nongonococcal bacterial arthritis

Epidemiology

Although hematogenous infections with virulent organisms such as *S. aureus*, *H. influenzae*, and pyogenic streptococci occur in healthy persons, there is an underlying host predisposition in many cases of septic arthritis. Patients with rheumatoid arthritis have the highest incidence of infective arthritis (most often secondary to *S. aureus*) because of chronically inflamed joints; glucocorticoid therapy; and frequent breakdown of rheumatoid nodules, vasculitic ulcers, and skin overlying deformed joints. Diabetes mellitus, glucocorticoid therapy, hemodialysis, and malignancy all carry an increased risk of infection with *S. aureus* and gram-negative bacilli. Tumor necrosis factor inhibitors (etanercept and infliximab), which increasingly are used for the treatment of rheumatoid arthritis, predispose to mycobacterial infections and possibly to other pyogenic bacterial infections and could be associated with septic arthritis in this population. Pneumococcal infections complicate alcoholism, deficiencies of humoral immunity, and hemoglobinopathies. Pneumococci, *Salmonella* species, and *H. influenzae* cause septic arthritis in persons infected with HIV. Persons with primary immunoglobulin deficiency are at risk for mycoplasmal arthritis, which results in permanent joint damage if tetracycline and replacement therapy with IV immunoglobulin are not administered promptly. IV drug users acquire staphylococcal and streptococcal infections from their own flora and acquire pseudomonal and other gram-negative infections from drugs and injection paraphernalia.

Clinical manifestations

Some 90% of patients present with involvement of a single joint—most commonly the knee; less frequently the hip; and still less often the shoulder, wrist, or elbow. Small joints of the hands and feet are more likely to be affected

after direct inoculation or a bite. Among IV drug users, infections of the spine, sacroiliac joints, and sternoclavicular joints **(Fig. 24-1)** are more common than infections of the appendicular skeleton. Polyarticular infection is most common among patients with rheumatoid arthritis and may resemble a flare of the underlying disease.

The usual presentation consists of moderate to severe pain that is uniform around the joint, effusion, muscle spasm, and decreased range of motion. Fever in the range of 38.3°–38.9°C (101°–102°F) and sometimes higher is common but may not be present, especially in persons with rheumatoid arthritis, renal or hepatic insufficiency, or conditions requiring immunosuppressive therapy. The inflamed, swollen joint is usually evident on examination except in the case of a deeply situated joint such as the hip, shoulder, or sacroiliac joint. Cellulitis, bursitis, and acute osteomyelitis, which may produce a similar clinical picture, should be distinguished from septic arthritis by their greater range of motion and less than circumferential swelling. A focus of extraarticular infection such as a boil or pneumonia should be sought. Peripheral-blood leukocytosis with a left shift and elevation of the erythrocyte sedimentation rate or C-reactive protein level are common.

Plain radiographs show evidence of soft tissue swelling, joint-space widening, and displacement of tissue planes by the distended capsule. Narrowing of the joint space and bony erosions indicate advanced infection and a poor prognosis. Ultrasound is useful for detecting effusions in the hip, and CT or MRI can demonstrate infections of the sacroiliac joint, the sternoclavicular joint, and the spine very well.

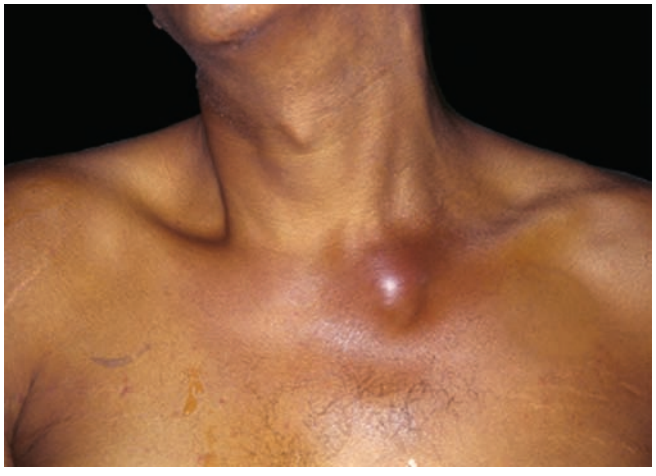


FIGURE 24-1
Acute septic arthritis of the sternoclavicular joint. A man in his forties with a history of cirrhosis presented with a new onset of fever and lower neck pain. He had no history of IV drug use or previous catheter placement. Jaundice and a painful swollen area over his left sternoclavicular joint were evident on physical examination. Cultures of blood drawn at admission grew group B *Streptococcus*. The patient recovered after treatment with IV penicillin. (*Courtesy of Francisco M. Marty, MD, Brigham and Women's Hospital, Boston; with permission.*)

Laboratory findings

Specimens of peripheral blood and synovial fluid should be obtained before antibiotics are administered. Blood cultures are positive in up to 50–70% of *S. aureus* infections, but are less frequently positive in infections due to other organisms. The synovial fluid is turbid, serosanguineous, or frankly purulent. Gram-stained smears confirm the presence of large numbers of neutrophils. Levels of total protein and lactate dehydrogenase in synovial fluid are elevated, and the glucose level is depressed; however, these findings are not specific for infection, and measurement of these levels is not necessary for diagnosis. The synovial fluid should be examined for crystals, because gout and pseudogout can resemble septic arthritis clinically, and infection and crystal-induced disease occasionally occur together. Organisms are seen on synovial fluid smears in nearly three-quarters of infections with *S. aureus* and streptococci and in 30–50% of infections due to gram-negative and other bacteria. Cultures of synovial fluid are positive in >90% of cases. Inoculation of synovial fluid into bottles containing liquid media for blood cultures increases the yield of a culture, especially if the pathogen is a fastidious organism or the patient is taking an antibiotic. Although not yet widely available, NAA-based assays for bacterial DNA will be useful for the diagnosis of partially treated or culture-negative bacterial arthritis.

TREATMENT Nongonococcal Bacterial Arthritis

Prompt administration of systemic antibiotics and drainage of the involved joint can prevent destruction of cartilage, postinfectious degenerative arthritis, joint instability, or deformity. Once samples of blood and synovial fluid have been obtained for culture, empirical antibiotics should be given that are directed against the bacteria visualized on smears or the pathogens that are likely in light of the patient's age and risk factors. Initial therapy should consist of IV administration of bactericidal agents; direct instillation of antibiotics into the joint is not necessary to achieve adequate levels in synovial fluid and tissue. An IV third-generation cephalosporin such as cefotaxime (1 g every 8 h) or ceftriaxone (1–2 g every 24 h) provides adequate empirical coverage for most community-acquired infections in adults when smears show no organisms. IV vancomycin (1 g every 12 h) is used if there are gram-positive cocci on the smear. If methicillin-resistant *S. aureus* is an unlikely pathogen (e.g., when it is not widespread in the community), either oxacillin or nafcillin (2 g every 4 h) should be given. In addition, an aminoglycoside or third-generation cephalosporin should be given to IV drug users or other patients in whom *Pseudomonas aeruginosa* may be the responsible agent.

Definitive therapy is based on the identity and antibiotic susceptibility of the bacteria isolated in culture. Infections due to staphylococci are treated with oxacillin, nafcillin, or vancomycin for 4 weeks. Pneumococcal and streptococcal infections due to penicillin-susceptible

organisms respond to 2 weeks of therapy with penicillin G (2 million units IV every 4 h); infections caused by *H. influenzae* and by strains of *Streptococcus pneumoniae* that are resistant to penicillin are treated with cefotaxime or ceftriaxone for 2 weeks. Most enteric gram-negative infections can be cured in 3–4 weeks by a second- or third-generation cephalosporin given IV or by a fluoroquinolone such as levofloxacin (500 mg IV or PO every 24 h). *P. aeruginosa* infection should be treated for at least 2 weeks with a combination regimen of an aminoglycoside plus either an extended-spectrum penicillin such as mezlocillin (3 g IV every 4 h) or an antipseudomonal cephalosporin such as ceftazidime (1 g IV every 8 h). If tolerated, this regimen is continued for an additional 2 weeks; alternatively, a fluoroquinolone such as ciprofloxacin (750 mg PO twice daily) is given by itself or with the penicillin or cephalosporin in place of the aminoglycoside.

Timely drainage of pus and necrotic debris from the infected joint is required for a favorable outcome. Needle aspiration of readily accessible joints such as the knee may be adequate if loculations or particulate matter in the joint does not prevent its thorough decompression. Arthroscopic drainage and lavage may be employed initially or within several days if repeated needle aspiration fails to relieve symptoms, decrease the volume of the effusion and the synovial white cell count, and clear bacteria from smears and cultures. In some cases, arthrotomy is necessary to remove loculations and debride infected synovium, cartilage, or bone. Septic arthritis of the hip is best managed with arthrotomy, particularly in young children, in whom infection threatens the viability of the femoral head. Septic joints do not require immobilization except for pain control before symptoms are alleviated by treatment. Weight bearing should be avoided until signs of inflammation have subsided, but frequent passive motion of the joint is indicated to maintain full mobility. Although addition of glucocorticoids to antibiotic treatment improves the outcome of *S. aureus* arthritis in experimental animals, no clinical trials have evaluated this approach in humans.

Gonococcal arthritis

Epidemiology

Although its incidence has declined in recent years, gonococcal arthritis (Chap. 49) has accounted for up to 70% of episodes of infectious arthritis in persons <40 years of age in the United States. Arthritis due to *N. gonorrhoeae* is a consequence of bacteremia arising from gonococcal infection or, more frequently, from asymptomatic gonococcal mucosal colonization of the urethra, cervix, or pharynx. Women are at greatest risk during menses and during pregnancy and overall are two to three times more likely than men to develop disseminated gonococcal infection (DGI) and arthritis. Persons with complement deficiencies, especially of the terminal components, are prone to recurrent episodes of gonococcemia. Strains of gonococci that are most likely to cause DGI include those which produce transparent colonies in culture, have the type IA outer-membrane protein, or are of the AUH-auxotroph type.

Clinical manifestations and laboratory findings

The most common manifestation of DGI is a syndrome of fever, chills, rash, and articular symptoms. Small numbers of papules that progress to hemorrhagic pustules develop on the trunk and the extensor surfaces of the distal extremities. Migratory arthritis and tenosynovitis of the knees, hands, wrists, feet, and ankles are prominent. The cutaneous lesions and articular findings are believed to be the consequence of an immune reaction to circulating gonococci and immune-complex deposition in tissues. Thus, cultures of synovial fluid are consistently negative, and blood cultures are positive in <45% of patients. Synovial fluid may be difficult to obtain from inflamed joints and usually contains only 10,000–20,000 leukocytes/μL.

True gonococcal septic arthritis is less common than the DGI syndrome and always follows DGI, which is unrecognized in one-third of patients. A single joint such as the hip, knee, ankle, or wrist is usually involved. Synovial fluid, which contains >50,000 leukocytes/μL, can be obtained with ease; the gonococcus is only occasionally evident in gram-stained smears, and cultures of synovial fluid are positive in <40% of cases. Blood cultures are almost always negative.

Because it is difficult to isolate gonococci from synovial fluid and blood, specimens for culture should be obtained from potentially infected mucosal sites. Cultures and gram-stained smears of skin lesions are occasionally positive. All specimens for culture should be plated onto Thayer-Martin agar directly or in special transport media at the bedside and transferred promptly to the microbiology laboratory in an atmosphere of 5% CO_2, as generated in a candle jar. NAA-based assays are extremely sensitive in detecting gonococcal DNA in synovial fluid. A dramatic alleviation of symptoms within 12–24 h after the initiation of appropriate antibiotic therapy supports a clinical diagnosis of the DGI syndrome if cultures are negative.

TREATMENT Gonococcal Arthritis

Initial treatment consists of ceftriaxone (1 g IV or IM every 24 h) to cover possible penicillin-resistant organisms. Once local and systemic signs are clearly resolving and if the sensitivity of the isolate permits, the 7-day course of therapy can be completed with an oral agent such as ciprofloxacin (500 mg twice daily). If penicillin-susceptible organisms are isolated, amoxicillin (500 mg three times daily) may be used. Suppurative arthritis usually responds to needle aspiration of involved joints and 7–14 days of antibiotic treatment. Arthroscopic lavage or arthrotomy is rarely required. Patients with DGI should be treated for *Chlamydia trachomatis* infection unless this infection is ruled out by appropriate testing.

It is noteworthy that arthritis symptoms similar to those seen in DGI occur in meningococcemia. A dermatitis-arthritis syndrome, purulent monarthritis, and reactive polyarthritis have been described. All respond to treatment with IV penicillin.

SPIROCHETAL ARTHRITIS

Lyme disease

Lyme disease (Chap. 78) due to infection with the spirochete *Borrelia burgdorferi* causes arthritis in up to 70% of persons who are not treated. Intermittent arthralgias and myalgias—but not arthritis—occur within days or weeks of inoculation of the spirochete by the *Ixodes* tick. Later, there are three patterns of joint disease: (1) Fifty percent of untreated persons experience intermittent episodes of monarthritis or oligoarthritis involving the knee and/or other large joints. The symptoms wax and wane without treatment over months, and each year 10–20% of patients report loss of joint symptoms. (2) Twenty percent of untreated persons develop a pattern of waxing and waning arthralgias. (3) Ten percent of untreated patients develop chronic inflammatory synovitis that results in erosive lesions and destruction of the joint. Serologic tests for IgG antibodies to *B. burgdorferi* are positive in >90% of persons with Lyme arthritis, and an NAA-based assay detects *Borrelia* DNA in 85%.

TREATMENT Lyme Arthritis

Lyme arthritis generally responds well to therapy. A regimen of oral doxycycline (100 mg twice daily for 30 days), oral amoxicillin (500 mg four times daily for 30 days), or parenteral ceftriaxone (2 g/d for 2–4 weeks) is recommended. Patients who do not respond to a total of 2 months of oral therapy or 1 month of parenteral therapy are unlikely to benefit from additional antibiotic therapy and are treated with anti-inflammatory agents or synovectomy. Failure of therapy is associated with host features such as the human leukocyte antigen DR4 (HLA-DR4) genotype, persistent reactivity to OspA (outer-surface protein A), and the presence of hLFA-1 (human leukocyte function–associated antigen 1), which cross-reacts with OspA.

Syphilitic arthritis

Articular manifestations occur in different stages of syphilis (Chap. 74). In early congenital syphilis, periarticular swelling and immobilization of the involved limbs (Parrot's pseudoparalysis) complicate osteochondritis of long bones. Clutton's joint, a late manifestation of congenital syphilis that typically develops between ages 8 and 15 years, is caused by chronic painless synovitis with effusions of large joints, particularly the knees and elbows. Secondary syphilis may be associated with arthralgias, with symmetric arthritis of the knees and ankles and occasionally of the shoulders and wrists, and with sacroiliitis. The arthritis follows a subacute to chronic course with a mixed mononuclear and neutrophilic synovial-fluid pleocytosis (typical cell counts, 5000–15,000/μL). Immunologic mechanisms may contribute to the arthritis, and symptoms usually improve rapidly with penicillin therapy. In tertiary syphilis, Charcot's joint results from sensory loss due to tabes dorsalis. Penicillin is not helpful in this setting.

MYCOBACTERIAL ARTHRITIS

Tuberculous arthritis (Chap. 70) accounts for ~1% of all cases of tuberculosis and 10% of extrapulmonary cases. The most common presentation is chronic granulomatous monarthritis. An unusual syndrome, Poncet's disease, is a reactive symmetric form of polyarthritis that affects persons with visceral or disseminated tuberculosis. No mycobacteria are found in the joints, and symptoms resolve with antituberculous therapy.

Unlike tuberculous osteomyelitis (Chap. 23), which typically involves the thoracic and lumbar spine (50% of cases), tuberculous arthritis primarily involves the large weight-bearing joints, in particular the hips, knees, and ankles, and only occasionally involves smaller non-weight-bearing joints. Progressive monarticular swelling and pain develop over months or years, and systemic symptoms are seen in only half of all cases. Tuberculous arthritis occurs as part of a disseminated primary infection or through late reactivation, often in persons with HIV infection or other immunocompromised hosts. Coexistent active pulmonary tuberculosis is unusual.

Aspiration of the involved joint yields fluid with an average cell count of 20,000/μL, with ~50% neutrophils. Acid-fast staining of the fluid yields positive results in fewer than one-third of cases, and cultures are positive in 80%. Culture of synovial tissue taken at biopsy is positive in ~90% of cases and shows granulomatous inflammation in most. NAA methods can shorten the time to diagnosis to 1 or 2 days. Radiographs reveal peripheral erosions at the points of synovial attachment, periarticular osteopenia, and eventually joint-space narrowing. Therapy for tuberculous arthritis is the same as that for tuberculous pulmonary disease, requiring the administration of multiple agents for 6–9 months. Therapy is more prolonged in immunosuppressed individuals such as those infected with HIV.

Various atypical mycobacteria (Chap. 72) found in water and soil may cause chronic indolent arthritis. Such disease results from trauma and direct inoculation associated with farming, gardening, or aquatic activities. Smaller joints, such as the digits, wrists, and knees, are usually involved. Involvement of tendon sheaths and bursae is typical. The mycobacterial species involved include *Mycobacterium marinum*, *M. avium-intracellulare*, *M. terrae*, *M. kansasii*, *M. fortuitum*, and *M. chelonae*.

In persons who have HIV infection or are receiving immunosuppressive therapy, hematogenous spread to the joints has been reported for *M. kansasii*, *M. avium-intracellulare*, and *M. haemophilum*. Diagnosis usually requires biopsy and culture, and therapy is based on antimicrobial susceptibility patterns.

FUNGAL ARTHRITIS

Fungi are an unusual cause of chronic monarticular arthritis. Granulomatous articular infection with the endemic dimorphic fungi *Coccidioides immitis*, *Blastomyces dermatitidis*, and (less commonly) *Histoplasma capsulatum* **(Fig. 24-2)** results from hematogenous seeding or direct extension from bony lesions in persons with disseminated disease. Joint involvement is an unusual complication of sporotrichosis (infection with *Sporothrix schenckii*) among gardeners and other persons who work with soil or sphagnum moss. Articular sporotrichosis is six times more common among men than among women, and alcoholics and other debilitated hosts are at risk for polyarticular infection.

Candida infection involving a single joint—usually the knee, hip, or shoulder—results from surgical procedures, intraarticular injections, or (among critically ill patients with debilitating illnesses such as diabetes mellitus or hepatic or renal insufficiency and patients receiving immunosuppressive therapy) hematogenous spread. *Candida* infections in IV drug users typically involve the spine, sacroiliac joints, or other fibrocartilaginous joints. Unusual cases of arthritis due to *Aspergillus* species, *Cryptococcus neoformans*, *Pseudallescheria boydii*, and the dematiaceous fungi also have resulted from direct inoculation or disseminated hematogenous infection in immunocompromised persons.

The synovial fluid in fungal arthritis usually contains 10,000–40,000 cells/μL, with ~70% neutrophils. Stained specimens and cultures of synovial tissue often confirm the diagnosis of fungal arthritis when studies of synovial fluid give negative results. Treatment consists of drainage and lavage of the joint and systemic administration of an antifungal agent directed at a specific pathogen. The doses and duration of therapy are the same as for disseminated disease. Intraarticular instillation of amphotericin B has been used in addition to IV therapy.

VIRAL ARTHRITIS

Viruses produce arthritis by infecting synovial tissue during systemic infection or by provoking an immunologic reaction that involves joints. As many as 50% of women report persistent arthralgias, and 10% report frank arthritis within 3 days of the rash that follows natural infection with rubella virus and within 2–6 weeks after receipt of live-virus vaccine. Episodes of symmetric inflammation of fingers, wrists, and knees uncommonly recur for >1 year, but a syndrome of chronic fatigue, low-grade fever, headaches, and myalgias can persist for months or years. IV immunoglobulin has been helpful in selected cases. Self-limited monarticular or migratory polyarthritis may develop within 2 weeks

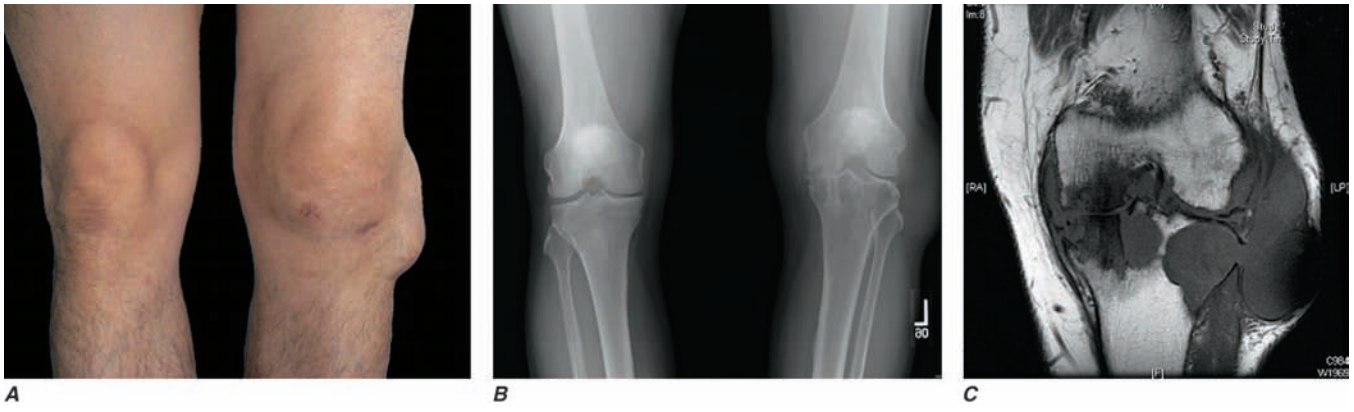


FIGURE 24-2
Chronic arthritis caused by *Histoplasma capsulatum* in the left knee. ***A.*** A man in his sixties from El Salvador presented with a history of progressive knee pain and difficulty walking for several years. He had undergone arthroscopy for a meniscal tear 7 years before presentation (without relief) and had received several intraarticular glucocorticoid injections. The patient developed significant deformity of the knee over time, including a large effusion in the lateral aspect. ***B.*** An x-ray of the knee showed multiple abnormalities, including severe medial femorotibial joint-space narrowing, several large subchondral cysts within the tibia and the patellofemoral compartment, a large suprapatellar joint effusion, and a large soft tissue mass projecting laterally over the knee. ***C.*** MRI further defined these abnormalities and demonstrated the cystic nature of the lateral knee abnormality. Synovial biopsies demonstrated chronic inflammation with giant cells, and cultures grew *H. capsulatum* after 3 weeks of incubation. All clinical cystic lesions and the effusion resolved after 1 year of treatment with itraconazole. The patient underwent a left total knee replacement for definitive treatment. (*Courtesy of Francisco M. Marty, MD, Brigham and Women's Hospital, Boston; with permission.*)

of the parotitis of mumps; this sequela is more common among men than among women. Approximately 10% of children and 60% of women develop arthritis after infection with parvovirus B19. In adults, arthropathy sometimes occurs without fever or rash. Pain and stiffness, with less prominent swelling (primarily of the hands but also of the knees, wrists, and ankles), usually resolve within weeks, although a small proportion of patients develop chronic arthropathy.

About 2 weeks before the onset of jaundice, up to 10% of persons with acute hepatitis B develop an immune complex–mediated, serum sickness–like reaction with maculopapular rash, urticaria, fever, and arthralgias. Less common developments include symmetric arthritis involving the hands, wrists, elbows, or ankles and morning stiffness that resembles a flare of rheumatoid arthritis. Symptoms resolve at the time jaundice develops. Many persons with chronic hepatitis C infection report persistent arthralgia or arthritis, both in the presence and in the absence of cryoglobulinemia.

Painful arthritis involving larger joints often accompanies the fever and rash of several arthropod-borne viral infections, including those caused by chikungunya, O'nyong-nyong, Ross River, Mayaro, and Barmah Forest viruses (Chap. 102). Symmetric arthritis involving the hands and wrists may occur during the convalescent phase of infection with lymphocytic choriomeningitis virus. Patients infected with an enterovirus frequently report arthralgias, and echovirus has been isolated from patients with acute polyarthritis.

Several arthritis syndromes are associated with HIV infection. Reactive arthritis (Reiter's syndrome) with painful lower-extremity oligoarthritis often follows an episode of urethritis in HIV-infected persons. HIV-associated reactive arthritis appears to be extremely common among persons with the HLA-B27 haplotype, but sacroiliac joint disease is unusual and is seen mostly in the absence of HLA-B27. Up to one-third of HIV-infected persons with psoriasis develop psoriatic arthritis. Painless monarthropathy and persistent symmetric polyarthropathy occasionally complicate HIV infection. Chronic persistent oligoarthritis of the shoulders, wrists, hands, and knees occurs in women infected with human T cell lymphotropic virus type I. Synovial thickening, destruction of articular cartilage, and leukemic-appearing atypical lymphocytes in synovial fluid are characteristic, but progression to T cell leukemia is unusual.

PARASITIC ARTHRITIS

Arthritis due to parasitic infection is rare. The guinea worm *Dracunculus medinensis* may cause destructive joint lesions in the lower extremities as migrating gravid female worms invade joints or cause ulcers in adjacent soft tissues that become secondarily infected. Hydatid cysts infect bones in 1–2% of cases of infection with *Echinococcus granulosus*. The expanding destructive cystic lesions may spread to and destroy adjacent joints, particularly the hip and pelvis. In rare cases, chronic synovitis has been associated with the presence of schistosomal eggs in synovial biopsies. Monarticular arthritis in children with lymphatic filariasis appears to respond to therapy with diethylcarbamazine even in the absence of microfilariae in synovial fluid. Reactive arthritis has been attributed to hookworm, *Strongyloides*, *Cryptosporidium*, and *Giardia* infection in case reports, but confirmation is required.

POSTINFECTIOUS OR REACTIVE ARTHRITIS

Reactive polyarthritis develops several weeks after ~1% of cases of nongonococcal urethritis and 2% of enteric infections, particularly those due to *Yersinia enterocolitica*, *Shigella flexneri*, *Campylobacter jejuni*, and *Salmonella* species. Only a minority of these patients have the other findings of classic reactive arthritis, including urethritis, conjunctivitis, uveitis, oral ulcers, and rash. Studies have identified microbial DNA or antigen in synovial fluid or blood, but the pathogenesis of this condition is poorly understood.

Reactive arthritis is most common among young men (except after *Yersinia* infection) and has been linked to the HLA-B27 locus as a potential genetic predisposing factor. Patients report painful, asymmetric oligoarthritis that affects mainly the knees, ankles, and feet. Low-back pain is common, and radiographic evidence of sacroiliitis is found in patients with long-standing disease. Most patients recover within 6 months, but prolonged recurrent disease is more common in cases that follow chlamydial urethritis. Anti-inflammatory agents help relieve symptoms, but the role of prolonged antibiotic therapy in eliminating microbial antigen from the synovium is controversial.

Migratory polyarthritis and fever constitute the usual presentation of acute rheumatic fever in adults (Chap. 41). This presentation is distinct from that of poststreptococcal reactive arthritis, which also follows infections with group A *Streptococcus*, but is not migratory, lasts beyond the typical 3-week maximum of acute rheumatic fever, and responds poorly to aspirin.

INFECTIONS IN PROSTHETIC JOINTS

Infection complicates 1–4% of total joint replacements. The majority of infections are acquired intraoperatively or immediately postoperatively as a result of wound breakdown or infection; less commonly, these joint infections develop later after joint replacement and are the result of hematogenous spread or direct inoculation. The presentation may be acute, with fever, pain, and local signs of inflammation, especially in infections due to *S. aureus*, pyogenic streptococci, and enteric bacilli. Alternatively, infection may persist for months or years without causing constitutional symptoms when less virulent organisms, such as coagulase-negative staphylococci or diphtheroids, are involved. Such indolent infections

usually are acquired during joint implantation and are discovered during evaluation of chronic unexplained pain or after a radiograph shows loosening of the prosthesis; the erythrocyte sedimentation rate and C-reactive protein level are usually elevated in such cases.

The diagnosis is best made by needle aspiration of the joint; accidental introduction of organisms during aspiration must be avoided meticulously. Synovial fluid pleocytosis with a predominance of polymorphonuclear leukocytes is highly suggestive of infection, since other inflammatory processes uncommonly affect prosthetic joints. Culture and Gram's stain usually yield the responsible pathogen. Sonication of explanted prosthetic material can improve the yield of culture, presumably by breaking up bacterial biofilms on the surfaces of prostheses. Use of special media for unusual pathogens such as fungi, atypical mycobacteria, and *Mycoplasma* may be necessary if routine and anaerobic cultures are negative.

TREATMENT **Prosthetic Joint Infections**

Treatment includes surgery and high doses of parenteral antibiotics, which are given for 4–6 weeks because bone is usually involved. In most cases, the prosthesis must be replaced to cure the infection. Implantation of a new prosthesis is best delayed for several weeks or months because relapses of infection occur most commonly within this time frame. In some cases, reimplantation is not possible, and the patient must manage without a joint, with a fused joint, or even with amputation. Cure of infection without removal of the prosthesis is occasionally possible in cases that are due to streptococci or pneumococci and that lack radiologic evidence of loosening of the prosthesis. In these cases, antibiotic therapy must be initiated within several days of the onset of infection, and the joint should be drained vigorously by open arthrotomy or arthroscopically. In selected patients who prefer to avoid the high morbidity rate associated with joint removal and reimplantation, suppression of the infection with antibiotics may be a reasonable goal. A high cure rate with retention of the prosthesis has been reported when the combination of oral rifampin and ciprofloxacin is given for 3–6 months to persons with staphylococcal prosthetic joint infection of short duration. This approach, which is based on the ability of rifampin to kill organisms adherent to foreign material and in the stationary growth phase, requires confirmation in prospective trials.

Prevention

To avoid the disastrous consequences of infection, candidates for joint replacement should be selected with care. Rates of infection are particularly high among patients with rheumatoid arthritis, persons who have undergone previous surgery on the joint, and persons with medical conditions requiring immunosuppressive therapy. Perioperative antibiotic prophylaxis, usually with cefazolin, and measures to decrease intraoperative contamination, such as laminar flow, have lowered the rates of perioperative infection to <1% in many centers. After implantation, measures should be taken to prevent or rapidly treat extraarticular infections that might give rise to hematogenous spread to the prosthesis. The effectiveness of prophylactic antibiotics for the prevention of hematogenous infection after dental procedures has not been demonstrated; in fact, viridans streptococci and other components of the oral flora are extremely unusual causes of prosthetic joint infection. Accordingly, the American Dental Association and the American Academy of Orthopaedic Surgeons do not recommend antibiotic prophylaxis for most dental patients with total joint replacements. They do, however, recommend prophylaxis for patients who may be at high risk of hematogenous infection, including those with inflammatory arthropathies, immunosuppression, type 1 diabetes mellitus, joint replacement within the preceding 2 years, previous prosthetic joint infection, malnourishment, or hemophilia. The recommended regimen is amoxicillin (2 g PO) 1 h before dental procedures associated with a high incidence of bacteremia. Clindamycin (600 mg PO) is suggested for patients allergic to penicillin.

ACKNOWLEDGMENTS

The contributions of James H. Maguire and the late Scott J. Thaler to this chapter in earlier editions of Harrison's Principles of Internal Medicine are gratefully acknowledged.

CHAPTER 25

INTRAABDOMINAL INFECTIONS AND ABSCESSES

Miriam J. Baron ■ Dennis L. Kasper

Intraperitoneal infections generally arise because a normal anatomic barrier is disrupted. This disruption may occur when the appendix, a diverticulum, or an ulcer ruptures; when the bowel wall is weakened by ischemia, tumor, or inflammation (e.g., in inflammatory bowel disease); or with adjacent inflammatory processes, such as pancreatitis or pelvic inflammatory disease, in which enzymes (in the former case) or organisms (in the latter) may leak into the peritoneal cavity. Whatever the inciting event, once inflammation develops and organisms usually contained within the bowel or another organ enter the normally sterile peritoneal space, a predictable series of events takes place. Intraabdominal infections occur in two stages: peritonitis and—if the patient survives this stage and goes untreated—abscess formation. The types of microorganisms predominating in each stage of infection are responsible for the pathogenesis of disease.

PERITONITIS

Peritonitis is a life-threatening event that is often accompanied by bacteremia and sepsis syndrome (Chap. 16). The peritoneal cavity is large but is divided into compartments. The upper and lower peritoneal cavities are divided by the transverse mesocolon; the greater omentum extends from the transverse mesocolon and from the lower pole of the stomach to line the lower peritoneal cavity. The pancreas, duodenum, and ascending and descending colon are located in the anterior retroperitoneal space; the kidneys, ureters, and adrenals are found in the posterior retroperitoneal space. The other organs, including liver, stomach, gallbladder, spleen, jejunum, ileum, transverse and sigmoid colon, cecum, and appendix, are within the peritoneal cavity. The cavity is lined with a serous membrane that can serve as a conduit for fluids—a property exploited in peritoneal dialysis **(Fig. 25-1)**. A small amount of serous fluid is normally present in the peritoneal space, with a protein content (consisting mainly of albumin) of <30 g/L and <300 white blood cells (WBCs, generally mononuclear cells) per microliter. In bacterial infections, leukocyte recruitment into the infected peritoneal cavity consists of an early influx of polymorphonuclear leukocytes (PMNs) and a prolonged subsequent phase of mononuclear cell migration. The phenotype of the infiltrating leukocytes during the course of inflammation is regulated primarily by resident-cell chemokine synthesis.

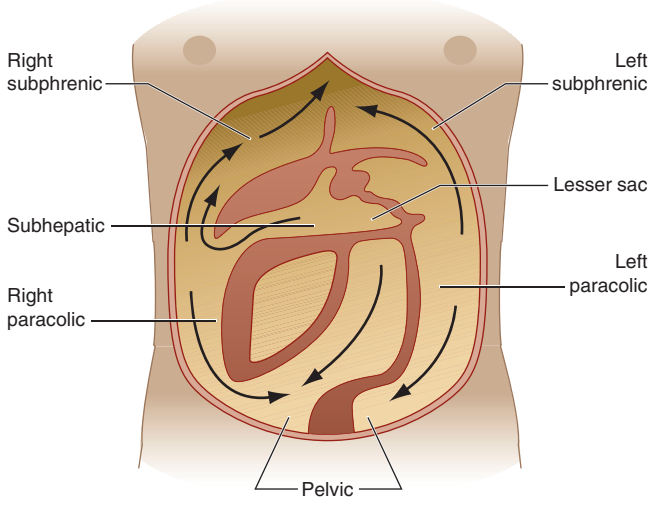


FIGURE 25-1
Diagram of the intraperitoneal spaces, showing the circulation of fluid and potential areas for abscess formation. Some compartments collect fluid or pus more often than others. These compartments include the pelvis (the lowest portion), the subphrenic spaces on the right and left sides, and Morrison's pouch, which is a posterosuperior extension of the subhepatic spaces and is the lowest part of the paravertebral groove when a patient is recumbent. The falciform ligament separating the right and left subphrenic spaces appears to act as a barrier to the spread of infection; consequently, it is unusual to find bilateral subphrenic collections. [*Reprinted with permission from B Lorber (ed): Atlas of Infectious Diseases, vol VII: Intra-abdominal Infections, Hepatitis, and Gastroenteritis. Philadelphia, Current Medicine, 1996, p 1.13.*]

PRIMARY (SPONTANEOUS) BACTERIAL PERITONITIS

Peritonitis is either primary (without an apparent source of contamination) or secondary. The types of organisms found and the clinical presentations of these two processes are different. In adults, primary bacterial peritonitis (PBP) occurs most commonly in conjunction with cirrhosis of the liver (frequently the result of alcoholism). However, the disease has been reported in adults with metastatic malignant disease, postnecrotic cirrhosis, chronic active hepatitis, acute viral hepatitis, congestive heart failure, systemic lupus erythematosus, and lymphedema as well as in patients with no underlying disease. Although PBP virtually always develops in patients with preexisting ascites, it is, in general, an uncommon event, occurring in ≤10% of cirrhotic patients. The cause of PBP has not been established definitively but is believed to involve hematogenous spread of organisms in a patient in whom a diseased liver and altered portal circulation result in a defect in the usual filtration function. Organisms multiply in ascites, a good medium for growth. The proteins of the complement cascade have been found in peritoneal fluid, with lower levels in cirrhotic patients than in patients with ascites of other etiologies. The opsonic and phagocytic properties of PMNs are diminished in patients with advanced liver disease.

The presentation of PBP differs from that of secondary peritonitis. The most common manifestation is fever, which is reported in up to 80% of patients. Ascites is found but virtually always predates infection. Abdominal pain, an acute onset of symptoms, and peritoneal irritation during physical examination can be helpful diagnostically, but the absence of any of these findings does not exclude this often-subtle diagnosis. Nonlocalizing symptoms (such as malaise, fatigue, or encephalopathy) without another clear etiology should also prompt consideration of PBP in a susceptible patient. It is vital to sample the peritoneal fluid of any cirrhotic patient with ascites and fever. The finding of >250 PMNs/μL is diagnostic for PBP, according to Conn (*http://jac.oxfordjournals.org/cgi/content/full/47/3/369*). This criterion does not apply to secondary peritonitis (see next). The microbiology of PBP is also distinctive. While enteric gram-negative bacilli such as *Escherichia coli* are most commonly encountered, gram-positive organisms such as streptococci, enterococci, or even pneumococci are sometimes found. In PBP, a single organism is typically isolated; anaerobes are found less frequently in PBP than in secondary peritonitis, in which a mixed flora including anaerobes is the rule. In fact, if PBP is suspected and multiple organisms including anaerobes are recovered from the peritoneal fluid, the diagnosis must be reconsidered and a source of secondary peritonitis sought.

The diagnosis of PBP is not easy. It depends on the exclusion of a primary intraabdominal source of infection. Contrast-enhanced CT is useful in identifying an intraabdominal source for infection. It may be difficult to recover organisms from cultures of peritoneal fluid, presumably because the burden of organisms is low. However, the yield can be improved if 10 mL of peritoneal fluid is placed directly into a blood culture bottle. Since bacteremia frequently accompanies PBP, blood should be cultured simultaneously. No specific radiographic studies are helpful in the diagnosis of PBP. A plain film of the abdomen would be expected to show ascites. Chest and abdominal radiography should be performed in patients with abdominal pain to exclude free air, which signals a perforation **(Fig. 25-2)**.

TREATMENT **Primary Bacterial Peritonitis**

Treatment for PBP is directed at the isolate from blood or peritoneal fluid. Gram's staining of peritoneal fluid often gives negative results in PBP. Therefore, until culture results become available, therapy should cover gram-negative aerobic bacilli and gram-positive cocci. Third-generation cephalosporins such as cefotaxime (2 g q8h, administered IV) provide reasonable initial coverage in moderately ill patients. Broad-spectrum antibiotics, such as penicillin/β-lactamase inhibitor combinations (e.g., piperacillin/tazobactam, 3.375 g q6h IV for adults with normal renal function) or ceftriaxone (2 g q24h IV), are also options. Empirical coverage for anaerobes is not

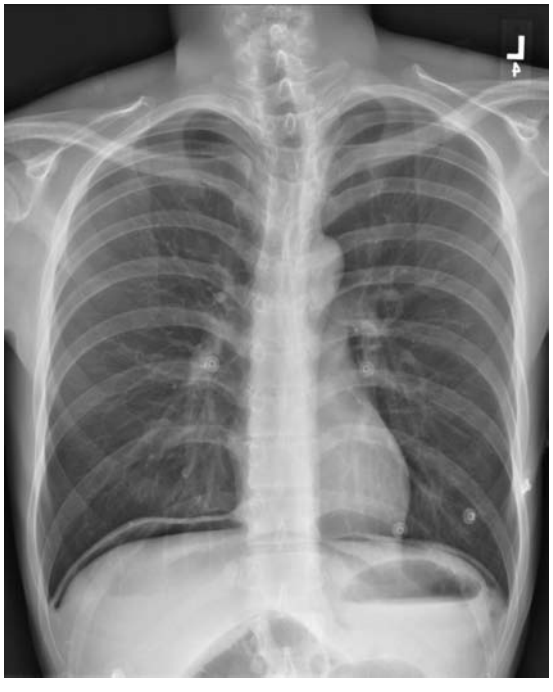


FIGURE 25-2
Pneumoperitoneum. Free air under the diaphragm on an upright chest film suggests the presence of a bowel perforation and associated peritonitis. (*Image courtesy of Dr. John Braver, with permission.*)

necessary. After the infecting organism is identified, therapy should be narrowed to target the specific pathogen. Patients with PBP usually respond within 72 h to appropriate antibiotic therapy. Antimicrobial treatment can be administered for as little as 5 days if rapid improvement occurs and blood cultures are negative, but a course of up to 2 weeks may be required for patients with bacteremia and for those whose improvement is slow. Persistence of WBCs in the ascitic fluid after therapy should prompt a search for additional diagnoses.

Prevention

Primary prevention

One observational study raises the concern that proton pump inhibitor (PPI) therapy may increase the risk of PBP. No prospective studies have yet addressed whether avoidance of PPI therapy may prevent PBP.

Secondary prevention

PBP has a high rate of recurrence. Up to 70% of patients experience a recurrence within 1 year. Antibiotic prophylaxis reduces this rate to <20% and improves short-term survival rates. Prophylactic regimens for adults with normal renal function include fluoroquinolones (ciprofloxacin, 750 mg weekly; norfloxacin, 400 mg/d) or trimethoprim-sulfamethoxazole (one double-strength tablet daily). However, long-term administration of broad-spectrum antibiotics in this setting has been shown to increase the risk of severe staphylococcal infections.

SECONDARY PERITONITIS

Secondary peritonitis develops when bacteria contaminate the peritoneum as a result of spillage from an intraabdominal viscus. The organisms found almost always constitute a mixed flora in which facultative gram-negative bacilli and anaerobes predominate, especially when the contaminating source is colonic. Early in the course of infection, when the host response is directed toward containment of the infection, exudate containing fibrin and PMNs is found. Early death in this setting is attributable to gram-negative bacillary sepsis and to potent endotoxins circulating in the bloodstream (Chap. 16). Gram-negative bacilli, particularly *E. coli*, are common bloodstream isolates, but *Bacteroides fragilis* bacteremia also occurs. The severity of abdominal pain and the clinical course depend on the inciting process. The organisms isolated from the peritoneum also vary with the source of the initial process and the normal flora at that site. Secondary peritonitis can result primarily from chemical irritation and/or bacterial contamination. For example, as long as the patient is not achlorhydric, a ruptured gastric ulcer will release low-pH gastric contents that will serve as a chemical irritant. The normal flora of the stomach comprises the same organisms found in the oropharynx (Chap. 69), but in lower numbers. Thus, the bacterial burden in a ruptured ulcer is negligible compared with that in a ruptured appendix. The normal flora of the colon below the ligament of Treitz contains ~10^{11} anaerobic organisms/g of feces but only 10^{8} aerobes/g; therefore, anaerobic species account for 99.9% of the bacteria. Leakage of colonic contents (pH 7–8) does not cause significant chemical peritonitis, but infection is intense because of the heavy bacterial load.

Depending on the inciting event, local symptoms may occur in secondary peritonitis—for example, epigastric pain from a ruptured gastric ulcer. In appendicitis (Chap. 27), the initial presenting symptoms are often vague, with periumbilical discomfort and nausea followed in a number of hours by pain more localized to the right lower quadrant. Unusual locations of the appendix (including a retrocecal position) can complicate this presentation further. Once infection has spread to the peritoneal cavity, pain increases, particularly with infection involving the parietal peritoneum, which is innervated extensively. Patients usually lie motionless, often with knees drawn up to avoid stretching the nerve fibers of the peritoneal cavity. Coughing and sneezing, which increase pressure within the peritoneal cavity, are associated with sharp pain. There may or may not be pain localized to the infected or diseased organ from which secondary peritonitis has arisen. Patients with secondary peritonitis generally have abnormal findings on abdominal examination, with marked voluntary and involuntary guarding of the anterior abdominal musculature. Later findings include tenderness, especially rebound tenderness. In addition, there may be localized findings in the area of the inciting event. In general, patients are febrile, with marked leukocytosis and a left shift of the WBCs to band forms.

While recovery of organisms from peritoneal fluid is easier in secondary than in primary peritonitis, a tap of the abdomen is rarely the procedure of choice in secondary peritonitis. An exception is in cases involving trauma, where the possibility of a hemoperitoneum may need to be excluded early. Emergent studies (such as abdominal CT) to find the source of peritoneal contamination should be undertaken if the patient is hemodynamically stable; unstable patients may require surgical intervention without prior imaging.

TREATMENT **Secondary Peritonitis**

Treatment for secondary peritonitis includes early administration of antibiotics aimed particularly at aerobic gram-negative bacilli and anaerobes (see below). Mild to moderate disease can be treated with many drugs covering these organisms, including broad-spectrum penicillin/β-lactamase inhibitor combinations (e.g., ticarcillin/clavulanate, 3.1 g q4–6h IV), cefoxitin (2 g q4–6h IV), or a combination of a fluoroquinolone (e.g., levofloxacin, 750 mg q24h IV) or a third-generation cephalosporin (e.g., ceftriaxone, 2 g q24h IV) plus metronidazole (500 mg q8h IV). Patients in intensive care units should receive imipenem (500 mg q6h IV), meropenem (1 g q8h IV), or combinations of drugs, such as ampicillin plus metronidazole plus ciprofloxacin. The role of enterococci and *Candida* spp. in mixed

infections is controversial. Secondary peritonitis usually requires both surgical intervention to address the inciting process and antibiotics to treat early bacteremia, to decrease the incidence of abscess formation and wound infection, and to prevent distant spread of infection. While surgery is rarely indicated in PBP in adults, it may be life-saving in secondary peritonitis. Recombinant human activated protein C has been shown to reduce mortality rates among patients with severe sepsis and may benefit some patients with secondary peritonitis.

Peritonitis may develop as a complication of abdominal surgeries. These infections may be accompanied by localizing pain and/or nonlocalizing symptoms such as fever, malaise, anorexia, and toxicity. As a nosocomial infection, postoperative peritonitis may be associated with organisms such as staphylococci, components of the gram-negative hospital microflora, and the microbes that cause PBP and secondary peritonitis, as described earlier.

PERITONITIS IN PATIENTS UNDERGOING CAPD

A third type of peritonitis arises in patients who are undergoing continuous ambulatory peritoneal dialysis (CAPD). Unlike PBP and secondary peritonitis, which are caused by endogenous bacteria, CAPD-associated peritonitis usually involves skin organisms. The pathogenesis of infection is similar to that of intravascular device–related infection, in which skin organisms migrate along the catheter, which both serves as an entry point and exerts the effects of a foreign body. Exit-site or tunnel infection may or may not accompany CAPD-associated peritonitis. Like PBP, CAPD-associated peritonitis is usually caused by a single organism. Peritonitis is, in fact, the most common reason for discontinuation of CAPD. Improvements in equipment design, especially the Y-set connector, have resulted in a decrease from one case of peritonitis per 9 months of CAPD to one case per 24 months.

The clinical presentation of CAPD peritonitis resembles that of secondary peritonitis in that diffuse pain and peritoneal signs are common. The dialysate is usually cloudy and contains >100 WBCs/μL, >50% of which are neutrophils. The most common organisms are *Staphylococcus* spp., which accounted for ~45% of cases in one series. Historically, coagulase-negative staphylococcal species were identified most commonly in these infections, but more recently these isolates have been decreasing in frequency. *Staphylococcus aureus* is more often involved among patients who are nasal carriers of the organism than among those who are not, and this organism is the most common pathogen in overt exit-site infections. Gram-negative bacilli and fungi such as *Candida* spp. are also found. Vancomycin-resistant enterococci and vancomycin-intermediate *S. aureus* have been reported to produce peritonitis in CAPD patients. The finding of more than one organism in dialysate culture should prompt evaluation for secondary peritonitis. As with PBP, culture of dialysate fluid in blood culture bottles improves the yield. To facilitate diagnosis, several hundred milliliters of removed dialysis fluid should be concentrated by centrifugation before culture.

TREATMENT **CAPD Peritonitis**

Empirical therapy for CAPD peritonitis should be directed at *S. aureus*, coagulase-negative *Staphylococcus*, and gram-negative bacilli until the results of cultures are available. Guidelines issued in 2005 suggest that agents should be chosen on the basis of local experience with resistant organisms. In some centers, a first-generation cephalosporin such as cefazolin (for gram-positive bacteria) and a fluoroquinolone or a third-generation cephalosporin such as ceftazidime (for gram-negative bacteria) may be reasonable; in areas with high rates of infection with methicillin-resistant *S. aureus*, vancomycin should be used instead of cefazolin, and gram-negative coverage may need to be broadened. Broad coverage including vancomycin should be particularly considered for toxic patients and for those with exit-site infections. Loading doses are administered intraperitoneally; doses depend on the dialysis method and the patient's renal function. Antibiotics are given either continuously (i.e., with each exchange) or intermittently (i.e., once daily, with the dose allowed to remain in the peritoneal cavity for at least 6 h). If the patient is severely ill, IV antibiotics should be added at doses appropriate for the patient's degree of renal failure. The clinical response to an empirical treatment regimen should be rapid; if the patient has not responded after 48–96 h of treatment, catheter removal should be considered.

TUBERCULOUS PERITONITIS

See Chap. 70.

INTRAABDOMINAL ABSCESSES

INTRAPERITONEAL ABSCESSES

Abscess formation is common in untreated peritonitis if overt gram-negative sepsis either does not develop or develops but is not fatal. In experimental models of abscess formation, mixed aerobic and anaerobic organisms have been implanted intraperitoneally. Without therapy directed at anaerobes, animals develop intraabdominal abscesses. As in humans, these experimental abscesses may stud the peritoneal cavity, lie within the omentum or mesentery, or even develop on the surface of or within viscera such as the liver.

Pathogenesis and immunity

There is often disagreement about whether an abscess represents a disease state or a host response. In a sense, it

represents both: while an abscess is an infection in which viable infecting organisms and PMNs are contained in a fibrous capsule, it is also a process by which the host confines microbes to a limited space, thereby preventing further spread of infection. In any event, abscesses do cause significant symptoms, and patients with abscesses can be quite ill. Experimental work has helped to define both the host cells and the bacterial virulence factors responsible—most notably in the case of *B. fragilis*. This organism, although accounting for only 0.5% of the normal colonic flora, is the anaerobe most frequently isolated from intraabdominal infections, is especially prominent in abscesses, and is the most common anaerobic bloodstream isolate. On clinical grounds, therefore, *B. fragilis* appears to be uniquely virulent. Moreover, *B. fragilis* acts alone to cause abscesses in animal models of intraabdominal infection, whereas most other *Bacteroides* species must act synergistically with a facultative organism to induce abscess formation.

Of the several virulence factors identified in *B. fragilis*, one is critical: the capsular polysaccharide complex (CPC) found on the bacterial surface. The CPC comprises at least eight distinct surface polysaccharides. Structural analysis of these polysaccharides has shown an unusual motif of oppositely charged sugars. Polysaccharides having these *zwitterionic* characteristics, such as polysaccharide A (PSA), evoke a host response in the peritoneal cavity that localizes bacteria into abscesses. *B. fragilis* and PSA have been found to adhere to primary mesothelial cells in vitro; this adherence, in turn, stimulates the production of tumor necrosis factor α (TNF-α) and intercellular adhesion molecule 1 (ICAM-1) by peritoneal macrophages. Although abscesses characteristically contain PMNs, the process of abscess induction depends on the stimulation of T lymphocytes by these unique zwitterionic polysaccharides. The stimulated CD4+ T lymphocytes secrete leukoattractant cytokines and chemokines. The alternative pathway of complement and fibrinogen also participate in abscess formation.

While antibodies to the CPC enhance bloodstream clearance of *B. fragilis*, CD4+ T cells are critical in immunity to abscesses. When administered subcutaneously, *B. fragilis* PSA has immunomodulatory characteristics and stimulates CD4+ T regulatory cells via an interleukin (IL) 2–dependent mechanism to produce IL-10. IL-10 downregulates the inflammatory response, thereby preventing abscess formation.

Clinical presentation

Of all intraabdominal abscesses, 74% are intraperitoneal or retroperitoneal and are not visceral. Most intraperitoneal abscesses result from fecal spillage from a colonic source, such as an inflamed appendix. Abscesses can also arise from other processes. They usually form within weeks of the development of peritonitis and may be found in a variety of locations—from omentum to mesentery, pelvis to psoas muscles, and subphrenic space to a visceral organ such as the liver, where they may develop either on the surface of the organ or within it. Periappendiceal and diverticular abscesses occur commonly. Diverticular abscesses are least likely to rupture. Infections of the female genital tract and pancreatitis are also among the more common causative events. When abscesses occur in the female genital tract—either as a primary infection (e.g., tuboovarian abscess) or as an infection extending into the pelvic cavity or peritoneum—*B. fragilis* figures prominently among the organisms isolated. *B. fragilis* is not found in large numbers in the normal vaginal flora. For example, it is encountered less commonly in pelvic inflammatory disease and endometritis without an associated abscess. In pancreatitis with leakage of damaging pancreatic enzymes, inflammation is prominent. Therefore, clinical findings such as fever, leukocytosis, and even abdominal pain do not distinguish pancreatitis itself from complications such as pancreatic pseudocyst, pancreatic abscess, or intraabdominal collections of pus. Especially in cases of necrotizing pancreatitis, in which the incidence of local pancreatic infection may be as high as 30%, needle aspiration under CT guidance is performed to sample fluid for culture. Many centers prescribe preemptive antibiotics for patients with necrotizing pancreatitis. Imipenem is frequently used for this purpose since it reaches high tissue levels in the pancreas (although it is not unique in this regard). If needle aspiration yields infected fluid in the setting of acute necrotizing pancreatitis, most experts agree that surgery is superior to percutaneous drainage. Infected pseudocysts that occur remotely from acute pancreatitis are unlikely to be associated with significant amounts of necrotic tissue and may be treated with either surgical or percutaneous catheter drainage in conjunction with appropriate antibiotic therapy.

Diagnosis

Scanning procedures have considerably facilitated the diagnosis of intraabdominal abscesses. Abdominal CT probably has the highest yield, although ultrasonography is particularly useful for the right upper quadrant, kidneys, and pelvis. Both indium-labeled WBCs and gallium tend to localize in abscesses and may be useful in finding a collection. Since gallium is taken up in the bowel, indium-labeled WBCs may have a slightly greater yield for abscesses near the bowel. Neither indium-labeled WBC nor gallium scans serve as a basis for a definitive diagnosis, however; both need to be followed by other, more specific studies, such as CT, if an area of possible abnormality is identified. Abscesses contiguous with or contained within diverticula are particularly difficult to diagnose with scanning procedures. Occasionally, a barium enema may detect a diverticular abscess not diagnosed by other procedures, although barium should not be injected if a perforation is suspected. If one study is negative, a second study sometimes reveals a collection. Although exploratory laparotomy has been less commonly used since the advent of CT, this procedure still must be undertaken on occasion if an abscess is strongly suspected on clinical grounds.

TREATMENT Intraperitoneal Abscesses

An algorithm for the management of patients with intraabdominal (including intraperitoneal) abscesses is presented in Fig. 25-3. The treatment of intraabdominal infections involves the determination of the initial focus of infection, the administration of broad-spectrum antibiotics targeting the organisms involved, and the performance of a drainage procedure if one or more definitive abscesses have formed. Antimicrobial therapy, in general, is adjunctive to drainage and/or surgical correction of an underlying lesion or process in intraabdominal abscesses. Unlike the intraabdominal abscesses resulting from most causes, for which drainage of some kind is generally required, abscesses associated with diverticulitis usually wall off locally after rupture of a diverticulum, so that surgical intervention is not routinely required.

A number of agents exhibit excellent activity against aerobic gram-negative bacilli. Since death in intraabdominal sepsis is linked to gram-negative bacteremia, empirical therapy for intraabdominal infection always needs to include adequate coverage of gram-negative aerobic, facultative, and anaerobic organisms. Even if anaerobes are not cultured from clinical specimens, they still must be covered by the therapeutic regimen. Empirical antibiotic therapy should be the same as that discussed earlier for secondary peritonitis.

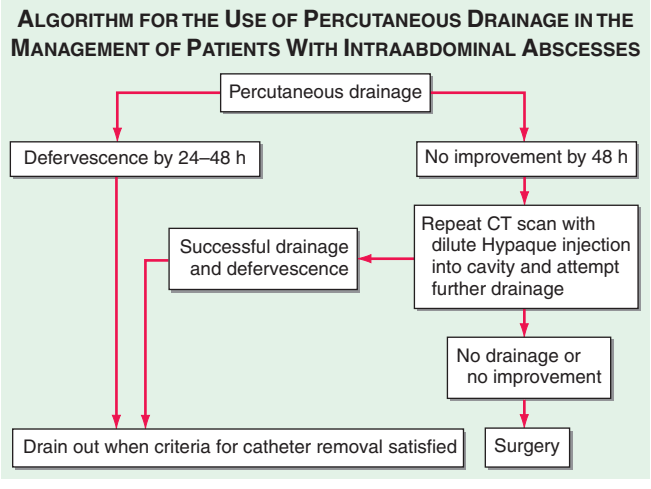


FIGURE 25-3
Algorithm for the management of patients with intraabdominal abscesses using percutaneous drainage. Antimicrobial therapy should be administered concomitantly. [*Reprinted with permission from B Lorber (ed): Atlas of Infectious Diseases, vol VII: Intra-abdominal Infections, Hepatitis, and Gastroenteritis. Philadelphia, Current Medicine, 1996, p 1.30, as adapted from OD Rotstein, RL Simmons, in SL Gorbach et al (eds): Infectious Diseases. Philadelphia, Saunders, 1992, p 668.*]

VISCERAL ABSCESSES

Liver abscesses

The liver is the organ most subject to the development of abscesses. In one study of 540 intraabdominal abscesses, 26% were visceral. Liver abscesses made up 13% of the total number, or 48% of all visceral abscesses. Liver abscesses may be solitary or multiple; they may arise from hematogenous spread of bacteria or from local spread from contiguous sites of infection within the peritoneal cavity. In the past, appendicitis with rupture and subsequent spread of infection was the most common source for a liver abscess. Currently, associated disease of the biliary tract is most common. Pylephlebitis (suppurative thrombosis of the portal vein), usually arising from infection in the pelvis but sometimes from infection elsewhere in the peritoneal cavity, is another common source for bacterial seeding of the liver.

Fever is the most common presenting sign of liver abscess. Some patients, particularly those with associated disease of the biliary tract, have symptoms and signs localized to the right upper quadrant, including pain, guarding, punch tenderness, and even rebound tenderness. Nonspecific symptoms, such as chills, anorexia, weight loss, nausea, and vomiting, may also develop. Only 50% of patients with liver abscesses, however, have hepatomegaly, right-upper-quadrant tenderness, or jaundice; thus, one-half of patients have no symptoms or signs to direct attention to the liver. Fever of unknown origin (FUO) may be the only manifestation of liver abscess, especially in the elderly. Diagnostic studies of the abdomen, especially the right upper quadrant, should be a part of any FUO workup. The single most reliable laboratory finding is an elevated serum concentration of alkaline phosphatase, which is documented in 70% of patients with liver abscesses. Other tests of liver function may yield normal results, but 50% of patients have elevated serum levels of bilirubin, and 48% have elevated concentrations of aspartate aminotransferase. Other laboratory findings include leukocytosis in 77% of patients, anemia (usually normochromic, normocytic) in 50%, and hypoalbuminemia in 33%. Concomitant bacteremia is found in one-third to one-half of patients. A liver abscess is sometimes suggested by chest radiography, especially if a new elevation of the right hemidiaphragm is seen; other suggestive findings include a right basilar infiltrate and a right pleural effusion.

Imaging studies are the most reliable methods for diagnosing liver abscesses. These studies include ultrasonography, CT (Fig. 25-4), indium-labeled WBC or gallium scan, and MRI. More than one such study may be required. Organisms recovered from liver abscesses vary with the source. In liver infection arising from the biliary tree, enteric gram-negative aerobic bacilli and enterococci are common isolates. Unless previous surgery has been performed, anaerobes are not generally involved in liver abscesses arising from biliary infections. In contrast, in liver abscesses arising from pelvic

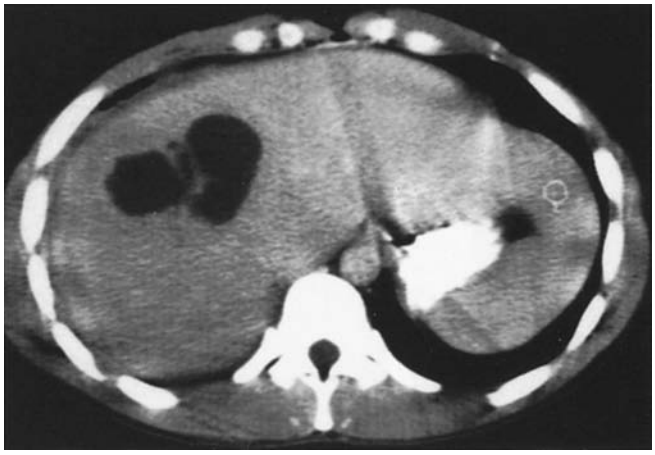


FIGURE 25-4
Multilocular liver abscess on CT scan. Multiple or multilocular abscesses are more common than solitary abscesses. [*Reprinted with permission from B Lorber (ed): Atlas of Infectious Diseases, Vol VII: Intra-abdominal Infections, Hepatitis, and Gastroenteritis. Philadelphia, Current Medicine, 1996, Fig. 1.22.*]

and other intraperitoneal sources, a mixed flora including both aerobic and anaerobic species is common; *B. fragilis* is the species most frequently isolated. With hematogenous spread of infection, usually only a single organism is encountered; this species may be *S. aureus* or a streptococcal species such as *S. milleri*. Results of cultures obtained from drain sites are not reliable for defining the etiology of infections. Liver abscesses may also be caused by *Candida* spp.; such abscesses usually follow fungemia in patients receiving chemotherapy for cancer and often present when PMNs return after a period of neutropenia. Amebic liver abscesses are not an uncommon problem (Chap. 118). Amebic serologic testing gives positive results in >95% of cases; thus, a negative result helps to exclude this diagnosis.

TREATMENT **Liver Abscesses**

(Fig. 25-3) While drainage—either percutaneous (with a pigtail catheter kept in place) or surgical—is the mainstay of therapy for intraabdominal abscesses (including liver abscesses), there is growing interest in medical management alone for pyogenic liver abscesses. The drugs used for empirical therapy include the same ones used in intraabdominal sepsis and secondary bacterial peritonitis. Usually, blood cultures and a diagnostic aspirate of abscess contents should be obtained before the initiation of empirical therapy, with antibiotic choices adjusted when the results of Gram's staining and culture become available. Cases treated without definitive drainage generally require longer courses of antibiotic therapy. When percutaneous drainage was compared with open surgical drainage, the average length of hospital stay for the former was almost twice that for the latter, although both the time required for fever to resolve and the mortality rate were the same for the two procedures. The mortality rate was appreciable despite treatment, averaging 15%. Several factors predict the failure of percutaneous drainage and therefore may favor primary surgical intervention. These factors include the presence of multiple, sizable abscesses; viscous abscess contents that tend to plug the catheter; associated disease (e.g., disease of the biliary tract) requiring surgery; or the lack of a clinical response to percutaneous drainage in 4–7 days.

Treatment of candidal liver abscesses often entails initial administration of amphotericin B or liposomal amphotericin, with subsequent fluconazole therapy (Chap. 110). In some cases, therapy with fluconazole alone (6 mg/kg daily) may be used—e.g., in clinically stable patients whose infecting isolate is susceptible to this drug.

Splenic abscesses

Splenic abscesses are much less common than liver abscesses. The incidence of splenic abscesses has ranged from 0.14% to 0.7% in various autopsy series. The clinical setting and the organisms isolated usually differ from those for liver abscesses. The degree of clinical suspicion for splenic abscess needs to be high, as this condition is frequently fatal if left untreated. Even in the most recently published series, diagnosis was made only at autopsy in 37% of cases. While splenic abscesses may arise occasionally from contiguous spread of infection or from direct trauma to the spleen, hematogenous spread of infection is more common. Bacterial endocarditis is the most common associated infection (Chap. 20). Splenic abscesses can develop in patients who have received extensive immunosuppressive therapy (particularly those with malignancy involving the spleen) and in patients with hemoglobinopathies or other hematologic disorders (especially sickle cell anemia).

While ~50% of patients with splenic abscesses have abdominal pain, the pain is localized to the left upper quadrant in only one-half of these cases. Splenomegaly is found in ~50% of cases. Fever and leukocytosis are generally present; the development of fever preceded diagnosis by an average of 20 days in one series. Left-sided chest findings may include abnormalities to auscultation, and chest radiographic findings may include an infiltrate or a left-sided pleural effusion. CT scan of the abdomen has been the most sensitive diagnostic tool. Ultrasonography can yield the diagnosis but is less sensitive. Liver-spleen scan or gallium scan may also be useful. Streptococcal species are the most common bacterial isolates from splenic abscesses, followed by *S. aureus*—presumably reflecting the associated endocarditis. An increase in the prevalence of gram-negative aerobic isolates from splenic abscesses has been reported; these organisms often derive from a

urinary tract focus, with associated bacteremia, or from another intraabdominal source. *Salmonella* species are seen fairly commonly, especially in patients with sickle cell hemoglobinopathy. Anaerobic species accounted for only 5% of isolates in the largest collected series, but the reporting of a number of "sterile abscesses" may indicate that optimal techniques for the isolation of anaerobes were not employed.

TREATMENT **Splenic Abscesses**

Because of the high mortality figures reported for splenic abscesses, splenectomy with adjunctive antibiotics has traditionally been considered standard treatment and remains the best approach for complex, multilocular abscesses or multiple abscesses. However, percutaneous drainage has worked well for single, small (<3-cm) abscesses in some studies and may also be useful for patients with high surgical risk. Patients undergoing splenectomy should be vaccinated against encapsulated organisms (*Streptococcus pneumoniae*, *Haemophilus influenzae*, *Neisseria meningitidis*). The most important factor in successful treatment of splenic abscesses is early diagnosis.

Perinephric and renal abscesses

Perinephric and renal abscesses are not common: The former accounted for only ~0.02% of hospital admissions and the latter for ~0.2% in Altemeier's series of 540 intraabdominal abscesses. Before antibiotics became available, most renal and perinephric abscesses were hematogenous in origin, usually complicating prolonged bacteremia, with *S. aureus* most commonly recovered. Now, in contrast, >75% of perinephric and renal abscesses arise from a urinary tract infection. Infection ascends from the bladder to the kidney, with pyelonephritis occurring prior to abscess development. Bacteria may directly invade the renal parenchyma from medulla to cortex. Local vascular channels within the kidney may also facilitate the transport of organisms. Areas of abscess developing within the parenchyma may rupture into the perinephric space. The kidneys and adrenal glands are surrounded by a layer of perirenal fat that, in turn, is surrounded by Gerota's fascia, which extends superiorly to the diaphragm and inferiorly to the pelvic fat. Abscesses extending into the perinephric space may track through Gerota's fascia into the psoas or transversalis muscles, into the anterior peritoneal cavity, superiorly to the subdiaphragmatic space, or inferiorly to the pelvis. Of the risk factors that have been associated with the development of perinephric abscesses, the most important is concomitant nephrolithiasis obstructing urinary flow. Of patients with perinephric abscess, 20–60% have renal stones. Other structural abnormalities of the urinary tract, prior urologic surgery, trauma, and diabetes mellitus have also been identified as risk factors.

The organisms most frequently encountered in perinephric and renal abscesses are *E. coli*, *Proteus* spp., and *Klebsiella* spp. *E. coli*, the aerobic species most commonly found in the colonic flora, seems to have unique virulence properties in the urinary tract, including factors promoting adherence to uroepithelial cells. The urease of *Proteus* spp. splits urea, thereby creating a more alkaline and more hospitable environment for bacterial proliferation. *Proteus* spp. are frequently found in association with large struvite stones caused by the precipitation of magnesium ammonium sulfate in an alkaline environment. These stones serve as a nidus for recurrent urinary tract infection. While a single bacterial species is usually recovered from a perinephric or renal abscess, multiple species may also be found. If a urine culture is not contaminated with periurethral flora and is found to contain more than one organism, a perinephric abscess or renal abscess should be considered in the differential diagnosis. Urine cultures may also be polymicrobial in cases of bladder diverticulum.

Candida spp. can cause renal abscesses. This fungus may spread to the kidney hematogenously or by ascension from the bladder. The hallmark of the latter route of infection is ureteral obstruction with large fungal balls.

The presentation of perinephric and renal abscesses is quite nonspecific. Flank pain and abdominal pain are common. At least 50% of patients are febrile. Pain may be referred to the groin or leg, particularly with extension of infection. The diagnosis of perinephric abscess, like that of splenic abscess, is frequently delayed, and the mortality rate in some series is appreciable, although lower than in the past. Perinephric or renal abscess should be most seriously considered when a patient presents with symptoms and signs of pyelonephritis and remains febrile after 4 or 5 days of treatment. Moreover, when a urine culture yields a polymicrobial flora, when a patient is known to have renal stones, or when fever and pyuria coexist with a sterile urine culture, these diagnoses should be entertained.

Renal ultrasonography and abdominal CT are the most useful diagnostic modalities. If a renal or perinephric abscess is diagnosed, nephrolithiasis should be excluded, especially when a high urinary pH suggests the presence of a urea-splitting organism.

TREATMENT **Perinephric and Renal Abscesses**

Treatment for perinephric and renal abscesses, like that for other intraabdominal abscesses, includes drainage of pus and antibiotic therapy directed at the organism(s) recovered. For perinephric abscesses, percutaneous drainage is usually successful.

Psoas abscesses

The psoas muscle is another location in which abscesses are encountered. Psoas abscesses may arise from a hematogenous source, by contiguous spread from an

intraabdominal or pelvic process, or by contiguous spread from nearby bony structures (e.g., vertebral bodies). Associated osteomyelitis due to spread from bone to muscle or from muscle to bone is common in psoas abscesses. When Pott's disease was common, *Mycobacterium tuberculosis* was a frequent cause of psoas abscess. Currently, either *S. aureus* or a mixture of enteric organisms including aerobic and anaerobic gram-negative bacilli is usually isolated from psoas abscesses in the United States. *S. aureus* is most likely to be isolated when a psoas abscess arises from hematogenous spread or a contiguous focus of osteomyelitis; a mixed enteric flora is the most likely etiology when the abscess has an intraabdominal or pelvic source. Patients with psoas abscesses frequently present with fever, lower abdominal or back pain, or pain referred to the hip or knee. CT is the most useful diagnostic technique.

TREATMENT **Psoas Abscesses**

Treatment includes surgical drainage and the administration of an antibiotic regimen directed at the inciting organism(s).

ACKNOWLEDGMENT

The substantial contributions of Dori F. Zaleznik, MD, to this chapter in previous editions of Harrison's Principles of Internal Medicine are gratefully acknowledged.

CHAPTER 26
ACUTE INFECTIOUS DIARRHEAL DISEASES AND BACTERIAL FOOD POISONING

Regina C. LaRocque ■ Edward T. Ryan ■ Stephen B. Calderwood

Ranging from a mild annoyance to a devastating dehydrating illness, acute diarrheal disease is a leading cause of illness globally, with an estimated 4.6 billion episodes worldwide per year. Diarrheal disease ranks second only to lower respiratory infection as the most common infectious cause of death worldwide. Among children <5 years old, diarrheal disease is a particularly important cause of death. Every year nearly 2 million children in this age group die of diarrheal disease; the majority of these young children are impoverished and live in resource-poor areas. By contributing to malnutrition and thereby reducing resistance to other infectious agents, diarrheal disease is also an indirect factor in a far greater burden of disease.

The wide range of clinical manifestations of acute gastrointestinal illnesses is matched by the wide variety of infectious agents involved, including viruses, bacteria, and parasitic pathogens **(Table 26-1)**. This chapter discusses factors that enable gastrointestinal pathogens to cause disease, reviews host defense mechanisms, and delineates an approach to the evaluation and treatment of patients presenting with acute diarrhea. Individual organisms causing acute gastrointestinal illnesses are discussed in detail in other chapters.

PATHOGENIC MECHANISMS

Enteric pathogens have developed a variety of tactics to overcome host defenses. Understanding the virulence factors employed by these organisms is important in the diagnosis and treatment of clinical disease.

Inoculum size

The number of microorganisms that must be ingested to cause disease varies considerably from species to species. For *Shigella*, enterohemorrhagic *Escherichia coli*, *Giardia lamblia*, or *Entamoeba*, as few as 10–100 bacteria or cysts can produce infection, while 10^5–10^8 *Vibrio cholerae* organisms must be ingested orally to cause disease. The infective dose of *Salmonella* varies widely, depending on the species, host, and food vehicle. The ability of organisms to overcome host defenses has important implications for transmission; *Shigella*, enterohemorrhagic *E. coli*, *Entamoeba*, and *Giardia* can spread by person-to-person contact, whereas under some circumstances *Salmonella* may have to grow in food for several hours before reaching an effective infectious dose.

TABLE 26-1

GASTROINTESTINAL PATHOGENS CAUSING ACUTE DIARRHEA

MECHANISM	LOCATION	ILLNESS	STOOL FINDINGS	EXAMPLES OF PATHOGENS INVOLVED
Noninflammatory (enterotoxin)	Proximal small bowel	Watery diarrhea	No fecal leukocytes; mild or no increase in fecal lactoferrin	*Vibrio cholerae*, enterotoxigenic *Escherichia coli* (LT and/or ST), enteroaggregative *E. coli, Clostridium perfringens, Bacillus cereus, Staphylococcus aureus, Aeromonas hydrophila, Plesiomonas shigelloides*, rotavirus, norovirus, enteric adenoviruses, *Giardia lamblia, Cryptosporidium* spp., *Cyclospora* spp., microsporidia
Inflammatory (invasion or cytotoxin)	Colon or distal small bowel	Dysentery or inflammatory diarrhea	Fecal polymorphonuclear leukocytes; substantial increase in fecal lactoferrin	*Shigella* spp., *Salmonella* spp., *Campylobacter jejuni,* enterohemorrhagic *E. coli,* enteroinvasive *E. coli, Yersinia enterocolitica, Listeria monocytogenes, Vibrio parahaemolyticus, Clostridium difficile, A. hydrophila, P. shigelloides, Entamoeba histolytica, Klebsiella oxytoca*
Penetrating	Distal small bowel	Enteric fever	Fecal mononuclear leukocytes	*Salmonella typhi, Y. enterocolitica*

Abbreviations: LT, heat-labile enterotoxin; ST, heat-stable enterotoxin.
Source: After TS Steiner, RL Guerrant: Principles and syndromes of enteric infection, in *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*, 7th ed, GL Mandell et al (eds). Philadelphia, Churchill Livingstone, 2010, pp. 1335-1351.

Adherence

Many organisms must adhere to the gastrointestinal mucosa as an initial step in the pathogenic process; thus, organisms that can compete with the normal bowel flora and colonize the mucosa have an important advantage in causing disease. Specific cell-surface proteins involved in attachment of bacteria to intestinal cells are important virulence determinants. *V. cholerae*, for example, adheres to the brush border of small-intestinal enterocytes via specific surface adhesins, including the toxin-coregulated pilus and other accessory colonization factors. Enterotoxigenic *E. coli*, which causes watery diarrhea, produces an adherence protein called *colonization factor antigen* that is necessary for colonization of the upper small intestine by the organism prior to the production of enterotoxin. Enteropathogenic *E. coli*, an agent of diarrhea in young children, and enterohemorrhagic *E. coli*, which causes hemorrhagic colitis and the hemolytic-uremic syndrome, produce virulence determinants that allow these organisms to attach to and efface the brush border of the intestinal epithelium.

Toxin production

The production of one or more exotoxins is important in the pathogenesis of numerous enteric organisms. Such toxins include *enterotoxins*, which cause watery diarrhea by acting directly on secretory mechanisms in the intestinal mucosa; *cytotoxins*, which cause destruction of mucosal cells and associated inflammatory diarrhea; and *neurotoxins*, which act directly on the central or peripheral nervous system.

The prototypical enterotoxin is cholera toxin, a heterodimeric protein composed of one A and five B subunits. The A subunit contains the enzymatic activity of the toxin, while the B subunit pentamer binds holotoxin to the enterocyte surface receptor, the ganglioside G_{M1}. After the binding of holotoxin, a fragment of the A subunit is translocated across the eukaryotic cell membrane into the cytoplasm, where it catalyzes the ADP-ribosylation of a GTP-binding protein and causes persistent activation of adenylate cyclase. The end result is an increase of cyclic AMP in the intestinal mucosa, which increases Cl^- secretion and decreases Na^+ absorption, leading to a loss of fluid and the production of diarrhea.

Enterotoxigenic strains of *E. coli* may produce a protein called *heat-labile enterotoxin* (LT) that is similar to cholera toxin and causes secretory diarrhea by the same mechanism. Alternatively, enterotoxigenic strains of *E. coli* may produce *heat-stable enterotoxin* (ST), one form of which causes diarrhea by activation of guanylate cyclase and elevation of intracellular cyclic GMP. Some enterotoxigenic strains of *E. coli* produce both LT and ST.

Bacterial cytotoxins, in contrast, destroy intestinal mucosal cells and produce the syndrome of dysentery, with bloody stools containing inflammatory cells. Enteric pathogens that produce such cytotoxins include *Shigella dysenteriae* type 1, *Vibrio parahaemolyticus*, and *Clostridium difficile*. *S. dysenteriae* type 1 and Shiga

toxin–producing strains of *E. coli* produce potent cytotoxins and have been associated with outbreaks of hemorrhagic colitis and hemolytic-uremic syndrome.

Neurotoxins are usually produced by bacteria outside the host and, therefore, cause symptoms soon after ingestion. Included are the staphylococcal and *Bacillus cereus* toxins, which act on the central nervous system to produce vomiting.

Invasion

Dysentery may result not only from the production of cytotoxins but also from bacterial invasion and destruction of intestinal mucosal cells. Infections due to *Shigella* and enteroinvasive *E. coli* are characterized by the organisms' invasion of mucosal epithelial cells, intraepithelial multiplication, and subsequent spread to adjacent cells. *Salmonella* causes inflammatory diarrhea by invasion of the bowel mucosa but generally is not associated with the destruction of enterocytes or the full clinical syndrome of dysentery. *Salmonella typhi* and *Yersinia enterocolitica* can penetrate intact intestinal mucosa, multiply intracellularly in Peyer's patches and intestinal lymph nodes, and then disseminate through the bloodstream to cause enteric fever, a syndrome characterized by fever, headache, relative bradycardia, abdominal pain, splenomegaly, and leukopenia.

HOST DEFENSES

Given the enormous number of microorganisms ingested with every meal, the normal host must combat a constant influx of potential enteric pathogens. Studies of infections in patients with alterations in defense mechanisms have led to a greater understanding of the variety of ways in which the normal host can protect itself against disease.

Normal flora

The large numbers of bacteria that normally inhabit the intestine act as an important host defense by preventing colonization by potential enteric pathogens. Persons with fewer intestinal bacteria, such as infants who have not yet developed normal enteric colonization or patients receiving antibiotics, are at significantly greater risk of developing infections with enteric pathogens. The composition of the intestinal flora is as important as the number of organisms present. More than 99% of the normal colonic flora is made up of anaerobic bacteria, and the acidic pH and volatile fatty acids produced by these organisms appear to be critical elements in resistance to colonization.

Gastric acid

The acidic pH of the stomach is an important barrier to enteric pathogens, and an increased frequency of infections due to *Salmonella*, *G. lamblia*, and a variety of helminths has been reported among patients who have undergone gastric surgery or are achlorhydric for some other reason. Neutralization of gastric acid with antacids, proton pump inhibitors, or H_2 blockers—a common practice in the management of hospitalized patients—similarly increases the risk of enteric colonization. In addition, some microorganisms can survive the extreme acidity of the gastric environment; rotavirus, for example, is highly stable to acidity.

Intestinal motility

Normal peristalsis is the major mechanism for clearance of bacteria from the proximal small intestine. When intestinal motility is impaired (e.g., by treatment with opiates or other antimotility drugs, anatomic abnormalities, or hypomotility states), the frequency of bacterial overgrowth and infection of the small bowel with enteric pathogens is increased. Some patients whose treatment for *Shigella* infection consists of diphenoxylate hydrochloride with atropine (Lomotil) experience prolonged fever and shedding of organisms, while patients treated with opiates for mild *Salmonella* gastroenteritis have a higher frequency of bacteremia than those not treated with opiates.

Immunity

Both cellular immune responses and antibody production play important roles in protection from enteric infections. Humoral immunity to enteric pathogens consists of systemic IgG and IgM as well as secretory IgA. The mucosal immune system may be the first line of defense against many gastrointestinal pathogens. The binding of bacterial antigens to the luminal surface of M cells in the distal small bowel and the subsequent presentation of antigens to subepithelial lymphoid tissue lead to the proliferation of sensitized lymphocytes. These lymphocytes circulate and populate all of the mucosal tissues of the body as IgA-secreting plasma cells.

Genetic determinants

Host genetic variation influences susceptibility to diarrheal diseases. People with blood group O show increased susceptibility to disease due to *V. cholerae*, *Shigella*, *E. coli* O157, and norovirus. Polymorphisms in genes encoding inflammatory mediators have been associated with the outcome of infection with enteroaggregative *E. coli*, enterotoxin-producing *E. coli*, *Salmonella*, *C. difficile*, and *V. cholerae*.

APPROACH TO THE PATIENT **Infectious Diarrhea or Bacterial Food Poisoning**

The approach to the patient with possible infectious diarrhea or bacterial food poisoning is shown in Fig. 26-1.

HISTORY The answers to questions with high discriminating value can quickly narrow the range of potential causes of diarrhea and help determine whether treatment is needed. Important elements of the narrative history are detailed in Fig. 26-1.

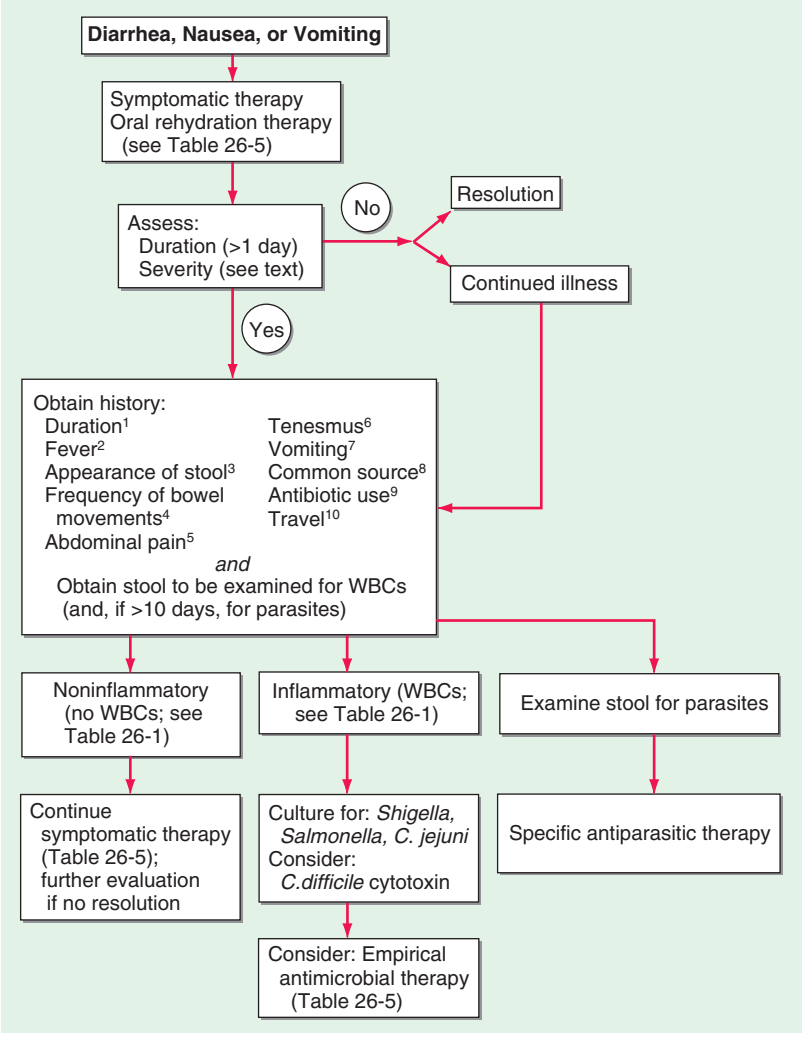


FIGURE 26-1

Clinical algorithm for the approach to patients with community-acquired infectious diarrhea or bacterial food poisoning. Key to superscripts: **1.** Diarrhea lasting >2 weeks is generally defined as chronic; in such cases, many of the causes of acute diarrhea are much less likely, and a new spectrum of causes needs to be considered. **2.** Fever often implies invasive disease, although fever and diarrhea may also result from infection outside the gastrointestinal tract, as in malaria. **3.** Stools that contain blood or mucus indicate ulceration of the large bowel. Bloody stools without fecal leukocytes should alert the laboratory to the possibility of infection with Shiga toxin–producing enterohemorrhagic *Escherichia coli*. Bulky white stools suggest a small-intestinal process that is causing malabsorption. Profuse "rice-water" stools suggest cholera or a similar toxigenic process. **4.** Frequent stools over a given period can provide the first warning of impending dehydration. **5.** Abdominal pain may be most severe in inflammatory processes like those due to *Shigella*, *Campylobacter*, and necrotizing toxins. Painful abdominal muscle cramps, caused by electrolyte loss, can develop in severe cases of cholera. Bloating is common in giardiasis. An appendicitis-like syndrome should prompt a culture for *Yersinia enterocolitica* with cold enrichment. **6.** Tenesmus (painful rectal spasms with a strong urge to defecate but little passage of stool) may be a feature of cases with proctitis, as in shigellosis or amebiasis. **7.** Vomiting implies an acute infection (e.g., a toxin-mediated illness or food poisoning) but can also be prominent in a variety of systemic illnesses (e.g., malaria) and in intestinal obstruction. **8.** Asking patients whether anyone else they know is sick is a more efficient means of identifying a common source than is constructing a list of recently eaten foods. If a common source seems likely, specific foods can be investigated. See text for a discussion of bacterial food poisoning. **9.** Current antibiotic therapy or a recent history of treatment suggests *Clostridium difficile* diarrhea (Chap. 47). Stop antibiotic treatment if possible and consider tests for *C. difficile* toxins. Antibiotic use may increase the risk of other infections, such as salmonellosis. **10.** See text (and Chap. 5) for a discussion of traveler's diarrhea. (*After TS Steiner, RL Guerrant: Principles and syndromes of enteric infection, in Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 7th ed, GL Mandell et al (eds). Philadelphia, Churchill Livingstone, 2010, pp. 1335-1351; RL Guerrant, DA Bobak: N Engl J Med 325:327, 1991; with permission.*)

PHYSICAL EXAMINATION The examination of patients for signs of dehydration provides essential information about the severity of the diarrheal illness and the need for rapid therapy. Mild dehydration is indicated by thirst, dry mouth, decreased axillary sweat, decreased urine output, and slight weight loss. Signs of moderate dehydration include an orthostatic fall in blood pressure, skin tenting, and sunken eyes (or, in infants, a sunken fontanelle). Signs of severe dehydration include lethargy, obtundation, feeble pulse, hypotension, and frank shock.

DIAGNOSTIC APPROACH After the severity of illness is assessed, the clinician must distinguish between *inflammatory* and *noninflammatory* disease. Using the history and epidemiologic features of the case as guides, the clinician can then rapidly evaluate the need for further efforts to define a specific etiology and for therapeutic intervention. Examination of a stool sample may supplement the narrative history. Grossly bloody or mucoid stool suggests an inflammatory process. A test for fecal leukocytes (preparation of a thin smear of stool on a glass slide, addition of a drop of methylene blue, and examination of the wet mount) can suggest inflammatory disease in patients with diarrhea, although the predictive value of this test is still debated. A test for fecal lactoferrin, which is a marker of fecal leukocytes, is more sensitive and is available in latex agglutination and enzyme-linked immunosorbent assay formats. Causes of acute infectious diarrhea, categorized as inflammatory and noninflammatory, are listed in Table 26-1.

POST-DIARRHEA COMPLICATIONS Chronic complications may follow the resolution of an acute diarrheal episode. The clinician should inquire about prior diarrheal illness if the conditions listed in Table 26-2 are observed.

TABLE 26-2

POST-DIARRHEA COMPLICATIONS OF ACUTE INFECTIOUS DIARRHEAL ILLNESS

COMPLICATION	COMMENTS
Chronic diarrhea • Lactase deficiency • Small-bowel bacterial overgrowth • Malabsorption syndromes (tropical and celiac sprue)	Occurs in ~1% of travelers with acute diarrhea • Protozoa account for ~1/3 of cases
Initial presentation or exacerbation of inflammatory bowel disease	May be precipitated by traveler's diarrhea
Irritable bowel syndrome	Occurs in ~10% of travelers with traveler's diarrhea
Reactive arthritis (formerly known as Reiter's syndrome)	Particularly likely after infection with invasive organisms (*Shigella, Salmonella, Campylobacter, Yersinia*)
Hemolytic-uremic syndrome (hemolytic anemia, thrombocytopenia, and renal failure)	Follows infection with Shiga toxin–producing bacteria (*Shigella dysenteriae* type 1 and enterohemorrhagic *Escherichia coli*)
Guillain-Barré syndrome	Particularly likely after *Campylobacter* infection

EPIDEMIOLOGY

Travel history

Of the several million people who travel from temperate industrialized countries to tropical regions of Asia, Africa, and Central and South America each year, 20–50% experience a sudden onset of abdominal cramps, anorexia, and watery diarrhea; thus *traveler's diarrhea* is the most common travel-related infectious illness (Chap. 5). The time of onset is usually 3 days to 2 weeks after the traveler's arrival in a resource-poor area; most cases begin within the first 3–5 days. The illness is generally self-limited, lasting 1–5 days. The high rate of diarrhea among travelers to underdeveloped areas is related to the ingestion of contaminated food or water.

The organisms that cause traveler's diarrhea vary considerably with location (Table 26-3), as does the pattern of antimicrobial resistance. In all areas, enterotoxigenic and enteroaggregative strains of *E. coli* are the most common isolates from persons with the classic secretory traveler's diarrhea syndrome. Infection with *Campylobacter jejuni* is especially common in areas of Asia.

Location

Day-care centers have particularly high attack rates of enteric infections. Rotavirus is most common among children <2 years old, with attack rates of 75–100% among those exposed. *G. lamblia* is more common among older children, with somewhat lower attack rates. Other common organisms, often spread by fecal-oral contact, are *Shigella*, *C. jejuni*, and *Cryptosporidium*. A characteristic feature of infection among children attending day-care centers is the high rate of secondary cases among family members.

Similarly, hospitals are sites in which enteric infections are concentrated. Diarrhea is one of the most common manifestations of nosocomial infections. *C. difficile* is the predominant cause of nosocomial diarrhea among adults in the United States. *Klebsiella oxytoca* has been identified as a cause of antibiotic-associated hemorrhagic colitis. Viral pathogens, especially rotavirus, can spread rapidly in pediatric wards. Enteropathogenic *E. coli* has been associated with outbreaks of diarrhea in nurseries for newborns. One-third of elderly patients in chronic-care institutions develop a significant diarrheal illness each year; more than one-half of these cases are caused by cytotoxin-producing *C. difficile*. Antimicrobial therapy can predispose to pseudomembranous colitis by altering the normal colonic flora and allowing the multiplication of *C. difficile* (Chap. 47).

TABLE 26-3

CAUSES OF TRAVELER'S DIARRHEA

ETIOLOGIC AGENT	APPROXIMATE PERCENTAGE OF CASES	COMMENTS
Bacteria	**50–75**	
Enterotoxigenic *Escherichia coli*	10–45	Single most important agent
Enteroaggregative *E. coli*	5–35	Emerging enteric pathogen with worldwide distribution
Campylobacter jejuni	5–25	More common in Asia
Shigella	0–15	Major cause of dysentery
Salmonella	0–15	
Others	0–5	Including *Aeromonas, Plesiomonas*, and *Vibrio cholerae*
Viruses	**0–20**	
Norovirus	0–10	Associated with cruise ships
Rotavirus	0–5	Particularly common among children
Parasites	**0–10**	
Giardia lamblia	0–5	Affects hikers and campers who drink from freshwater streams; contaminates water supplies in Russia
Cryptosporidium	0–5	Resistant to chlorine treatment
Entamoeba histolytica	<1	
Cyclospora	<1	
Other	**0–10**	
Acute food poisoning[a]	0–5	
No pathogen identified	10–50	

[a]For etiologic agents, see Table 26-4.
Source: After DR Hill et al: Clin Infect Dis 43:1499, 2006.

Age

Globally, most morbidity and mortality from enteric pathogens involves children <5 years of age. Breast-fed infants are protected from contaminated food and water and derive some protection from maternal antibodies, but their risk of infection rises dramatically when they begin to eat solid foods. Exposure to rotavirus is universal, with most children experiencing their first infection in the first or second year of life. Older children and adults are more commonly infected with norovirus. Other organisms with higher attack rates among children than among adults include enterotoxigenic, enteropathogenic, and enterohemorrhagic *E. coli*; *Shigella*; *C. jejuni*; and *G. lamblia*.

Host immune status

Immunocompromised hosts are at elevated risk of acute and chronic infectious diarrhea. Individuals with defects in cell-mediated immunity (including those with AIDS) are at particularly high risk of invasive enteropathies, including salmonellosis, listeriosis, and cryptosporidiosis. Individuals with hypogammaglobulinemia are at particular risk of *C. difficile* colitis and giardiasis. Patients with cancer are more likely to develop *C. difficile* infection as a result of chemotherapy and frequent hospitalizations. Infectious diarrhea can be life-threatening in immunocompromised hosts, with complications including bacteremia and metastatic seeding of infection. Furthermore, dehydration may compromise renal function and increase the toxicity of immunosuppressive drugs.

Bacterial food poisoning

If the history and the stool examination indicate a noninflammatory etiology of diarrhea and there is evidence of a common-source outbreak, questions concerning the ingestion of specific foods and the time of onset of the diarrhea after a meal can provide clues to the bacterial cause of the illness. Potential causes of bacterial food poisoning are shown in **Table 26-4**.

Bacterial disease caused by an enterotoxin elaborated outside the host, such as that due to *Staphylococcus aureus* or *B. cereus*, has the shortest incubation period (1–6 h) and generally lasts <12 h. Most cases of staphylococcal food poisoning are caused by contamination from infected human carriers. Staphylococci can multiply at a wide range of temperatures; thus, if food is left to cool slowly and remains at room temperature after cooking, the organisms will have the opportunity to form enterotoxin. Outbreaks following picnics where potato salad, mayonnaise, and cream pastries have been served offer classic examples of staphylococcal food poisoning. Diarrhea, nausea, vomiting, and abdominal cramping are common, while fever is less so.

B. cereus can produce either a syndrome with a short incubation period—the *emetic* form, mediated by a staphylococcal type of enterotoxin—or one with a longer incubation period (8–16 h)—the *diarrheal* form, caused by an enterotoxin resembling *E. coli* LT, in which diarrhea and abdominal cramps are characteristic but vomiting is uncommon. The emetic form of *B. cereus* food poisoning is associated with contaminated fried rice; the organism is common in uncooked rice, and its heat-resistant spores survive boiling. If cooked rice is not refrigerated, the spores can germinate and produce toxin. Frying before serving may not destroy the preformed, heat-stable toxin.

Food poisoning due to *Clostridium perfringens* also has a slightly longer incubation period (8–14 h) and results from the survival of heat-resistant spores in inadequately cooked meat, poultry, or legumes. After ingestion, toxin is produced in the intestinal tract, causing moderately severe abdominal cramps and

TABLE 26-4

BACTERIAL FOOD POISONING

INCUBATION PERIOD, ORGANISM	SYMPTOMS	COMMON FOOD SOURCES
1–6 h		
Staphylococcus aureus	Nausea, vomiting, diarrhea	Ham, poultry, potato or egg salad, mayonnaise, cream pastries
Bacillus cereus	Nausea, vomiting, diarrhea	Fried rice
8–16 h		
Clostridium perfringens	Abdominal cramps, diarrhea (vomiting rare)	Beef, poultry, legumes, gravies
B. cereus	Abdominal cramps, diarrhea (vomiting rare)	Meats, vegetables, dried beans, cereals
>16 h		
Vibrio cholerae	Watery diarrhea	Shellfish, water
Enterotoxigenic *Escherichia coli*	Watery diarrhea	Salads, cheese, meats, water
Enterohemorrhagic *E. coli*	Bloody diarrhea	Ground beef, roast beef, salami, raw milk, raw vegetables, apple juice
Salmonella spp.	Inflammatory diarrhea	Beef, poultry, eggs, dairy products
Campylobacter jejuni	Inflammatory diarrhea	Poultry, raw milk
Shigella spp.	Dysentery	Potato or egg salad, lettuce, raw vegetables
Vibrio parahaemolyticus	Dysentery	Mollusks, crustaceans

diarrhea; vomiting is rare, as is fever. The illness is self-limited, rarely lasting >24 h.

Not all food poisoning has a bacterial cause. Nonbacterial agents of short-incubation food poisoning include capsaicin, which is found in hot peppers, and a variety of toxins found in fish and shellfish (Chap. 131).

LABORATORY EVALUATION

Many cases of noninflammatory diarrhea are self-limited or can be treated empirically, and in these instances the clinician may not need to determine a specific etiology. Potentially pathogenic *E. coli* cannot be distinguished from normal fecal flora by routine culture, and tests to detect enterotoxins are not available in most clinical laboratories. In situations in which cholera is a concern, stool should be cultured on selective media such as thiosulfate–citrate–bile salts–sucrose (TCBS) or tellurite-taurocholate-gelatin (TTG) agar. A latex agglutination test has made the rapid detection of rotavirus in stool practical for many laboratories, while reverse-transcriptase polymerase chain reaction and specific antigen enzyme immunoassays have been developed for the identification of norovirus. Stool specimens should be examined by immunofluorescence-based rapid assays or (less sensitive) standard microscopy for *Giardia* cysts or *Cryptosporidium* if the level of clinical suspicion regarding the involvement of these organisms is high.

All patients with fever and evidence of inflammatory disease acquired outside the hospital should have stool cultured for *Salmonella*, *Shigella*, and *Campylobacter*. *Salmonella* and *Shigella* can be selected on MacConkey agar as non-lactose-fermenting (colorless) colonies or can be grown on *Salmonella-Shigella* agar or in selenite enrichment broth, both of which inhibit most organisms except these pathogens. Evaluation of nosocomial diarrhea should initially focus on *C. difficile*; stool culture for other pathogens in this setting has an extremely low yield and is not cost-effective. Toxins A and B produced by pathogenic strains of *C. difficile* can be detected by rapid enzyme immunoassays and latex agglutination tests (Chap. 47). Isolation of *C. jejuni* requires inoculation of fresh stool onto selective growth medium and incubation at 42°C in a microaerophilic atmosphere. In many laboratories in the United States, *E. coli* O157:H7 is among the most common pathogens isolated from visibly bloody stools. Strains of this enterohemorrhagic serotype can be identified in specialized laboratories by serotyping but also can be identified presumptively in hospital laboratories as lactose-fermenting, indole-positive colonies of sorbitol nonfermenters (white colonies) on sorbitol MacConkey plates. If the clinical presentation suggests the possibility of intestinal amebiasis, stool should be examined by a rapid antigen detection assay or by (less sensitive) microscopy.

TREATMENT Infectious Diarrhea or Bacterial Food Poisoning

In many cases, a specific diagnosis is not necessary or not available to guide treatment. The clinician can proceed with the information obtained from the history, stool examination, and evaluation of dehydration severity. Empirical regimens for the treatment of traveler's diarrhea are listed in Table 26-5.

The mainstay of treatment is adequate rehydration. The treatment of cholera and other dehydrating diarrheal diseases was revolutionized by the promotion of oral rehydration solution (ORS), the efficacy of which depends on the fact that glucose-facilitated absorption of sodium and water in the small intestine remains intact in the presence of cholera toxin. The use of ORS has reduced mortality rates for cholera from >50% (in untreated cases) to <1%. A number of ORS formulas have been used. Initial preparations were based on the treatment of patients with cholera and included a solution containing 3.5 g of

TABLE 26-5

TREATMENT OF TRAVELER'S DIARRHEA ON THE BASIS OF CLINICAL FEATURES[a]

CLINICAL SYNDROME	SUGGESTED THERAPY
Watery diarrhea (no blood in stool, no fever), 1 or 2 unformed stools per day without distressing enteric symptoms	Oral fluids (oral rehydration solution, Pedialyte, Lytren, or flavored mineral water) and saltine crackers
Watery diarrhea (no blood in stool, no fever), 1 or 2 unformed stools per day with distressing enteric symptoms	Bismuth subsalicylate (for adults): 30 mL or 2 tablets (262 mg/tablet) every 30 min for 8 doses; or loperamide[b]: 4 mg initially followed by 2 mg after passage of each unformed stool, not to exceed 8 tablets (16 mg) per day (prescription dose) or 4 caplets (8 mg) per day (over-the-counter dose); drugs can be taken for 2 days
Watery diarrhea (no blood in stool, no distressing abdominal pain, no fever), >2 unformed stools per day	Antibacterial drug[c] plus (for adults) loperamide[b] (see dose above)
Dysentery (passage of bloody stools) or fever (>37.8°C)	Antibacterial drug[c]
Vomiting, minimal diarrhea	Bismuth subsalicylate (for adults; see dose above)
Diarrhea in infants (<2 years old)	Fluids and electrolytes (oral rehydration solution, Pedialyte, Lytren); continue feeding, especially with breast milk; seek medical attention for moderate dehydration, fever lasting >24 h, bloody stools, or diarrhea lasting more than several days

[a]All patients should take oral fluids (Pedialyte, Lytren, or flavored mineral water) plus saltine crackers. If diarrhea becomes moderate or severe, if fever persists, or if bloody stools or dehydration develops, the patient should seek medical attention.
[b]Loperamide should not be used by patients with fever or dysentery; its use may prolong diarrhea in patients with infection due to *Shigella* or other invasive organisms.
[c]The recommended antibacterial drugs are as follows:
Travel to high-risk country other than Thailand: *Adults:* (1) A fluoroquinolone such as ciprofloxacin, 750 mg as a single dose or 500 mg bid for 3 days; levofloxacin, 500 mg as a single dose or 500 mg qd for 3 days; or norfloxacin, 800 mg as a single dose or 400 mg bid for 3 days. (2) Azithromycin, 1000 mg as a single dose or 500 mg qd for 3 days. (3) Rifaximin, 200 mg tid or 400 mg bid for 3 days (not recommended for use in dysentery).
Children: Azithromycin, 10 mg/kg on day 1, 5 mg/kg on days 2 and 3 if diarrhea persists. Alternative agent: furazolidone, 7.5 mg/kg per day in four divided doses for 5 days.
Travel to Thailand (with risk of fluoroquinolone-resistant *Campylobacter*):
Adults: Azithromycin (at above dose for adults). Alternative agent: a fluoroquinolone (at above doses for adults).
Children: Same as for children traveling to other areas (see above).
Source: After DR Hill et al: Clin Infect Dis 43:1499, 2006.

sodium chloride, 2.5 g of sodium bicarbonate, 1.5 g of potassium chloride, and 20 g of glucose (or 40 g of sucrose) per liter of water. Such a preparation can still be used for the treatment of severe cholera. Many causes of secretory diarrhea, however, are associated with less electrolyte loss than occurs in cholera; beginning in 2002, the World Health Organization recommended a "reduced-osmolarity/reduced-salt" ORS that is better tolerated and more effective than classic ORS. This preparation contains 2.6 g of sodium chloride, 2.9 g of trisodium citrate, 1.5 g of potassium chloride, and 13.5 g of glucose (or 27 g of sucrose) per liter of water. ORS formulations containing rice or cereal as the carbohydrate source may be even more effective than glucose-based solutions. Patients who are severely dehydrated or in whom vomiting precludes the use of oral therapy should receive IV solutions such as Ringer's lactate.

Although most secretory forms of traveler's diarrhea (usually due to enterotoxigenic or enteroaggregative *E. coli* or to *Campylobacter*) can be treated effectively with rehydration, bismuth subsalicylate, or antiperistaltic agents, antimicrobial agents can shorten the duration of illness from 3–4 days to 24–36 h. Changes in diet have not been shown to have an impact on the duration of illness, while the efficacy of probiotics continues to be debated. Most individuals who present with dysentery (bloody diarrhea and fever) should be treated empirically with an antimicrobial agent (e.g., a fluoroquinolone or a macrolide) pending microbiologic analysis of stool. Individuals with shigellosis should be treated with a 3- to 7-day course. Individuals with *Campylobacter* infection often benefit from antimicrobial treatment as well. Because of increasing resistance of *Campylobacter* to fluoroquinolones, especially in parts of Asia, a macrolide antibiotic such as erythromycin or azithromycin may be preferred for this infection.

Treatment of salmonellosis must be tailored to the individual patient. Since administration of antimicrobial agents often prolongs intestinal colonization with *Salmonella*, these drugs are usually reserved for individuals at high risk of complications from disseminated salmonellosis, such as young children, patients with prosthetic devices, elderly patients, and immunocompromised persons. Antimicrobial agents should not be administered to individuals (especially children) in whom enterohemorrhagic *E. coli* infection is suspected. Laboratory studies of enterohemorrhagic *E. coli* strains have demonstrated that

a number of antibiotics induce replication of Shiga toxin–producing lambdoid bacteriophages, thereby significantly increasing toxin production by these strains. Clinical studies have supported these laboratory results, and antibiotics may increase by twentyfold the risk of hemolytic-uremic syndrome and renal failure during enterohemorrhagic *E. coli* infection. A clinical clue in the diagnosis of the latter infection is bloody diarrhea with low fever or none at all.

PROPHYLAXIS

Improvements in hygiene to limit fecal-oral spread of enteric pathogens will be necessary if the prevalence of diarrheal diseases is to be significantly reduced in developing countries. Travelers can reduce their risk of diarrhea by eating only hot, freshly cooked food; by avoiding raw vegetables, salads, and unpeeled fruit; and by drinking only boiled or treated water and avoiding ice. Historically, few travelers to tourist destinations adhere to these dietary restrictions. Bismuth subsalicylate is an inexpensive agent for the prophylaxis of traveler's diarrhea; it is taken at a dosage of 2 tablets (525 mg) four times a day. Treatment appears to be effective and safe for up to 3 weeks, but adverse events such as temporary darkening of the tongue and tinnitus can occur. A meta-analysis suggests that probiotics may lessen the likelihood of traveler's diarrhea by ~15%. Prophylactic antimicrobial agents, although effective, are not generally recommended for the prevention of traveler's diarrhea except when travelers are immunosuppressed or have other underlying illnesses that place them at high risk for morbidity from gastrointestinal infection. The risk of side effects and the possibility of developing an infection with a drug-resistant organism or with more harmful, invasive bacteria make it more reasonable to institute an empirical short course of treatment if symptoms develop. If prophylaxis is indicated, the nonabsorbed antibiotic rifaximin can be considered for use in regions such as Latin America and Africa, where noninvasive *E. coli* predominates as the cause of traveler's diarrhea. Rifaximin is not effective against invasive enteropathogens.

The possibility of exerting a major impact on the worldwide morbidity and mortality associated with diarrheal diseases has led to intense efforts to develop effective vaccines against the common bacterial and viral enteric pathogens. An effective rotavirus vaccine is currently available. Vaccines against *S. typhi* and *V. cholerae* are also available, although the protection they offer is incomplete and/or short lived. At present, there is no effective commercially available vaccine against *Shigella*, enterotoxigenic *E. coli*, *Campylobacter*, nontyphoidal *Salmonella*, norovirus, or intestinal parasites.

ACKNOWLEDGMENT

The substantial contributions of Joan R. Butterton, MD, an author of this chapter in previous editions of Harrison's Principles of Internal Medicine are gratefully acknowledged.

CHAPTER 27

ACUTE APPENDICITIS AND PERITONITIS

William Silen

ACUTE APPENDICITIS

INCIDENCE AND EPIDEMIOLOGY

With more than 250,000 appendectomies performed annually, appendicitis is the most common abdominal surgical emergency in the United States. The peak incidence of acute appendicitis is in the second and third decades of life; it is relatively rare at the extremes of age. However, perforation is more common in infancy and in the elderly, during which periods mortality rates are highest. Males and females are equally affected, except between puberty and age 25, when males predominate in a 3:2 ratio. The incidence of appendicitis has remained stable in the United States over the last 30 years, while the incidence of appendicitis is much lower in underdeveloped countries, especially parts of Africa, and in lower socioeconomic groups. The mortality rate in the United States decreased eightfold between 1941 and 1970 but has remained at <1 per 100,000 since then.

PATHOGENESIS

Appendicitis is believed to occur as a result of appendiceal luminal obstruction. Obstruction is most commonly caused by a fecalith, which results from accumulation and inspissation of fecal matter around vegetable fibers. Enlarged lymphoid follicles associated with viral infections (e.g., measles), inspissated barium, worms (e.g., pinworms, *Ascaris*, and *Taenia*), and tumors (e.g., carcinoid or carcinoma) may also obstruct the lumen. Other common pathologic findings include appendiceal ulceration. The cause of the ulceration is unknown, although a viral etiology has been postulated. Infection with *Yersinia* organisms may cause the disease, since high complement fixation antibody titers have been found in up to 30% of cases of proven appendicitis. Luminal bacteria multiply and invade the appendiceal wall as venous engorgement and subsequent arterial compromise result from the high intraluminal pressures. Finally, gangrene and perforation occur. If the process evolves slowly, adjacent organs such as the terminal ileum, cecum, and omentum may wall off the appendiceal area so that a localized abscess will develop, whereas rapid progression of vascular impairment may cause perforation with free access to the peritoneal cavity. Subsequent rupture of primary appendiceal abscesses may produce fistulas between the appendix and bladder, small intestine, sigmoid, or cecum. Occasionally, acute appendicitis may be the first manifestation of Crohn's disease.

While chronic infection of the appendix with tuberculosis, amebiasis, and actinomycosis may occur, a useful clinical aphorism states that *chronic appendiceal inflammation is not usually the cause of prolonged abdominal pain of weeks' or months' duration*. In contrast, recurrent acute appendicitis does occur, often with complete resolution of inflammation and symptoms between attacks. Recurrent acute appendicitis may also occur if a long appendiceal stump is left after initial appendectomy.

CLINICAL MANIFESTATIONS

The sequence of abdominal discomfort and anorexia associated with acute appendicitis is pathognomonic. The pain is described as being located in the periumbilical region initially and then migrating to the right lower quadrant. This classic sequence of symptoms occurs in only 66% of patients. The differential diagnoses for periumbilical and right lower quadrant pain are listed in Table 27-1. The periumbilical abdominal pain is of the visceral type, resulting from distention of the appendiceal lumen. This pain is carried on slow-conducting C fibers and is usually poorly localized in the periumbilical or epigastric region. In general, this visceral pain is mild, often cramping and usually lasting 4–6 h, but it may not be noted by stoic individuals. As inflammation spreads to the parietal peritoneal surfaces, the pain becomes somatic, steady, and more severe and aggravated by motion or cough. Parietal afferent nerves are A delta fibers, which are fast-conducting and unilateral. These fibers localize the pain to the *right lower quadrant*. *Anorexia* is very common; a hungry patient almost invariably does not have acute appendicitis. *Nausea* and *vomiting* occur in 50–60% of cases, but vomiting is usually self-limited. Change in bowel habit is of little diagnostic value, since any or no alteration may be observed, although the presence of diarrhea caused by an inflamed appendix in juxtaposition to the sigmoid may cause diagnostic difficulties. Urinary frequency and dysuria occur if the appendix lies adjacent to the bladder.

TABLE 27-1

THE ANATOMIC ORIGIN OF PERIUMBILICAL AND RIGHT LOWER QUADRANT PAIN IN THE DIFFERENTIAL DIAGNOSIS OF APPENDICITIS

Periumbilical	
Appendicitis	
Small-bowel obstruction	
Gastroenteritis	
Mesenteric ischemia	
Right Lower Quadrant	
Gastrointestinal causes	Gynecologic causes
Appendicitis	Ovarian tumor/torsion
Inflammatory bowel disease	Pelvic inflammatory disease
Right-sided diverticulitis	Renal causes
Gastroenteritis	Pyelonephritis
Inguinal hernia	Perinephric abscess
	Nephrolithiasis

Physical findings vary with time after onset of the illness and according to the location of the appendix, which may be situated deep in the pelvic cul-de-sac; in the right lower quadrant in any relation to the peritoneum, cecum, and small intestine; in the right upper quadrant (especially during pregnancy); or even in the left lower quadrant. *The diagnosis cannot be established unless tenderness can be elicited*. While tenderness is sometimes absent in the early visceral stage of the disease, it ultimately always develops and is found in any location corresponding to the position of the appendix. Typically, tenderness to palpation will often occur at McBurney's point, anatomically located on a line one-third of the way between the anterior iliac spine and the umbilicus. Abdominal tenderness may be completely absent if a retrocecal or pelvic appendix is present, in which case the sole physical finding may be tenderness in the flank or on rectal or pelvic examination. Referred rebound tenderness is often present and is most likely to be absent early in the illness. Flexion of the right hip and guarded movement by the patient are due to parietal peritoneal involvement. Hyperesthesia of the skin of the right lower quadrant and a positive psoas or obturator sign are often late findings and are rarely of diagnostic value.

The temperature is usually normal or slightly elevated [37.2°–38°C (99°–100.5°F)], but a temperature >38.3°C (101°F) should suggest perforation. Tachycardia is commensurate with the elevation of the temperature. Rigidity and tenderness become more marked as the disease progresses to perforation and localized or diffuse peritonitis. Distention is rare unless severe diffuse

peritonitis has developed. A mass may develop if localized perforation has occurred, but will not usually be detectable before 3 days after onset. Earlier presence of a mass suggests carcinoma of the cecum or Crohn's disease. Perforation is rare before 24 h after onset of symptoms, but the rate may be as high as 80% after 48 h.

Although moderate leukocytosis of 10,000–18,000 cells/μL is frequent (with a concomitant left shift), the absence of leukocytosis does not rule out acute appendicitis. Leukocytosis of >20,000 cells/μL suggests probable perforation. Anemia and blood in the stool suggest a primary diagnosis of carcinoma of the cecum, especially in elderly individuals. The urine may contain a few white or red blood cells without bacteria if the appendix lies close to the right ureter or bladder. Urinalysis is most useful in excluding genitourinary conditions that may mimic acute appendicitis.

Radiographs are rarely of value except when an opaque fecalith (5% of patients) is observed in the right lower quadrant (especially in children). Consequently, abdominal films are not routinely obtained unless other conditions such as intestinal obstruction or ureteral calculus may be present. The diagnosis may also be established by the ultrasonic demonstration of an enlarged and thick-walled appendix. Ultrasound is most useful to exclude ovarian cysts, ectopic pregnancy, or tuboovarian abscess. Several studies have recently demonstrated the benefit of contrast-enhanced or nonenhanced CT over ultrasound and plain radiographs in the diagnosis of acute appendicitis. The findings on CT will include a thickened appendix with periappendiceal stranding and often the presence of a fecalith **(Figs. 27-1 and 27-2)**. The reported positive predictive value of CT is 95–97% and the overall accuracy is 90–98%. Furthermore, nonvisualization of the appendix on CT is associated with the findings of a normal appendix 98% of the time. Free peritoneal air is uncommon, even in perforated appendicitis.

While the typical historic sequence and physical findings are present in 50–60% of cases, a wide variety of atypical patterns of disease are encountered, especially at the age extremes and during pregnancy. Infants under 2 years of age have a 70–80% incidence of perforation and generalized peritonitis. This is thought to be the result of a delay in diagnosis. Any infant or child with diarrhea, vomiting, and abdominal pain is highly suspect. Fever is much more common in this age group, and abdominal distention is often the only physical finding. In the elderly, pain and tenderness are often blunted, and thus the diagnosis is also frequently delayed and leads to a 30% incidence of perforation in patients older than age 70 years. Elderly patients often present initially with a slightly painful mass (a primary appendiceal abscess) or with adhesive intestinal obstruction 5 or 6 days after a previously undetected perforated appendix.

Appendicitis occurs about once in every 500–2000 pregnancies and is the most common extrauterine condition requiring abdominal operation. The diagnosis may be missed or delayed because of the frequent occurrence of mild abdominal discomfort and nausea and vomiting during pregnancy, and because of the gradual shift of the appendix from the right lower quadrant to the right upper quadrant during the second and third trimester of pregnancy. Appendicitis tends to be most common during the second trimester. The diagnosis is best made with ultrasound, which is 80% accurate; however, if perforation has already occurred, the accuracy of ultrasound decreases to 30%. Early intervention is warranted because the incidence of fetal loss with a normal appendix is 1.5%. With perforation, the incidence of fetal loss is 20–35%.

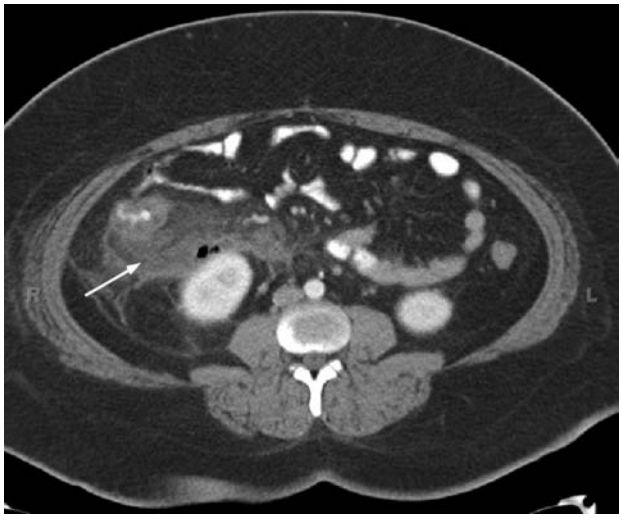


FIGURE 27-1
CT with oral and intravenous contrast of acute appendicitis. There is thickening of the wall of the appendix and periappendiceal stranding *(arrow)*.

DIFFERENTIAL DIAGNOSIS

Acute appendicitis has been labeled the *masquerader*, and the diagnosis is often more difficult to make in young females. Obtaining a good history, including sexual activity and the presence of a vaginal discharge, will

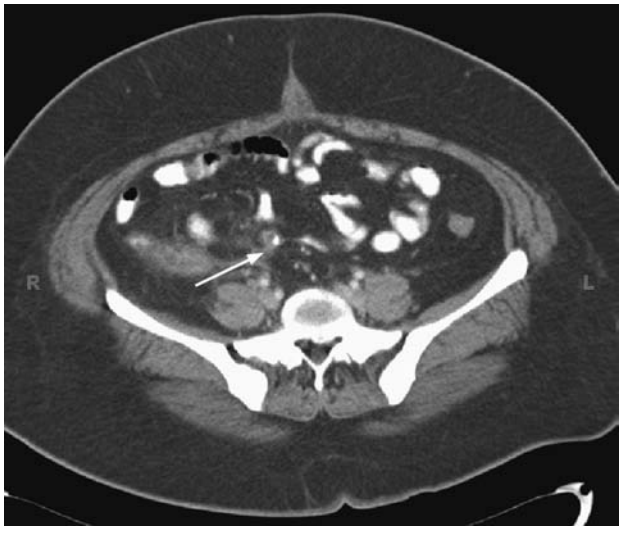


FIGURE 27-2
Appendiceal fecalith *(arrow)*.

help differentiate acute appendicitis from pelvic inflammatory disease (PID). The presence of a malodorous vaginal discharge and gram-negative intracellular diplococci are pathognomonic for PID. Pain on movement of the cervix is also more specific for PID but may occur in appendicitis if perforation has occurred or if the appendix lies adjacent to the uterus or adnexa. *Rupture of a graafian follicle* (mittelschmerz) occurs at midcycle and will produce pain and tenderness more diffuse and usually of a less severe degree than in appendicitis. *Rupture of a corpus luteum cyst* is identical clinically to rupture of a graafian follicle, but develops about the time of menstruation. The presence of an adnexal mass, evidence of blood loss, and a positive pregnancy test help differentiate *ruptured tubal pregnancy*. *Twisted ovarian cyst* and *endometriosis* are occasionally difficult to distinguish from appendicitis. In all these female conditions, ultrasonography and laparoscopy may be of great value.

Acute mesenteric lymphadenitis and *acute gastroenteritis* are the diagnoses usually given when enlarged, slightly reddened lymph nodes at the root of the mesentery and a normal appendix are encountered at operation in a patient who usually has right lower quadrant tenderness. Retrospectively, these patients may have had a higher temperature, diarrhea, more diffuse pain and abdominal tenderness, and a lymphocytosis. Between cramps, the abdomen is completely relaxed. Children seem to be affected more frequently than adults. Some of these patients have infection with *Y. pseudotuberculosis* or *Y. enterocolitica*, in which case the diagnosis can be established by culture of the mesenteric nodes or by serologic titers (Chap. 64). In *Salmonella* gastroenteritis, the abdominal findings are similar, although the pain may be more severe and more localized, and fever and chills are common. The occurrence of similar symptoms among other members of the family may be helpful. *Regional enteritis* (Crohn's disease) is usually associated with a more prolonged history, often with earlier exacerbations regarded as episodes of gastroenteritis unless the diagnosis has been established previously. Often an inflammatory mass is palpable. In addition, acute cholecystitis, perforated ulcer, acute pancreatitis, acute diverticulitis, strangulating intestinal obstruction, ureteral calculus, and pyelonephritis may present diagnostic difficulties.

TREATMENT **Acute Appendicitis**

If the diagnosis is in question, 4–6 h of observation with serial abdominal exams is always more beneficial than harmful. Antibiotics should not be administered when the diagnosis is in question, since they will only mask the perforation. The treatment of presumed acute appendicitis is early operation and appendectomy as soon as the patient can be prepared. Appendectomy is frequently accomplished laparoscopically and is associated with less postoperative narcotic use and earlier discharge. It is acceptable to have a 15–20% incidence of a normal appendix at the time of appendectomy to avoid perforation. The use of early laparoscopy instead of close clinical observation has not shown a clinical benefit in the management of patients with nonspecific abdominal pain.

A different approach is indicated if a palpable mass is found 3–5 days after the onset of symptoms. This finding usually represents the presence of a phlegmon or abscess, and complications from attempted surgical excision are frequent. Such patients treated with broad-spectrum antibiotics, drainage of abscesses >3 cm, parenteral fluids, and bowel rest usually show resolution of symptoms within 1 week. *Interval appendectomy* can be performed safely 6–12 weeks later. A randomized clinical trial has demonstrated that antibiotics alone can effectively treat acute, nonperforated appendicitis in 86% of male patients. However, antibiotics alone were associated with a higher recurrence rate than when followed by surgical intervention. If the mass enlarges or the patient becomes more toxic, the abscess should be drained. Free perforation is associated with generalized peritonitis and its complications, including subphrenic, pelvic, or other abscesses, and can be avoided by early diagnosis. The mortality rate for nonperforated appendicitis is 0.1%, little more than the risk of general anesthesia; for perforated appendicitis, mortality is 3% (and can reach 15% in the elderly).

ACUTE PERITONITIS

Peritonitis is an inflammation of the peritoneum; it may be localized or diffuse in location, acute or chronic in natural history, and infectious or aseptic in pathogenesis. Acute peritonitis is most often infectious and is usually related to a perforated viscus (and called *secondary peritonitis*). When no intraabdominal source is identified, infectious peritonitis is called *primary* or *spontaneous*. Acute peritonitis is associated with decreased intestinal motor activity, resulting in distention of the intestinal lumen with gas and fluid (adynamic ileus). The accumulation of fluid in the bowel together with the lack of oral intake leads to rapid intravascular volume depletion with effects on cardiac, renal, and other systems.

ETIOLOGY

Infectious agents gain access to the peritoneal cavity through a perforated viscus, a penetrating wound of the abdominal wall, or external introduction of a foreign object that is or becomes infected (e.g., a chronic peritoneal dialysis catheter). In the absence of immune compromise, host defenses are capable of eradicating small contaminations. The conditions that most commonly result in the introduction of bacteria into the peritoneum are ruptured appendix, ruptured diverticulum, perforated peptic ulcer, incarcerated hernia, gangrenous gall bladder, volvulus, bowel infarction, cancer, inflammatory bowel disease, or intestinal obstruction. However, a wide range of mechanisms may play a

TABLE 27-2

CONDITIONS LEADING TO SECONDARY BACTERIAL PERITONITIS

Perforations of bowel	Volvulus
Trauma, blunt or penetrating	Intussusception
Inflammation	Neoplasms
Appendicitis	Ingested foreign body, toothpick, fish bone
Diverticulitis	**Perforations or leaking of other organs**
Peptic ulcer disease	Pancreas—pancreatitis
Inflammatory bowel disease	Gallbladder—cholecystitis
Iatrogenic	Urinary bladder—trauma, rupture
Endoscopic perforation	Liver—bile leak after biopsy
Anastomotic leaks	Fallopian tubes—salpingitis
Catheter perforation	Bleeding into the peritoneal cavity
Vascular	**Disruption of integrity of peritoneal cavity**
Embolus	Trauma
Ischemia	Continuous ambulatory peritoneal dialysis (indwelling catheter)
Obstructions	Intraperitoneal chemotherapy
Adhesions	Perinephric abscess
Strangulated hernias	Iatrogenic—postoperative, foreign body

role (Table 27-2). Bacterial peritonitis can also occur in the apparent absence of an intraperitoneal source of bacteria (primary or spontaneous bacterial peritonitis). This condition occurs in the setting of ascites and liver cirrhosis in 90% of the cases, usually in patients with ascites with low protein concentration (<1 g/L). Bacterial peritonitis is discussed in detail in Chap. 25.

Aseptic peritonitis may be due to peritoneal irritation by abnormal presence of physiologic fluids (e.g., gastric juice, bile, pancreatic enzymes, blood, or urine) or sterile foreign bodies (e.g., surgical sponges or instruments, starch from surgical gloves) in the peritoneal cavity or as a complication of rare systemic diseases such as lupus erythematosus, porphyria, or familial Mediterranean fever. Chemical irritation of the peritoneum is greatest for acidic gastric juice and pancreatic enzymes. Secondary bacterial infection is common in chemical peritonitis.

CLINICAL FEATURES

The cardinal manifestations of peritonitis are acute abdominal pain and tenderness, usually with fever. The location of the pain depends on the underlying cause and whether the inflammation is localized or generalized. Localized peritonitis is most common in uncomplicated appendicitis and diverticulitis, and physical findings are limited to the area of inflammation. Generalized peritonitis is associated with widespread inflammation and diffuse abdominal tenderness and rebound. Rigidity of the abdominal wall is common in both localized and generalized peritonitis. Bowel sounds are usually but not always absent. Tachycardia, hypotension, and signs of dehydration are common. Leukocytosis and marked acidosis are common laboratory findings. Plain abdominal films may show dilation of large and small bowel with edema of the bowel wall. Free air under the diaphragm is associated with a perforated viscus. CT and/or ultrasonography can identify the presence of free fluid or an abscess. When ascites is present, diagnostic paracentesis with cell count (>250 neutrophils/μL is usual in peritonitis), protein and lactate dehydrogenase levels, and culture is essential. In elderly and immunosuppressed patients, signs of peritoneal irritation may be more difficult to detect.

THERAPY AND PROGNOSIS

Treatment relies on rehydration, correction of electrolyte abnormalities, antibiotics, and surgical correction of the underlying defect. Mortality rates are <10% for uncomplicated peritonitis associated with a perforated ulcer or ruptured appendix or diverticulum in an otherwise healthy person. Mortality rates of ≥40% have been reported for elderly people, those with underlying illnesses, and when peritonitis has been present for >48 h.

CHAPTER 28

URINARY TRACT INFECTIONS, PYELONEPHRITIS, AND PROSTATITIS

Kalpana Gupta ■ Barbara W. Trautner

Urinary tract infection (UTI) is a common and painful human illness that, fortunately, is rapidly responsive to modern antibiotic therapy. In the preantibiotic era, UTI caused significant morbidity. Hippocrates, writing about a disease that appears to have been acute cystitis, said that the illness could last for a year before either resolving or worsening to involve the kidneys. When chemotherapeutic agents used to treat UTI were introduced in the early twentieth century, they were relatively ineffective, and persistence of infection after 3 weeks of therapy was common. Nitrofurantoin, which became available in the 1950s, was the first tolerable and effective agent for the treatment of UTI.

Since the most common manifestation of UTI is acute cystitis and since acute cystitis is far more prevalent among women than among men, most clinical research on UTI has involved women. Many studies have enrolled women from college campuses or large health maintenance organizations in the United States. Therefore, when reviewing the literature and recommendations concerning UTI, clinicians must consider whether the findings are applicable to their patient populations.

DEFINITIONS

UTI may be asymptomatic (subclinical infection) or symptomatic (disease). Thus, the term *UTI* encompasses a variety of clinical entities, including asymptomatic bacteriuria (ABU), cystitis, prostatitis, and pyelonephritis. The distinction between symptomatic UTI and ABU has major clinical implications. Both UTI and ABU connote the presence of bacteria in the urinary tract, usually accompanied by white blood cells and inflammatory cytokines in the urine. However, ABU occurs in the absence of symptoms attributable to the bacteria in the urinary tract and does not usually require treatment, while UTI has more typically been assumed to imply symptomatic disease that warrants antimicrobial therapy. Much of the literature concerning UTI, particularly catheter-associated infection, does not differentiate between UTI and ABU. In this chapter, the term *UTI* denotes symptomatic disease; *cystitis*, symptomatic infection of the bladder; and *pyelonephritis*, symptomatic infection of the kidneys. *Uncomplicated UTI* refers to acute cystitis or pyelonephritis in nonpregnant outpatient women without anatomic abnormalities or instrumentation of the urinary tract; *complicated UTI* is a catch-all term that encompasses all other types of UTI. *Recurrent UTI* is not necessarily complicated; individual episodes can be uncomplicated and treated as such. *Catheter-associated bacteriuria* can be either symptomatic (CAUTI) or asymptomatic.

EPIDEMIOLOGY AND RISK FACTORS

Except among infants and the elderly, UTI occurs far more commonly in females than in males. During the neonatal period, the incidence of UTI is slightly higher among males than among females because male infants more commonly have congenital urinary tract anomalies. After 50 years of age, obstruction from prostatic hypertrophy becomes common in men, and the incidence of UTI is almost as high among men as among women. Between 1 year and ~50 years of age, UTI and recurrent UTI are predominantly diseases of females. The prevalence of ABU is ~5% among women between ages 20 and 40 and may be as high as 40–50% among elderly women and men.

As many as 50–80% of women in the general population acquire at least one UTI during their lifetime—uncomplicated cystitis in most cases. Recent use of a diaphragm with spermicide, frequent sexual intercourse, and a history of UTI are independent risk factors for acute cystitis. Cystitis is temporally related to recent sexual intercourse, with a sixtyfold increase in the relative odds of acute cystitis in the 48 h after intercourse. In healthy postmenopausal women, sexual activity, diabetes mellitus, and incontinence are risk factors for UTI.

Many factors predisposing women to cystitis also increase the risk of pyelonephritis. Factors independently

associated with pyelonephritis in young healthy women include frequent sexual intercourse, a new sexual partner, a UTI in the previous 12 months, a maternal history of UTI, diabetes, and incontinence. The common risk factors for cystitis and pyelonephritis are not surprising given that pyelonephritis typically arises through the ascent of bacteria from the bladder to the upper urinary tract. However, pyelonephritis can occur without clear antecedent cystitis.

About 20–30% of women who have had one episode of UTI will have recurrent episodes. Early recurrence (within 2 weeks) is usually regarded as relapse rather than reinfection and may indicate the need to evaluate the patient for a sequestered focus. Intracellular pods of infecting organisms within the bladder epithelium have been demonstrated in animal models of UTI, but the importance of this phenomenon in humans is not yet clear. The rate of recurrence ranges from 0.3 to 7.6 infections per patient per year, with an average of 2.6 infections per year. It is not uncommon for multiple recurrences to follow an initial infection, resulting in clustering of episodes. Clustering may be related temporally to the presence of a new risk factor or to the sloughing of the protective outer bladder epithelial layer in response to bacterial attachment during acute cystitis. The likelihood of a recurrence decreases with increasing time since the last infection. A case-control study of predominantly white premenopausal women with recurrent UTI identified frequent sexual intercourse, use of spermicide, a new sexual partner, a first UTI before 15 years of age, and a maternal history of UTI as independent risk factors for recurrent UTI. The only consistently documented behavioral risk factors for recurrent UTI include frequent sexual intercourse and spermicide use. In postmenopausal women, anatomic factors affecting bladder emptying, such as cystoceles, urinary incontinence, and residual urine, are most strongly associated with recurrent UTI.

In pregnant women, ABU has clinical consequences, and both screening for and treatment of this condition are indicated. Specifically, ABU during pregnancy is associated with preterm birth and perinatal mortality for the fetus and with pyelonephritis for the mother. A Cochrane meta-analysis found that treatment of ABU in pregnant women decreased the risk of pyelonephritis by 75%.

The majority of men with UTI have a functional or anatomic abnormality of the urinary tract, most commonly urinary obstruction secondary to prostatic hypertrophy. That said, not all men with UTI have detectable urinary abnormalities; this point is particularly relevant for men ≤45 years of age. Lack of circumcision is also associated with an increased risk of UTI, because *Escherichia coli* is more likely to colonize the glans and prepuce and subsequently migrate into the urinary tract.

Women—but not men—with diabetes have a two- to threefold higher rate of ABU and UTI than women without diabetes. Increased duration of diabetes and the use of insulin rather than oral medication are also associated with a higher risk of UTI among women with diabetes. Poor bladder function, obstruction in urinary flow, and incomplete voiding are additional factors commonly found in patients with diabetes that increase the risk of UTI. Impaired cytokine secretion may contribute to ABU in diabetic women.

ETIOLOGY

The uropathogens causing UTI vary by clinical syndrome, but are usually enteric gram-negative rods that have migrated to the urinary tract. The susceptibility patterns of these organisms vary by clinical syndrome and by geography. In acute uncomplicated cystitis in the United States, the etiologic agents are highly predictable: *E. coli* accounts for 75–90% of isolates; *Staphylococcus saprophyticus* for 5–15% (with particularly frequent isolation from younger women); and *Klebsiella* species, *Proteus* species, *Enterococcus* species, *Citrobacter species*, and other organisms for 5–10%. Similar etiologic agents are found in Europe and Brazil. The spectrum of agents causing uncomplicated pyelonephritis is similar, with *E. coli* predominating. In complicated UTI (e.g., CAUTI), *E. coli* remains the predominant organism, but other aerobic gram-negative rods, such as *Klebsiella* species, *Proteus* species, *Citrobacter* species, *Acinetobacter* species, *Morganella* species, and *Pseudomonas aeruginosa*, also are frequently isolated. Gram-positive bacteria (e.g., enterococci and *Staphylococcus aureus*) and yeasts are also important pathogens in complicated UTI. Data on etiology and resistance are generally obtained from laboratory surveys and should be understood in the context that organism identification is performed only in cases in which urine is sent for culture—i.e., typically when complicated UTI or pyelonephritis is suspected. The available data demonstrate a worldwide increase in the resistance of *E. coli* to antibiotics commonly used to treat UTI. North American and European surveys of *E. coli* isolates from women with acute cystitis have documented rates of resistance to trimethoprim-sulfamethoxazole (TMP-SMX) greater than 20% and rates of resistance to ciprofloxacin between 5% and 10% in some regions. Since resistance rates vary by local geographic region, with individual patient characteristics, and over time, it is important to use current and local data when choosing a treatment regimen.

PATHOGENESIS

The urinary tract can be viewed as an anatomic unit united by a continuous column of urine extending from the urethra to the kidneys. In the majority of UTIs, bacteria establish infection by ascending from the urethra to the bladder. Continuing ascent up the ureter to the kidney is the pathway for most renal parenchymal infections. However, introduction of bacteria into the bladder does not inevitably lead to sustained and symptomatic infection. The interplay of host, pathogen, and environmental factors determines whether tissue invasion and symptomatic infection will ensue **(Fig. 28-1)**. For example, bacteria often enter the bladder after sexual intercourse, but normal voiding and innate host defense

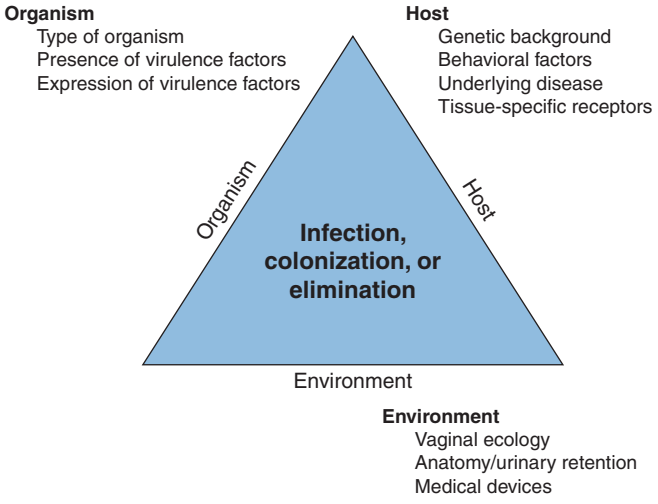


FIGURE 28-1
Pathogenesis of urinary tract infection. The relationship between specific host, pathogen, and environmental factors determines the clinical outcome.

mechanisms in the bladder eliminate these organisms. Any foreign body in the urinary tract, such as a urinary catheter or stone, provides an inert surface for bacterial colonization. Abnormal micturition and/or significant residual urine volume promotes true infection. In the simplest of terms, anything that increases the likelihood of bacteria entering the bladder and staying there increases the risk of UTI.

Bacteria can also gain access to the urinary tract through the bloodstream. However, hematogenous spread accounts for <2% of documented UTIs and usually results from bacteremia caused by relatively virulent organisms, such as *Salmonella* and *S. aureus*. Indeed, the isolation of either of these pathogens from a patient without a catheter or other instrumentation warrants a search for a bloodstream source. Hematogenous infections may produce focal abscesses or areas of pyelonephritis within a kidney and result in positive urine cultures. The pathogenesis of candiduria is distinct in that the hematogenous route is common. The presence of *Candida* in the urine of a noninstrumented immunocompetent patient implies either genital contamination or potentially widespread visceral dissemination.

Environmental factors

Vaginal ecology

In women, vaginal ecology is an important environmental factor affecting the risk of UTI. Colonization of the vaginal introitus and perirurethral area with organisms from the intestinal flora (usually *E. coli*) is the critical initial step in the pathogenesis of UTI. Sexual intercourse is associated with an increased risk of vaginal colonization with *E. coli* and thereby increases the risk of UTI. Nonoxynol-9 in spermicide is toxic to the normal vaginal microflora and, thus, is likewise associated with an increased risk of *E. coli* vaginal colonization and bacteriuria. In postmenopausal women, the previously predominant vaginal lactobacilli are replaced with gram-negative colonization. The use of topical estrogens to prevent UTI in postmenopausal women is controversial; given the side effects of systemic hormone replacement, oral estrogens should not be used to prevent UTI.

Anatomic and functional abnormalities

Any condition that permits urinary stasis or obstruction predisposes the individual to UTI. Foreign bodies such as stones or urinary catheters provide an inert surface for bacterial colonization and formation of a persistent biofilm. Thus, vesicoureteral reflux, ureteral obstruction secondary to prostatic hypertrophy, neurogenic bladder, and urinary diversion surgery create an environment favorable to UTI. In persons with such conditions, *E. coli* strains lacking typical urinary virulence factors are often the cause of infection. Inhibition of ureteral peristalsis and decreased ureteral tone leading to vesicoureteral reflux are important in the pathogenesis of pyelonephritis in pregnant women. Anatomic factors—specifically, the distance of the urethra from the anus—are considered to be the primary reason why UTI is predominantly an illness of young women rather than of young men.

Host factors

The genetic background of the host influences the individual's susceptibility to recurrent UTI, at least among women. A familial disposition to UTI and to pyelonephritis is well documented. Women with recurrent UTI are more likely to have had their first UTI before age 15 years and to have a maternal history of UTI. A component of the underlying pathogenesis of this familial predisposition to recurrent UTI may be persistent vaginal colonization with *E. coli*, even during asymptomatic periods. Vaginal and periurethral mucosal cells from women with recurrent UTI bind threefold more uropathogenic bacteria than do mucosal cells from women without recurrent infection. Epithelial cells from susceptible women may possess specific types or greater numbers of receptors to which *E. coli* can bind, thereby facilitating colonization and invasion. Mutations in host response genes (e.g., those coding for Toll-like receptors and the interleukin 8 receptor) have also been linked to recurrent UTI and pyelonephritis. Polymorphisms in the interleukin 8–specific receptor gene *CXCR1* are associated with increased susceptibility to pyelonephritis. Lower-level expression of *CXCR1* on the surface of neutrophils impairs neutrophil-dependent host defense against bacterial invasion of the renal parenchyma.

Microbial factors

An anatomically normal urinary tract presents a stronger barrier to infection than a compromised urinary tract. Thus, strains of *E. coli* that cause invasive symptomatic infection of the urinary tract in otherwise normal hosts often possess and express genetic

virulence factors, including surface adhesins that mediate binding to specific receptors on the surface of uroepithelial cells. The best-studied adhesins are the P fimbriae, hairlike protein structures that interact with a specific receptor on renal epithelial cells. (The letter *P* denotes the ability of these fimbriae to bind to blood group antigen P, which contains a D-galactose-D-galactose residue.) P fimbriae are important in the pathogenesis of pyelonephritis and subsequent bloodstream invasion from the kidney.

Another adhesin is the type 1 pilus (fimbria), which all *E. coli* strains possess but not all *E. coli* strains express. Type 1 pili are thought to play a key role in initiating *E. coli* bladder infection; they mediate binding to uroplakins on the luminal surface of bladder uroepithelial cells. The binding of type 1 fimbriae of *E. coli* to receptors on uroepithelial cells initiates a complex series of signaling events that leads to apoptosis and exfoliation of uroepithelial cells, with the attached *E. coli* organisms carried away in the urine.

APPROACH TO THE PATIENT: Clinical Manifestations

The most important issue to be addressed when a UTI is suspected is the characterization of the clinical syndrome as ABU, uncomplicated cystitis, pyelonephritis, prostatitis, or complicated UTI. This information will shape the diagnostic and therapeutic approach.

Asymptomatic Bacteriuria A diagnosis of ABU can be considered only when the patient does not have local or systemic symptoms referable to the urinary tract. The clinical presentation is usually that of a patient who undergoes a screening urine culture for a reason unrelated to the genitourinary tract and is incidentally found to have bacteriuria. The presence of systemic signs or symptoms such as fever, altered mental status, and leukocytosis in the setting of a positive urine culture does not merit a diagnosis of symptomatic UTI unless other potential etiologies have been considered.

Cystitis The typical symptoms of cystitis are dysuria, urinary frequency, and urgency. Nocturia, hesitancy, suprapubic discomfort, and gross hematuria are often noted as well. Unilateral back or flank pain is generally an indication that the upper urinary tract is involved. Fever is also an indication of invasive infection of either the kidney or the prostate.

Pyelonephritis Mild pyelonephritis can present as low-grade fever with or without lower-back or costovertebral-angle pain, whereas severe pyelonephritis can manifest as high fever, rigors, nausea, vomiting, and flank and/or loin pain. Symptoms are generally acute in onset, and symptoms of cystitis may not be present. Fever is the main feature distinguishing cystitis and pyelonephritis. The fever of pyelonephritis typically exhibits a high, spiking "picket-fence" pattern and resolves over 72 h of therapy. Bacteremia develops in 20–30% of cases of pyelonephritis. Patients with diabetes may present with obstructive uropathy associated with acute papillary necrosis when the sloughed papillae obstruct the ureter. Papillary necrosis may also be evident in some cases of pyelonephritis complicated by obstruction, sickle cell disease, analgesic nephropathy, or combinations of these conditions. In the rare cases of bilateral papillary necrosis, a rapid rise in the serum creatinine level may be the first indication of the condition. *Emphysematous* pyelonephritis is a particularly severe form of the disease that is associated with the production of gas in renal and perinephric tissues and occurs almost exclusively in diabetic patients (Fig. 28-2). *Xanthogranulomatous* pyelonephritis occurs when chronic urinary obstruction (often by staghorn calculi), together with chronic infection, leads to suppurative destruction of renal tissue (Fig. 28-3). On pathologic examination, the residual renal tissue frequently has a yellow coloration with infiltration by lipid-laden macrophages. Pyelonephritis can also be complicated by intraparenchymal abscess formation; this situation should be suspected when a patient has continued fever and/or bacteremia despite antibacterial therapy.

Prostatitis Prostatitis includes both infectious and noninfectious abnormalities of the prostate gland. Infections can be acute or chronic, are almost always bacterial in nature, and are far less common than the noninfectious entity of chronic pelvic pain syndrome (formerly known as chronic prostatitis). Acute bacterial prostatitis presents as dysuria, frequency, and pain in the prostatic, pelvic, or perineal area. Fever and chills

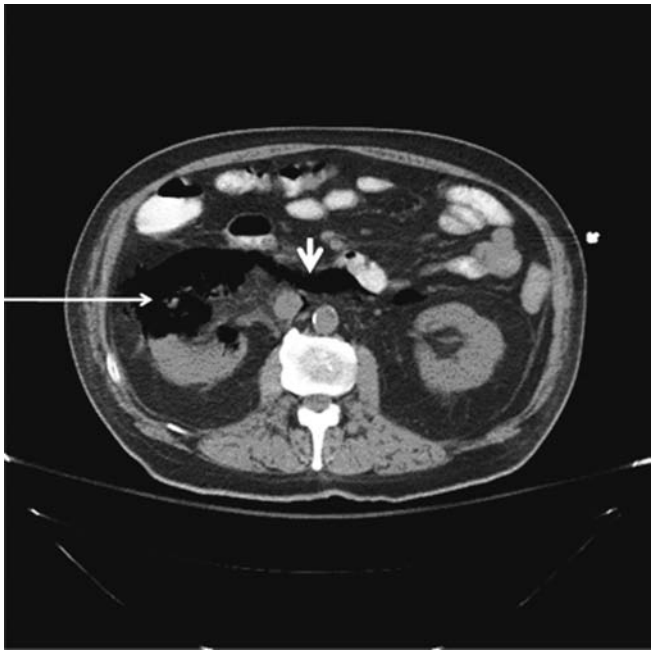
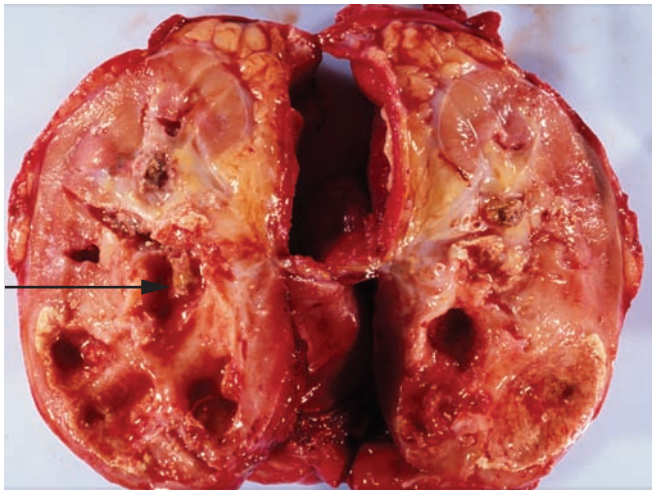
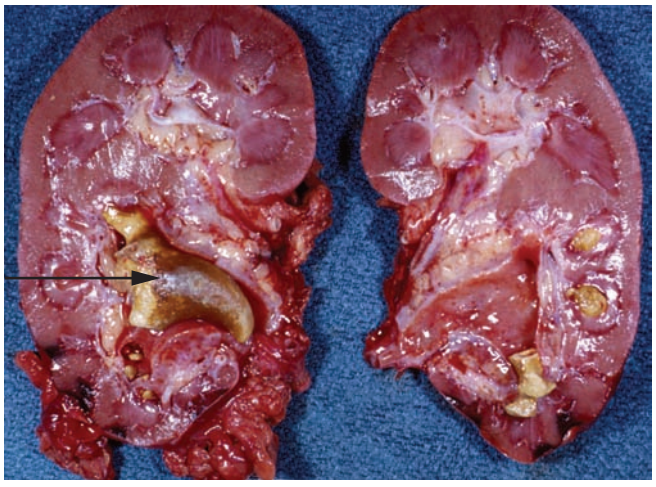


FIGURE 28-2
Emphysematous pyelonephritis. Infection of the right kidney of a diabetic man by *Escherichia coli*, a gas-forming, facultative anaerobic uropathogen, has led to destruction of the renal parenchyma (*arrow*) and tracking of gas through the retroperitoneal space (*arrowhead*).



A



B

FIGURE 28-3

Xanthogranulomatous pyelonephritis. *A.* This photograph shows extensive destruction of renal parenchyma due to long-standing suppurative inflammation. The precipitating factor was obstruction by a staghorn calculus, which has been removed, leaving a depression (*arrow*). The mass effect of xanthogranulomatous pyelonephritis can mimic renal malignancy. ***B.*** A large staghorn calculus (*arrow*) is seen obstructing the renal pelvis and calyceal system. The lower pole of the kidney shows areas of hemorrhage and necrosis with collapse of cortical areas. (*Both images: Courtesy of Dharam M. Ramnani, MD, Virginia Urology Pathology Laboratory, Richmond, VA.*)

are usually present, and symptoms of bladder outlet obstruction are common. Chronic bacterial prostatitis presents more insidiously as recurrent episodes of cystitis, sometimes with associated pelvic and perineal pain. Men who present with recurrent cystitis should be evaluated for a prostatic focus.

Complicated UTI Complicated UTI presents as a symptomatic episode of cystitis or pyelonephritis in a man or woman with an anatomic predisposition to infection, with a foreign body in the urinary tract, or with factors predisposing to a delayed response to therapy.

DIAGNOSTIC TOOLS

History

The diagnosis of any the UTI syndromes or ABU begins with a detailed history **(Fig. 28-4)**. The history given by the patient has a high predictive value in uncomplicated cystitis. A meta-analysis evaluating the probability of acute UTI on the basis of history and physical findings concluded that, in women presenting with at least one symptom of UTI (dysuria, frequency, hematuria, or back pain) and without complicating factors, the probability of acute cystitis or pyelonephritis is 50%. The even higher rates of accuracy of self-diagnosis among women with recurrent UTI probably account for the success of patient-initiated treatment of recurrent cystitis. If vaginal discharge and complicating factors are absent and risk factors for UTI are present, then the probability of UTI is close to 90%, and no laboratory evaluation is needed. Similarly, a combination of dysuria and urinary frequency in the absence of vaginal discharge increases the probability of UTI to 96%. Further laboratory evaluation with dipstick testing or urine culture is not necessary in such patients before the initiation of definitive therapy.

When the patient's history is applied as a diagnostic tool, it is important to recall that the studies included in the meta-analysis cited earlier did not enroll children, adolescents, pregnant women, men, or patients with complicated UTI. One significant concern is that sexually transmitted disease—that caused by *Chlamydia trachomatis* in particular—may be inappropriately treated as UTI. This concern is particularly relevant for female patients under the age of 25. The differential diagnosis to be considered when women present with dysuria includes cervicitis (*C. trachomatis*, *Neisseria gonorrhoeae*), vaginitis (*Candida albicans*, *Trichomonas vaginalis*), herpetic urethritis, interstitial cystitis, and noninfectious vaginal or vulvar irritation. Women with more than one sexual partner and inconsistent use of condoms are at high risk for both UTI and sexually transmitted disease, and symptoms alone do not always distinguish between these conditions.

The urine dipstick test, urinalysis, and urine culture

Useful diagnostic tools include the urine dipstick test and urinalysis, both of which provide point-of-care information, and the urine culture, which can retrospectively confirm a prior diagnosis. Understanding the parameters of the dipstick test is important in interpreting its results. Only members of the family Enterobacteriaceae convert nitrate to nitrite, and enough nitrite must accumulate in the urine to reach the threshold of detection. If a woman with acute cystitis is forcing fluids and voiding frequently, the dipstick test for nitrite is less likely to be positive,

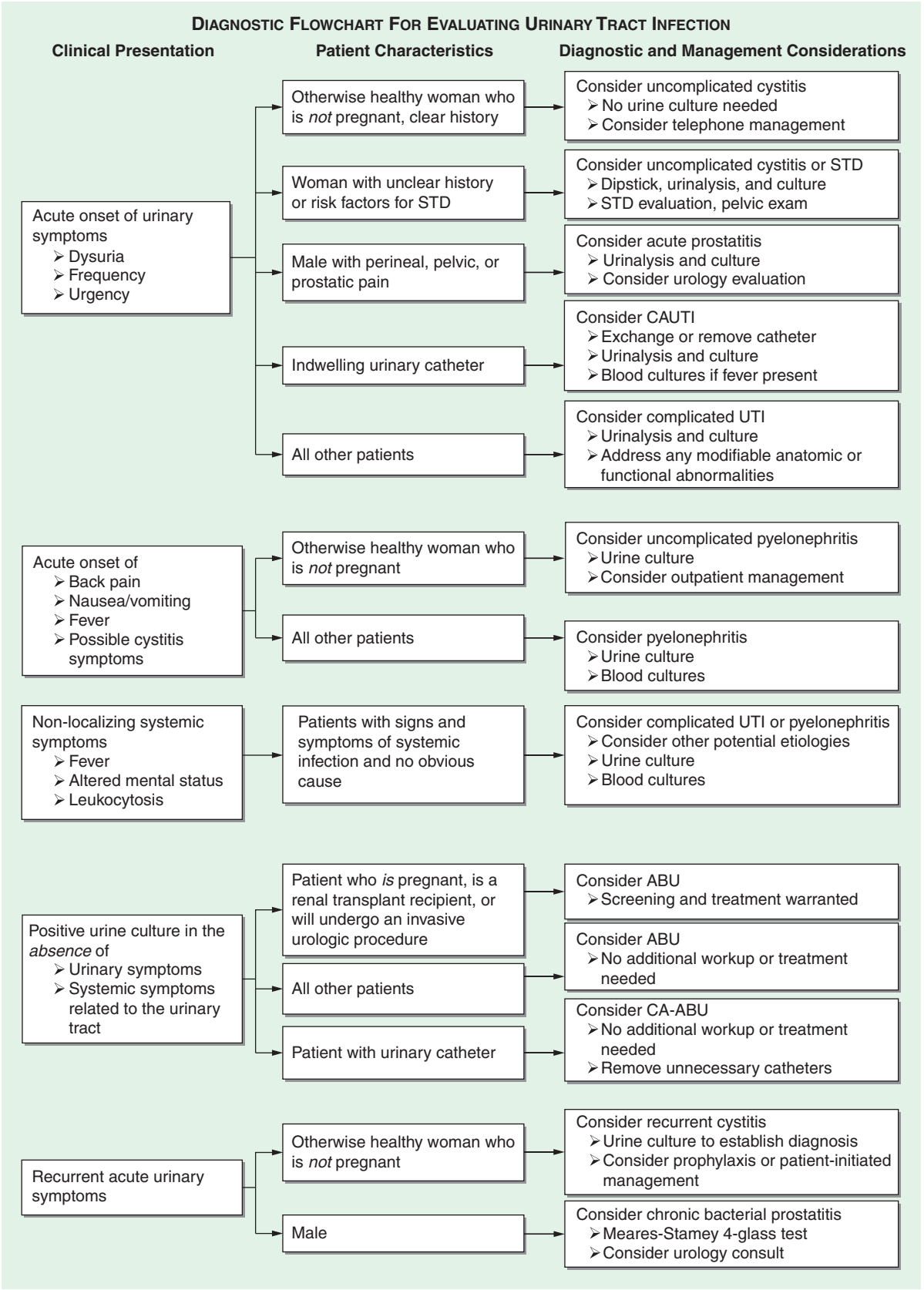


FIGURE 28-4

Diagnostic approach to urinary tract infection. STD, sexually transmitted disease; CAUTI, catheter-associated UTI; ABU, asymptomatic bacteriuria; CA-ABU, catheter-associated ABU.

even when *E. coli* is present. The leukocyte esterase test detects this enzyme in the host's polymorphonuclear leukocytes in the urine, whether the cells are intact or lysed. Many reviews have attempted to describe the diagnostic accuracy of dipstick testing. The bottom line for clinicians is that a urine dipstick test can confirm the diagnosis of uncomplicated cystitis in a patient with a reasonably high pretest probability of this disease. Either nitrite or leukocyte esterase positivity can be interpreted as a positive result. Blood in the urine may also suggest a diagnosis of UTI. A dipstick test negative for both nitrite and leukocyte esterase in the same type of patient should prompt consideration of other explanations for the patient's symptoms and collection of urine for culture. A negative dipstick test is not sufficiently sensitive to rule out bacteriuria in pregnant women, in whom it is important to detect all episodes of bacteriuria. Performance characteristics of the dipstick test differ in men (highly specific) and in noncatheterized nursing home residents (highly sensitive).

Urine microscopy reveals pyuria in nearly all cases of cystitis and hematuria in ~30% of cases. In current practice, most hospital laboratories use an automated system rather than manual examination for urine microscopy. A machine aspirates a sample of the urine and then classifies the particles in the urine by size, shape, contrast, light scatter, volume, and other properties. These automated systems can be overwhelmed by high numbers of dysmorphic red blood cells, white blood cells, or crystals; in general, counts of bacteria are less accurate than are counts of red and white blood cells. Our clinical recommendation is that the patient's symptoms and presentation should outweigh an incongruent result on automated urinalysis.

The detection of bacteria in a urine culture is the diagnostic "gold standard" for UTI; unfortunately, however, culture results do not become available until 24 h after the patient's presentation. Identifying specific organism(s) can require an additional 24 h. Studies of women with symptoms of cystitis have found that a colony count threshold of $>10^2$ bacteria/mL is more sensitive (95%) and specific (85%) than a threshold of 10^5/mL for the diagnosis of acute cystitis in women. In men, the minimal level indicating infection appears to be 10^3/mL. Urine specimens frequently become contaminated with the normal microbial flora of the distal urethra, vagina, or skin. These contaminants can grow to high numbers if the collected urine is allowed to stand at room temperature. In most instances, a culture that yields mixed bacterial species is contaminated except in settings of long-term catheterization, chronic urinary retention, or the presence of a fistula between the urinary tract and the gastrointestinal or genital tract.

DIAGNOSIS

The approach to diagnosis is influenced by which of the clinical UTI syndromes is suspected (Fig. 28-4).

Uncomplicated cystitis in women

Uncomplicated cystitis in women can be treated on the basis of history alone. However, if the symptoms are not specific or if a reliable history cannot be obtained, then a urine dipstick test should be performed. A positive nitrite or leukocyte esterase result in a woman with one symptom of UTI increases the probability of UTI from 50% to ~80%, and empirical treatment can be considered without further testing. In this setting, a negative dipstick result does not rule out UTI, and a urine culture, close clinical follow-up, and possibly a pelvic examination are recommended. These recommendations are made with the caveat that factors associated with complicated UTI, such as pregnancy, are not present.

Cystitis in men

The signs and symptoms of cystitis in men are similar to those in women, but this disease differs in several important ways in the male population. Collection of urine for culture is strongly recommended when a man has symptoms of UTI, as the documentation of bacteriuria can differentiate the less common syndromes of acute and chronic bacterial prostatitis from the very common entity of chronic pelvic pain syndrome, which is not associated with bacteriuria and thus is not usually responsive to antibacterial therapy. If the diagnosis is unclear, localization cultures using the two- or four-glass Meares-Stamey test (urine collection after prostate massage) should be undertaken to differentiate between bacterial and nonbacterial prostatic syndromes, and the patient should be referred to a urologist. Men with febrile UTI often have an elevated serum level of prostate-specific antigen as well as an enlarged prostate and enlarged seminal vesicles on ultrasound—findings indicative of prostate involvement. In 85 men with febrile UTI, symptoms of urinary retention, early recurrence of UTI, hematuria at follow-up, and voiding difficulties were predictive of surgically correctable disorders. Men with none of these symptoms had normal upper and lower urinary tracts on urologic workup.

Asymptomatic bacteriuria

The diagnosis of ABU involves both microbiologic and clinical criteria. The microbiologic criterion is usually $\geq 10^5$ bacterial cfu/mL except in catheter-associated disease, in which case $\geq 10^2$ cfu/mL is the cutoff. The clinical criterion is that the person has no signs or symptoms referable to UTI.

TREATMENT Urinary Tract Infections

Antimicrobial therapy is warranted for any symptomatic UTI. The choice of antimicrobial agent and the dose and duration of therapy depend on the site of infection and

the presence or absence of complicating conditions. Each category of UTI warrants a different approach based on the particular clinical syndrome.

UNCOMPLICATED CYSTITIS IN WOMEN

Since the species and antimicrobial susceptibilities of the bacteria that cause acute uncomplicated cystitis are highly predictable, many episodes of uncomplicated cystitis can be managed over the telephone (Fig. 28-4). Most patients with other UTI syndromes require further diagnostic evaluation. Although the risk of serious complications with telephone management appears to be low, studies of telephone management algorithms generally have involved otherwise healthy white women who are at low risk for complications of UTI.

In 1999, TMP-SMX was recommended as the first-line agent for treatment of uncomplicated UTI in the published guidelines of the Infectious Diseases Society of America. Antibiotic resistance among uropathogens causing uncomplicated cystitis has since increased, appreciation of the importance of collateral damage (as defined below) has increased, and newer agents have been studied. Unfortunately, there is no longer a single best agent for acute uncomplicated cystitis.

Collateral damage refers to the adverse ecologic effects of antimicrobial therapy, including killing of the normal flora and selection of drug-resistant organisms. Outbreaks of *Clostridium difficile* infection offer an example of collateral damage in the hospital environment. The implication of collateral damage in this context is that a drug that is highly efficacious for the treatment of UTI is not necessarily the optimal first-line agent if it also has pronounced secondary effects on the normal flora or is likely to change resistance patterns. Drugs used for UTI that have a minimal effect on fecal flora include pivmecillinam, fosfomycin, and nitrofurantoin. In contrast, trimethoprim, TMP-SMX, quinolones, and ampicillin affect the fecal flora more significantly; these drugs are notably the agents for which rising resistance levels have been documented.

Several effective therapeutic regimens are available for acute uncomplicated cystitis in women (Table 28-1). Well-studied first-line agents include TMP-SMX and nitrofurantoin. Second-line agents include fluoroquinolone and β-lactam compounds. Single-dose fosfomycin treatment for acute cystitis is widely used in Europe, but has produced mixed results in randomized trials. Pivmecillinam is not currently available in the United States or Canada, but is a popular agent in some European countries. The pros and cons of other therapies are discussed briefly below.

Traditionally, TMP-SMX has been recommended as first-line treatment for acute cystitis, and it remains appropriate to consider the use of this drug in regions with resistance rates not exceeding 20%. TMP-SMX resistance has clinical significance: in TMP-SMX-treated patients with resistant isolates, the time to symptom resolution is longer and rates of both clinical and microbiologic failure are higher. Individual host factors associated with an elevated risk of UTI caused by a strain of *E. coli* resistant to TMP-SMX include recent use of TMP-SMX or another antimicrobial agent and recent travel to an area with high rates of TMP-SMX resistance. The optimal setting for empirical use of TMP-SMX is uncomplicated UTI in a female patient who has an established relationship with the practitioner and who can thus seek further care if her symptoms do not respond promptly.

Resistance to nitrofurantoin remains low despite >60 years of use. Since this drug affects bacterial metabolism in multiple pathways, several mutational steps are required for the development of resistance. Nitrofurantoin remains highly active against *E. coli* and most non–*E. coli* isolates. *Proteus*, *Pseudomonas*, *Serratia*,

TABLE 28-1

TREATMENT STRATEGIES FOR ACUTE UNCOMPLICATED CYSTITIS

DRUG AND DOSE	ESTIMATED CLINICAL EFFICACY (%)	ESTIMATED BACTERIAL EFFICACY (%)	COMMON SIDE EFFECTS
Nitrofurantoin, 100 mg bid × 5–7 d	84–95	86–92	Nausea, headache
TMP-SMX, 1 DS tablet bid × 3 d	90–100	91–100	Rash, urticaria, nausea, vomiting, hematologic abnormalities
Fosfomycin, 3-g single-dose sachet	70–91	78–83	Diarrhea, nausea, headache
Pivmecillinam, 400 mg bid × 3–7 d	55–82	74–84	Nausea, vomiting, diarrhea
Fluoroquinolones, dose varies by agent; 3-d regimen	85–95	81–98	Nausea, vomiting, diarrhea, headache, drowsiness, insomnia
β-Lactams, dose varies by agent; 5- to 7-d regimen	79–98	74–98	Diarrhea, nausea, vomiting, rash, urticaria

Note: Efficacy rates are averages or ranges calculated from the data and studies included in the 2010 Infectious Diseases Society of America/European Society of Clinical Microbiology and Infectious Diseases Guideline for Treatment of Uncomplicated UTI. TMP-SMX, trimethoprim-sulfamethoxazole; DS, double-strength.

Enterobacter, and yeasts are all intrinsically resistant to this drug. Although nitrofurantoin has traditionally been prescribed as a 7-day regimen, similar microbiologic and clinical efficacies are noted with a 5-day course of nitrofurantoin or a 3-day course of TMP-SMX for treatment of women with acute cystitis; 3-day courses of nitrofurantoin are not recommended for acute cystitis. Nitrofurantoin does not reach significant levels in tissue and cannot be used to treat pyelonephritis.

Most fluoroquinolones are highly effective for short-course therapy for cystitis; the exception is moxifloxacin, which does not achieve adequate urinary levels. The fluoroquinolones commonly used for UTI include ofloxacin, ciprofloxacin, and levofloxacin. The main concern about fluoroquinolone use for acute cystitis is the propagation of fluoroquinolone resistance, not only among uropathogens but also among other organisms causing more serious and difficult-to-treat infections at other sites. Fluoroquinolone use is also a factor driving the emergence of *C. difficile* outbreaks in hospital settings. Most experts now call for restricting fluoroquinolones to specific instances of uncomplicated cystitis in which other antimicrobial agents are not suitable. Quinolone use in the elderly has been associated with an increased risk of Achilles tendon rupture.

Except for pivmecillinam, β-lactam agents generally have not performed as well as TMP-SMX or fluoroquinolones in acute cystitis. Rates of pathogen eradication are lower and relapse rates are higher with β-lactam drugs. The generally accepted explanation is that β-lactams fail to eradicate uropathogens from the vaginal reservoir. A proposed role for intracellular biofilm communities is intriguing. Many strains of *E. coli* that are resistant to TMP-SMX are also resistant to amoxicillin and cephalexin; thus, these drugs should be used only for patients infected with susceptible strains.

Urinary analgesics are appropriate in certain situations to speed resolution of bladder discomfort. The urinary tract analgesic phenazopyridine is widely used but can cause significant nausea. Combination analgesics containing urinary antiseptics (methenamine, methylene blue), a urine-acidifying agent (sodium phosphate), and an antispasmodic agent (hyoscyamine) are also available.

PYELONEPHRITIS Since patients with pyelonephritis have tissue-invasive disease, the treatment regimen chosen should have a very high likelihood of eradicating the causative organism and should reach therapeutic blood levels quickly. High rates of TMP-SMX-resistant *E. coli* in patients with pyelonephritis have made fluoroquinolones the first-line therapy for acute uncomplicated pyelonephritis. Whether the fluoroquinolones are given orally or parenterally depends on the patient's tolerance for oral intake. A randomized clinical trial demonstrated that a 7-day course of therapy with oral ciprofloxacin (500 mg twice daily, with or without an initial IV 400-mg dose) was highly effective for the initial management of pyelonephritis in the outpatient setting. Oral TMP-SMX (one double-strength tablet twice daily for 14 days) is also effective for treatment of acute uncomplicated pyelonephritis if the uropathogen is known to be susceptible. If the pathogen's susceptibility is not known and TMP-SMX is used, an initial IV 1-g dose of ceftriaxone is recommended. Oral β-lactam agents are less effective than the fluoroquinolones and should be used with caution and close follow-up. Options for parenteral therapy for uncomplicated pyelonephritis include fluoroquinolones, an aminoglycoside with or without ampicillin, an extended-spectrum cephalosporin with or without an aminoglycoside, or a carbapenem. Combinations of a β-lactam and a β-lactamase inhibitor (e.g., ampicillin-sulbactam, ticarcillin-clavulanate, and piperacillin-tazobactam) or imipenem-cilastatin can be used in patients with more complicated histories, previous episodes of pyelonephritis, or recent urinary tract manipulations; in general, the treatment of such patients should be guided by urine culture results. Once the patient has responded clinically, oral therapy should be substituted for parenteral therapy.

UTI IN PREGNANT WOMEN Nitrofurantoin, ampicillin, and the cephalosporins are considered relatively safe in early pregnancy. One retrospective case-control study suggesting an association between nitrofurantoin and birth defects awaits confirmation. Sulfonamides should clearly be avoided both in the first trimester (because of possible teratogenic effects) and near term (because of a possible role in the development of kernicterus). Fluoroquinolones are avoided because of possible adverse effects on fetal cartilage development. Ampicillin and the cephalosporins have been used extensively in pregnancy and are the drugs of choice for the treatment of asymptomatic or symptomatic UTI in this group of patients. For pregnant women with overt pyelonephritis, parenteral β-lactam therapy with or without aminoglycosides is the standard of care.

UTI IN MEN Since the prostate is involved in the majority of cases of febrile UTI in men, the goal in these patients is to eradicate the prostatic infection as well as the bladder infection. In men with apparently uncomplicated UTI, a 7- to 14-day course of a fluoroquinolone or TMP-SMX is recommended. If acute bacterial prostatitis is suspected, antimicrobial therapy should be initiated after urine and blood are obtained for cultures. Therapy can be tailored to urine culture results and should be continued for 2–4 weeks. For documented chronic bacterial prostatitis, a 4- to 6-week course of antibiotics is often necessary. Recurrences, which are not uncommon in chronic prostatitis, often warrant a 12-week course of treatment.

COMPLICATED UTI Complicated UTI (other than that discussed earlier) occurs in a heterogeneous group of patients with a wide variety of structural and functional abnormalities of the urinary tract and kidneys. The range of species and their susceptibility to antimicrobial agents are likewise heterogeneous. As a consequence, therapy for complicated UTI must be individualized and guided by urine culture results. Frequently, a patient with complicated UTI will have prior urine culture data

that can be used to guide empirical therapy while current culture results are awaited. Xanthogranulomatous pyelonephritis is treated with nephrectomy. Percutaneous drainage can be used as the initial therapy in emphysematous pyelonephritis and can be followed by elective nephrectomy as needed. Papillary necrosis with obstruction requires intervention to relieve the obstruction and to preserve renal function.

ASYMPTOMATIC BACTERIURIA Treatment of ABU does not decrease the frequency of symptomatic infections or complications except in pregnant women, persons undergoing urologic surgery, and perhaps neutropenic patients and renal transplant recipients. Treatment of ABU in pregnant women and patients undergoing urologic procedures should be directed by urine culture results. In all other populations, screening for and treatment of ABU are discouraged. The majority of cases of catheter-associated bacteriuria are asymptomatic and do not warrant antimicrobial therapy.

CATHETER-ASSOCIATED UTI Multiple institutions have released guidelines for the treatment of CAUTI, which is defined by bacteriuria and symptoms in a catheterized patient. The signs and symptoms either are localized to the urinary tract or can include otherwise unexplained systemic manifestations, such as fever. The accepted threshold for bacteriuria varies from $\geq 10^3$ cfu/mL to $\geq 10^5$ cfu/mL.

The formation of biofilm—a living layer of uropathogens—on the urinary catheter is central to the pathogenesis of CAUTI and affects both therapeutic and preventive strategies. Organisms in a biofilm are relatively resistant to killing by antibiotics, and eradication of a catheter-associated biofilm is difficult without removal of the device itself. Furthermore, because catheters provide a conduit for bacteria to enter the bladder, bacteriuria is inevitable with long-term catheter use.

The typical signs and symptoms of UTI, including pain, urgency, dysuria, fever, peripheral leukocytosis, and pyuria, have less predictive value for the diagnosis of infection in catheterized patients. Furthermore, the presence of bacteria in the urine of a patient who is febrile and catheterized does not necessarily predict CAUTI, and other explanations for the fever should be considered.

The etiology of CAUTI is diverse, and urine culture results are essential to guide treatment. Fairly good evidence supports the practice of catheter change during treatment for CAUTI. The goal is to remove biofilm-associated organisms that could serve as a nidus for reinfection. Pathology studies reveal that many patients with long-term catheters have occult pyelonephritis. A randomized trial in persons with spinal cord injury who were practicing intermittent catheterization found that relapse was more common after 3 days of therapy than after 14 days. In general, a 7- to 14-day course of antibiotics is recommended, but further studies on the optimal duration of therapy are needed.

In the setting of long-term catheter use, systemic antibiotics, bladder-acidifying agents, antimicrobial bladder washes, topical disinfectants, and antimicrobial drainage-bag solutions have all been ineffective at preventing the onset of bacteriuria and have been associated with the emergence of resistant organisms. The best strategy for prevention of CAUTI is to avoid insertion of unnecessary catheters and to remove catheters once they are no longer necessary. Evidence is insufficient to recommend suprapubic catheters and condom catheters as alternatives to indwelling urinary catheters as a means to prevent CAUTI. However, intermittent catheterization may be preferable to long-term indwelling urethral catheterization in certain populations (e.g., spinal cord–injured persons) to prevent both infectious and anatomic complications. Antimicrobial catheters impregnated with silver or nitrofurazone have not been shown to provide significant clinical benefit in terms of reducing rates of symptomatic UTI.

CANDIDURIA The appearance of *Candida* in the urine is an increasingly common complication of indwelling catheterization, particularly for patients in the intensive care unit, those taking broad-spectrum antimicrobial drugs, and those with underlying diabetes mellitus. *C. albicans* is still the most common isolate, although *C. glabrata* and other non-*albicans* species are also isolated frequently. The clinical presentation varies from an asymptomatic laboratory finding to pyelonephritis and even sepsis. In asymptomatic patients, removal of the urethral catheter results in resolution of candiduria in more than one-third of cases. Treatment is recommended for patients who have symptomatic cystitis or pyelonephritis and for those who are at high risk for disseminated disease. High-risk patients include those with neutropenia, those who are undergoing urologic manipulation, and low-birth-weight infants. Fluconazole (200–400 mg/d for 14 days) achieves high levels in urine and is the first-line regimen for *Candida* infections of the urinary tract. The newer azoles and echinocandins are characterized by only low-level urinary excretion and thus are not recommended, although cases of successful eradication of candiduria with some of these agents have been reported. For *Candida* isolates with high levels of resistance to fluconazole, oral flucytosine and/or parenteral amphotericin B are options. Bladder irrigation with amphotericin B generally is not recommended.

PREVENTION OF RECURRENT UTI IN WOMEN

Recurrence of uncomplicated cystitis in reproductive-age women is common, and a preventive strategy is indicated if recurrent UTIs are interfering with a patient's lifestyle. The threshold of two or more symptomatic episodes per year is not absolute; decisions about interventions should take the patient's preferences into account.

Three prophylactic strategies are available: continuous, postcoital, or patient-initiated therapy. Continuous prophylaxis and postcoital prophylaxis usually entail low doses of TMP-SMX, a fluoroquinolone, or nitrofurantoin. These regimens are all highly effective during the period of active antibiotic intake. Typically, a prophylactic regimen is prescribed for 6 months and then discontinued, at which point the rate of recurrent UTI often returns to baseline. If bothersome infections recur, the prophylactic program can be reinstituted for a longer period.

Patient-initiated therapy involves supplying the patient with materials for urine culture and self-medication with a course of antibiotics at the first symptoms of infection. The urine culture is refrigerated and delivered to the physician's office for confirmation of the diagnosis. When an established and reliable patient-provider relationship exists, the urine culture can be omitted as long as the symptomatic episodes respond completely to short-course therapy and are not followed by relapse.

PROGNOSIS

Cystitis is a risk factor for recurrent cystitis and pyelonephritis. ABU is common among elderly and catheterized patients but does not in itself increase the risk of death. The relationships among recurrent UTI, chronic pyelonephritis, and renal insufficiency have been widely studied. In the absence of anatomic abnormalities, recurrent infection in children and adults does not lead to chronic pyelonephritis or to renal failure. Moreover, infection does not play a primary role in chronic interstitial nephritis; the primary etiologic factors in this condition are analgesic abuse, obstruction, reflux, and toxin exposure. In the presence of underlying renal abnormalities (particularly obstructing stones), infection as a secondary factor can accelerate renal parenchymal damage. In spinal cord–injured patients, use of a long-term indwelling bladder catheter is a well-documented risk factor for bladder cancer. Chronic bacteriuria resulting in chronic inflammation is one possible explanation for this observation.

CHAPTER 29

INTERSTITIAL CYSTITIS/PAINFUL BLADDER SYNDROME

John W. Warren

Most clinicians with outpatient practices see undiagnosed cases of interstitial cystitis/painful bladder syndrome (IC/PBS). This chronic condition is characterized by pain perceived to be from the urinary bladder, urinary urgency and frequency, and nocturia. As currently diagnosed, the great majority of cases occur in women. Symptoms wax and wane for months or years or possibly even for the patient's lifetime. The spectrum of symptom intensity is broad. The pain can be excruciating, urgency can be distressing, frequency can be up to 60 times per 24 h, and nocturia can cause sleep deprivation. These symptoms can be disabling in terms of daily activities, work schedules, and personal relationships; patients with IC/PBS report less life satisfaction than do those with end-stage renal disease. The etiology of IC/PBS is unknown. It is not a new disease, having first been described in the late nineteenth century in a patient with the symptoms described earlier and a single ulcer visible on cystoscopy (now called Hunner's ulcer after the urologist who first reported it). Over the ensuing decades, it became clear that many patients with similar symptoms had no ulcer. It is now appreciated that ≥10% of patients with IC/PBS have a Hunner's ulcer.

The definition of IC/PBS, its diagnostic features, and even its name continue to evolve. The International Continence Society, a body devoted to studying disorders of the lower urinary tract and pelvic floor, has defined PBS as "the complaint of suprapubic pain related to bladder filling, accompanied by other symptoms such as increased daytime and night-time frequency, in the absence of proven urinary infection or other obvious pathology." In practice, clinicians have interpreted this definition to include any chronic pelvic pain that increases with bladder filling and/or decreases with voiding and that cannot be explained by reference to another identifiable disease.

Many patients with IC/PBS also have other syndromes, such as fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, vulvodynia, and migraine. These syndromes collectively are known as functional somatic syndromes (FSSs): chronic conditions in which pain and fatigue are prominent features but laboratory tests and histologic findings are normal. Like IC/PBS, the FSSs often are associated with depression and anxiety. The majority of cases affect women, and more than one FSS can affect a single patient. Because of its similar features and comorbidity, IC/PBS sometimes is considered an FSS.

EPIDEMIOLOGY

Contemporary population studies of IC/PBS in the United States indicate prevalences of 2–3% among women and 1–2% among men. For decades, it was thought that 90% of IC/PBS cases occurred in women. These prevalence findings, however, have generated research aimed at determining the proportion of men with symptoms usually diagnosed as chronic prostatitis (now known as chronic prostatitis/chronic pelvic pain syndrome) who actually have IC/PBS. Well-designed studies of the incidence of IC/PBS have not been reported.

Among women, the average age at onset of IC/PBS symptoms is the early forties, but the range is from childhood through the early sixties. Risk factors (antecedent features that distinguish cases from controls) primarily have been FSSs. Indeed, the odds of IC/PBS increase with the number of such syndromes present. Surgery was long thought to be a risk factor for IC/PBS, but analyses adjusting for FSSs refuted that association. A minority of patients have a bacterial urinary tract infection (UTI) at the onset of IC/PBS.

The natural history of IC/PBS is not known. Although studies from urology and urogynecology practices have been interpreted as showing that IC/PBS lasts for the lifetime of the patient, population studies suggest that some individuals with IC/PBS do not consult specialists and may not seek medical care at all, and most prevalence studies do not show an upward trend with age—a pattern that would be expected with incident cases throughout adulthood followed by lifetime persistence of a nonfatal disease. It may be reasonable to conclude that patients in a urology practice represent those with the most severe and recalcitrant IC/PBS.

PATHOLOGY

For the ≥10% of IC/PBS patients who have a Hunner's ulcer, the term *interstitial cystitis* may indeed describe the histopathologic picture. Most of these patients have substantive inflammation, mast cells, and granulation tissue. However, in the 90% of patients without such ulcers, the bladder mucosa is relatively normal, with scant inflammation.

ETIOLOGY

Numerous theories about the pathogenesis of IC/PBS have been put forward. It is not surprising that most early theories focused on the bladder. For instance, IC/PBS has been investigated as a chronic bladder infection. Sophisticated technologies have not identified a causative organism in urine or in bladder tissue; however, the patients studied by these methods had IC/PBS of chronic duration, and the results do not preclude the possibility that infection may trigger the syndrome or may be a feature of early IC/PBS. Other inflammatory factors, including a role for mast cells, have been postulated, but as was noted earlier, the 90% of patients without a Hunner's ulcer have little bladder inflammation and do not exhibit a prominence of mast cells. Autoimmunity has been considered, but autoantibodies are low in titer, nonspecific, and thought to be a result rather than a cause of IC/PBS. Increased permeability of the bladder mucosa due to defective epithelium or glycosaminoglycan (the bladder's mucous coating) has been studied frequently, but the findings have been inconclusive.

Investigations of causes outside the bladder have been prompted by the presence of comorbid FSSs. Many patients with FSSs have abnormal pain sensitivity as evidenced by (1) low pain thresholds in body areas unrelated to the diagnosed syndrome, (2) dysfunctional descending neurologic control of tactile signals, and (3) enhanced brain responses to touch in functional neuroimaging studies. Moreover, in patients with IC/PBS, body surfaces remote from the bladder are more sensitive to pain than is the case in individuals without IC/PBS. All these findings are consistent with upregulation of sensory processing in the brain. Indeed, the prevailing theory is that these concomitantly occurring syndromes have in common an abnormality of brain processing of sensory input. However, antecedence is a critical criterion for causality, and no study has demonstrated that abnormal pain sensitivity precedes either IC/PBS or FSSs.

CLINICAL PRESENTATION

In some patients, IC/PBS has a gradual onset and/or the cardinal symptoms of pain, urgency, frequency, and nocturia appear sequentially in no consistent order. Other patients can identify the exact date of onset of IC/PBS symptoms. More than half of the latter patients describe burning or pain with urination beginning on that date. This symptom, usually termed *dysuria*, is characteristic of a UTI. As was stated earlier, only a minority of IC/PBS patients who obtain medical care soon after symptom onset have uropathogenic bacteria or leukocytes in urine. These patients and many others with new-onset IC/PBS are treated with antibiotics for a presumptive UTI. Men presenting with such symptoms generally are treated for chronic bacterial prostatitis. Persistent or recurring symptoms without bacteriuria eventually prompt a differential diagnosis, and IC/PBS is considered. Traditionally, the diagnosis of IC/PBS has been delayed (sometimes for years), but recent interest in the disease has shortened this interval.

The pain of IC/PBS includes suprapubic prominence and changes with the voiding cycle. Two-thirds of

women with IC/PBS report two or more sites of pain. The most common site (involved in 80% of women) and generally the one with the most severe pain is the suprapubic area. About 35% of female patients have pain in the urethra, 25% in other parts of the vulva, and 30% in nonurogenital areas, mostly the low back and also the anterior or posterior thighs or the buttocks. The pain of IC/PBS most commonly is described as aching, pressing, throbbing, tender, and/or piercing. What may distinguish IC/PBS from other pelvic pain is that in 95% of patients bladder filling exacerbates the pain and/or bladder emptying relieves it. Almost as many patients report a puzzling pattern in which certain dietary substances worsen the pain of IC/PBS. Smaller proportions—but still the majority—of patients report that their IC/PBS pain is worsened by menstruation, stress, tight clothing, exercise, and riding in a car as well as during or after vaginal intercourse.

The urethral and vulvar pain of IC/PBS merits special mention. In addition to the descriptive adjectives for IC/PBS mentioned earlier, this pain commonly is described as burning, stinging, and sharp and as being worsened by touch, tampons, and vaginal intercourse. Patients report that urethral pain increases during urination and generally lessens afterward. These characteristics have commonly caused the urethral pain of IC/PBS to be diagnosed as chronic urethral syndrome and the vulvar pain as vulvodynia.

In many patients with IC/PBS, there is a link between pain and urinary urgency; that is, two-thirds of patients describe the urge to urinate as a desire to relieve pain. Only 20% report that the urge stems from a desire to prevent incontinence; indeed, very few patients with IC/PBS are incontinent. Urinary frequency can be severe, with ~85% of patients voiding >10 times per 24 h and some as often as 60 times. Voiding continues through the night, and nocturia is common, frequent, and often associated with symptoms of sleep deprivation.

Beyond these common symptoms of IC/PBS, additional urinary and other symptoms may be present. Among the urinary symptoms are difficulty in starting urine flow and perceptions of difficulty in emptying the bladder and bladder spasms. Among the other symptoms are the manifestations of comorbid FSSs as well as symptoms that do not constitute recognized syndromes, such as numbness, muscle spasms, dizziness, ringing in the ears, and blurred vision.

The pain, urgency, and frequency of IC/PBS can be debilitating. Proximity to a bathroom is a continuous focus, and patients report difficulties in the workplace, leisure activities, travel, or simply leaving home. Familial and sexual relationships can be strained.

DIAGNOSIS

Traditionally, IC/PBS has been considered a rare condition that is diagnosed by urologists at cystoscopy. However, this disorder is much more common than once was thought; it is now being considered earlier in its course and is being diagnosed and managed more often by primary care clinicians. Results of physical examination, urinalysis, and urologic procedures are insensitive and/or nonspecific. Thus, diagnosis is based on the presence of appropriate symptoms and the exclusion of diseases with a similar presentation.

Three categories of disorders can be considered in the differential diagnosis of IC/PBS. The first represents other identifiable diseases that manifest as pelvic pain and/or urinary symptoms, including common infections (recurrent UTI, vaginitis, genital herpes); cystitis caused by irradiation, cyclophosphamide treatment, or tuberculosis; neurogenic bladder, bladder stones, or urethral diverticulum; cancer of the bladder, uterus, cervix, vagina, or urethra; and, in men, prostate cancer. Overactive bladder is a chronic condition of women and men that manifests as urgency and frequency and that can be distinguished from IC/PBS by the patient's history: pain is not a feature of overactive bladder, and its urgency arises from the need to avoid incontinence. Endometriosis is a special case: it can be asymptomatic or can cause pelvic pain, dysmenorrhea, and dyspareunia—i.e., types of pain that mimic IC/PBS. Endometrial implants on the bladder (although uncommon) can cause urinary symptoms, and the resulting syndrome can mimic IC/PBS. Even if endometriosis is identified, it is difficult in the absence of bladder implants to determine whether it is causative of or incidental to the symptoms of IC/PBS in a specific woman.

The second category of disorders encompasses the FSSs that can accompany IC/PBS. IC/PBS can be misdiagnosed as chronic pelvic pain, irritable bowel syndrome, or fibromyalgia. The correct diagnosis may be entertained only when changes of pain with altered bladder volume or urinary symptoms appear or become more prominent.

The third category involves syndromes that IC/PBS mimics by way of its referred pain. These syndromes include vulvodynia and chronic urethral syndrome. In studies of adults with chronic urinary symptoms, the distribution of symptoms is similar in men and women, a finding that calls into question the distinctions among IC/PBS, overactive bladder, benign prostatic hyperplasia, and chronic prostatitis /chronic pelvic pain syndrome.

Therefore, IC/PBS should be considered in the differential diagnosis of persistent or recurrent "UTI" but sterile urine cultures; "overactive bladder" with pain; chronic pelvic pain, endometriosis, vulvodynia, or FSSs with urinary symptoms; and "chronic prostatitis." As was mentioned earlier, important clues to the diagnosis of IC/PBS are the exacerbation of pain with bladder filling or with the consumption of certain foods or drinks and the alleviation of pain after urination.

Cystoscopy under anesthesia formerly was thought to be necessary for the diagnosis because of its capacity to reveal a Hunner's ulcer or—in the 90% of patients without an ulcer—petechial hemorrhages after bladder distention. However, because these findings are nonspecific, many experts find this procedure unnecessary. Because other urologic diagnostic procedures are not particularly helpful, the indications for urologic referral have evolved toward the need to rule out other diseases or administer more advanced treatment.

A typical patient presents to the primary clinician after days, weeks, or months of pain, urgency, frequency, and/or nocturia. The presence of urinary nitrites, leukocytes, or uropathogenic bacteria should prompt treatment for a UTI and bacterial prostatitis in women and men, respectively. Persistence or recurrence of symptoms in the absence of bacteriuria should prompt a pelvic examination for women, an assay for serum prostate-specific antigen for men, and urine cytology and inclusion of IC/PBS in the differential diagnosis in both sexes.

In the diagnosis of IC/PBS, inquiries about pain, pressure, and discomfort are useful; IC/PBS should be considered if any of those sensations are noted in one or more anterior or posterior sites between the umbilicus and the upper thighs. Nondirective questions about the effect of bladder volume changes include "As your next urination approaches, does this pain get better, get worse, or stay the same?" and "After you urinate, does this pain get better, get worse, or stay the same?" Establishing that the pain is exacerbated by the consumption of certain foods and drinks can not only support the diagnosis of IC/PBS but also serve as the basis for one of the first steps in managing this syndrome. A nondirective way to ask about urgency is to describe it to the patient as a compelling urge to urinate that is difficult to postpone; follow-up questions can determine whether this urge is intended to relieve pain or prevent incontinence. To assess severity and provide quantitative baseline measures, pain and urgency should be estimated by the patient on a scale of 0–10, with 0 being none and 10 the worst imaginable. Frequency per 24-h period should be determined and nocturia assessed as the number of times per night the patient is awakened by the need to urinate.

About half of patients with IC/PBS have intermittent or persistent microscopic hematuria; this manifestation and the need to exclude bladder stones or cancer require urologic or urogynecologic referral. Initiation of therapy for IC/PBS does not hamper subsequent urologic evaluation.

TREATMENT Interstitial Cystitis/Painful Bladder Syndrome

The goal of therapy is to relieve the symptoms of IC/PBS; the challenge lies in the fact that no treatment is uniformly successful. However, most patients eventually obtain relief, generally with a multifaceted approach. The correct strategy is to begin with less invasive therapies and move to more invasive measures only if necessary and under the supervision of a urologist or urogynecologist. Tactics include education, dietary changes, medications, pelvic-floor physical therapy, and treatment of associated FSSs.

Months or even years may have passed since the onset of symptoms, and the patient's life may have been disrupted continually, with repeated medical visits provoking frustration and dismay in both the patient and physicians. In this circumstance, simply giving a name to the syndrome is beneficial. The physician should discuss the disease, the diagnostic and therapeutic strategies, and the prognosis with the patient and with the spouse and/or other pertinent family members, who may need to be made aware that although IC/PBS has no visible manifestations, the patient is undergoing substantial pain and suffering. This information is particularly important for sexual partners, as exacerbation of pain during and after intercourse is a common feature of IC/PBS. The Interstitial Cystitis Association (*http://www.ichelp.org*) and the Interstitial Cystitis Network (*http://www.ic-network.com*) can be useful in this educational process.

Over time, many patients identify particular foods and drinks that exacerbate their symptoms. Common among these are chilies, chocolate, citrus fruits, tomatoes, alcohol, caffeinated drinks, and carbonated beverages; full lists of common trigger foods are available at the websites cited earlier. To construct a benign diet, some patients find it useful to exclude all possible offenders and add those items back into the diet one at a time to identify the ones that worsen IC/PBS symptoms. Patients also should experiment with fluid volumes; some find relief with less fluid, others with more.

Among oral medications, nonsteroidal anti-inflammatory drugs are commonly used first but are often unsuccessful. A small randomized controlled trial suggested that amitriptyline is a reasonable choice for the next agent. This drug is used not for its antidepressant activity but because of its proven effects on neuropathic pain. The initial dose of 25 mg at bedtime is increased weekly by 25 mg up to 100 mg (or less if adequate relief of symptoms is obtained with a lower dose). Side effects can be expected and include dry mouth, weight gain, sedation, and constipation. If this regimen does not control symptoms adequately, pentosan polysulfate, a semisynthetic polysaccharide, can be added at a dose of 100 mg three times a day. Its theoretical effect is to replenish a possibly defective glycosaminoglycan layer over the bladder mucosa, but randomized clinical trials suggest only a modest benefit over placebo. Adverse reactions are uncommon and include gastrointestinal symptoms, headache, and alopecia. Pentosan polysulfate has weak anticoagulant effects and perhaps should be avoided by patients with coagulation abnormalities.

Tenderness of the pelvic floor often is reported by IC/PBS patients. A small but cleverly designed randomized clinical trial suggested that weekly physical therapy directed at muscles and soft tissues of the pelvis yields significantly more relief than a similar schedule of general body massage. This intervention can be initiated under the direction of a knowledgeable physical therapist while trials of medications are under way.

Anecdotal reports suggest that successful therapy for one FSS is accompanied by diminished symptoms of other FSSs. As has been noted here, IC/PBS often is

associated with one or several FSSs. Thus, it seems reasonable to hope that, to the extent that accompanying FSSs can be treated successfully, the symptoms of IC/PBS may be relieved as well.

If several months of these therapies in combination do not relieve symptoms adequately, the patient should be referred to a urologist or urogynecologist who has access to additional modalities. Cystoscopy under anesthesia allows distention of the bladder with water, a procedure that provides ~40% of patients with several months of relief and can be repeated. For those few patients with a Hunner's ulcer, fulguration may offer relief. Bladder instillation of solutions containing lidocaine can be repeated. A small randomized clinical trial indicates that bladder instillation of dimethyl sulfoxide is effective in significantly more patients than is placebo. Physicians experienced in the care of IC/PBS patients have used anticonvulsants, narcotics, and cyclosporine as components of therapy. Pain specialists can be of assistance. Sacral neuromodulation can be tested with a temporary percutaneous electrode and, if effective, can be administered with an implanted device. In a very small number of patients with recalcitrant symptoms, surgeries, including cystoplasty, partial or total cystectomy, and urinary diversion, can be valuable.

CHAPTER 30

SEXUALLY TRANSMITTED INFECTIONS: OVERVIEW AND CLINICAL APPROACH

Jeanne M. Marrazzo ■ King K. Holmes

CLASSIFICATION AND EPIDEMIOLOGY

Worldwide, most adults acquire at least one sexually transmitted infection (STI), and many remain at risk for complications. Each year, for example, an estimated 6.2 million persons in the United States acquire a new genital human papillomavirus (HPV) infection, and many of these individuals are at risk for genital neoplasias. Certain STIs, such as syphilis, gonorrhea, HIV infection, hepatitis B, and chancroid, are most concentrated within "core populations" characterized by high rates of partner change, multiple concurrent partners, or "dense," highly connected sexual networks—e.g., involving sex workers and their clients, some men who have sex with men (MSM), and persons involved in the use of illicit drugs, particularly crack cocaine and methamphetamine. Other STIs are distributed more evenly throughout societies. For example, chlamydial infections, genital infections with HPV, and genital herpes can spread widely, even in relatively low-risk populations.

In general, the product of three factors determines the initial rate of spread of any STI within a population: rate of sexual exposure of susceptible to infectious people, efficiency of transmission per exposure, and duration of infectivity of those infected. Accordingly, efforts to prevent and control STIs aim to decrease the rate of sexual exposure of susceptibles to infected persons (e.g., through individual counseling and efforts to change the norms of sexual behavior and through a variety of STI control efforts aimed at reducing the proportion of the population infected), to decrease the duration of infectivity (through early diagnosis and curative or suppressive treatment), and to decrease the efficiency of transmission (e.g., through promotion of condom use and safer sexual practices, through use of effective vaccines, and recently through male circumcision).

In all societies, STIs rank among the most common of all infectious diseases, with >30 infections now classified as predominantly sexually transmitted or as frequently sexually transmissible **(Table 30-1)**. In developing countries, with three-quarters of the world's population and 90% of the world's STIs, factors such as population growth (especially in adolescent and young-adult age groups), rural-to-urban migration, wars, limited or no provision of reproductive health services for women, and poverty create exceptional vulnerability to disease

TABLE 30-1

SEXUALLY TRANSMITTED AND SEXUALLY TRANSMISSIBLE MICROORGANISMS

BACTERIA	VIRUSES	OTHER[a]
Transmitted in Adults Predominantly by Sexual Intercourse		
Neisseria gonorrhoeae	HIV (types 1 and 2)	*Trichomonas vaginalis*
Chlamydia trachomatis	Human T-cell lymphotropic virus type I	*Pthirus pubis*
Treponema pallidum	Herpes simplex virus type 2	
Haemophilus ducreyi	Human papillomavirus (multiple genital genotypes)	
Klebsiella (Calymmatobacterium) granulomatis	Hepatitis B virus[b]	
Ureaplasma urealyticum	Molluscum contagiosum virus	
Mycoplasma genitalium		
Sexual Transmission Repeatedly Described but Not Well Defined or Not the Predominant Mode		
Mycoplasma hominis	Cytomegalovirus	*Candida albicans*
Gardnerella vaginalis and other vaginal bacteria	Human T-cell lymphotropic virus type II	*Sarcoptes scabiei*
Group B *Streptococcus*	Hepatitis C virus	
Mobiluncus spp.	(?) Hepatitis D virus	
Helicobacter cinaedi	Herpes simplex virus type 1	
Helicobacter fennelliae	(?) Epstein-Barr virus	
	Human herpesvirus type 8	
Transmitted by Sexual Contact Involving Oral-Fecal Exposure; of Declining Importance in Men Who Have Sex with Men		
Shigella spp.	Hepatitis A virus	*Giardia lamblia*
Campylobacter spp.		*Entamoeba histolytica*

[a]Includes protozoa, ectoparasites, and fungi.
[b]Among U.S. patients for whom a risk factor can be ascertained, most hepatitis B virus infections are transmitted sexually.

resulting from unprotected sex. During the 1990s in China, Russia, the other states of the former Soviet Union, and South Africa, internal social structures changed rapidly as borders opened to the West, unleashing enormous new epidemics of HIV infection and other STIs. Despite advances in the provision of highly effective antiretroviral therapy worldwide, HIV remains the leading cause of death in some developing countries, and HPV and hepatitis B virus (HBV) remain important causes of cervical and hepatocellular carcinoma, respectively—two of the most common malignancies in the developing world. Sexually transmitted herpes simplex virus (HSV) infections now cause most genital ulcer disease throughout the world and an increasing proportion of cases of genital herpes in developing countries with generalized HIV epidemics, where the positive-feedback loop between HSV and HIV transmission is a growing, intractable problem. Despite this consistent link, randomized trials evaluating the efficacy of antiviral therapy in suppressing HSV in both HIV-uninfected and HIV-infected persons have not demonstrated a protective effect against acquisition or transmission of HIV. Globally, ~350 million new cases of five curable STIs—gonorrhea, chlamydial infection, syphilis, chancroid, and trichomoniasis—were reported annually in the mid-1990s. Up to 50% of women of reproductive age in developing countries have bacterial vaginosis (arguably acquired sexually). All five of these curable infections have been associated with increased risk of HIV transmission or acquisition.

In the United States, the prevalence of antibody to HSV-2 began to fall in the late 1990s, especially among adolescents and young adults; the decline is presumably due to delayed sexual debut, increased condom use, and lower rates of multiple (≥4) sex partners, as is well documented by the U.S. Youth Risk Behavior Surveillance System. The estimated annual incidence of HBV infection has also declined dramatically since the mid-1980s; this decrease is probably attributable more to adoption of safer sexual practices and reduced needle sharing among injection drug users than to use of hepatitis B vaccine, for which coverage among young adults (including those at high risk for this infection) initially was very limited. Genital HPV remains the most common sexually transmitted pathogen in this country, infecting 60% of a cohort of initially HPV-negative, sexually active Washington state college women within 5 years in a study conducted from 1990 to 2000. The scale-up of HPV vaccine coverage among young women promises to lower the incidence of infection with the HPV types included in the vaccines.

In industrialized countries, fear of HIV infection since the mid-1980s, coupled with widespread behavioral interventions and better-organized systems of care for the curable STIs, initially helped curb the transmission of the latter diseases. However, foci of hyperendemic transmission persist in the southeastern United States and in most large U.S. cities. Rates of gonorrhea and syphilis remain higher in the United States than in any other Western industrialized country.

In the United States, the Centers for Disease Control and Prevention (CDC) has compiled reported rates of STIs since 1941. The incidence of reported gonorrhea peaked at 468 cases per 100,000 population in the mid-1970s, fell to a low of 112 cases per 100,000 in 2004, and remained relatively unchanged through 2008. Because of increased testing and more sensitive tests, the incidence of reported *Chlamydia trachomatis* infection has been increasing steadily since reporting began in 1984, reaching an all-time peak of 401 cases per 100,000 in 2008. The incidence of primary and secondary syphilis per 100,000 peaked at 71 cases in 1946, fell rapidly to 3.9 cases in 1956, ranged from ~10 to 15 cases through 1987 (with markedly increased rates among MSM and African Americans), and then fell to a nadir of 2.1 cases in 2000–2001 (with rates falling most rapidly among heterosexual African Americans). Unfortunately, since 1996, with the introduction of highly active antiretroviral therapy, the increased use of "serosorting" (i.e., the avoidance of unprotected sex with HIV-serodiscordant partners but not with HIV-seroconcordant partners, a strategy that provides no protection against STIs other than HIV infection), and an ongoing epidemic of methamphetamine use, gonorrhea, syphilis, and chlamydial infection have had a remarkable resurgence among MSM in North America and Europe, where outbreaks of a rare type of chlamydial infection (lymphogranuloma venereum; LGV) that had virtually disappeared during the AIDS era have occurred. These developments have resulted in a high degree of co-infection with HIV and other sexually transmitted pathogens (particularly syphilis and LGV), primarily among MSM.

MANAGEMENT OF COMMON SEXUALLY TRANSMITTED DISEASE (STD) SYNDROMES

Although other chapters discuss management of specific STIs, delineating treatment based on diagnosis of a specific infection, most patients are actually managed (at least initially) on the basis of presenting symptoms and signs and associated risk factors, even in industrialized countries. **Table 30-2** lists some of the most common clinical STD syndromes and their microbial etiologies. Strategies for their management are outlined next. Chapter 93 addresses the management of infections with human retroviruses.

STD care and management begin with risk assessment and proceed to clinical assessment, diagnostic testing or screening, treatment, and prevention. Indeed, the routine care of any patient begins with risk assessment (e.g., for risk of heart disease, cancer). STD/HIV risk assessment is important in primary care, urgent care, and emergency care settings as well as in specialty clinics providing adolescent, HIV/AIDS, prenatal, and family planning services. STD/HIV risk assessment guides detection and interpretation of symptoms that could

TABLE 30-2
MAJOR STD SYNDROMES AND SEXUALLY TRANSMITTED MICROBIAL ETIOLOGIES

SYNDROME	ST MICROBIAL ETIOLOGIES
AIDS	HIV types 1 and 2
Urethritis: males	*Neisseria gonorrhoeae, Chlamydia trachomatis, Mycoplasma genitalium, Ureaplasma urealyticum* (?subspecies *urealyticum*), *Trichomonas vaginalis,* HSV
Epididymitis	*C. trachomatis, N. gonorrhoeae*
Lower genital tract infections: females	
Cystitis/urethritis	*C. trachomatis, N. gonorrhoeae,* HSV
Mucopurulent cervicitis	*C. trachomatis, N. gonorrhoeae, M. genitalium*
Vulvitis	*Candida albicans,* HSV
Vulvovaginitis	*C. albicans, T. vaginalis*
Bacterial vaginosis (BV)	BV-associated bacteria (see text)
Acute pelvic inflammatory disease	*N. gonorrhoeae, C. trachomatis,* BV-associated bacteria, *M. genitalium,* group B streptococci
Infertility	*N. gonorrhoeae, C. trachomatis,* BV-associated bacteria
Ulcerative lesions of the genitalia	HSV-1, HSV-2, *Treponema pallidum*, *Haemophilus ducreyi, C. trachomatis* (LGV strains), *Klebsiella (Calymmatobacterium) granulomatis*
Complications of pregnancy/puerperium	Several agents implicated
Intestinal infections	
Proctitis	*C. trachomatis, N. gonorrhoeae,* HSV, *T. pallidum*
Proctocolitis or enterocolitis	*Campylobacter* spp., *Shigella* spp., *Entamoeba histolytica,* other enteric pathogens
Enteritis	*Giardia lamblia*
Acute arthritis with urogenital infection or viremia	*N. gonorrhoeae* (e.g., DGI), C. *trachomatis* (e.g., reactive arthritis), HBV
Genital and anal warts	HPV (30 genital types)
Mononucleosis syndrome	CMV, HIV, EBV
Hepatitis	Hepatitis viruses, *T. pallidum*, CMV, EBV

(*continued*)

TABLE 30-2

MAJOR STD SYNDROMES AND SEXUALLY TRANSMITTED MICROBIAL ETIOLOGIES (*CONTINUED*)

SYNDROME	ST MICROBIAL ETIOLOGIES
Neoplasias	
Squamous cell dysplasias and cancers of the cervix, anus, vulva, vagina, or penis	HPV (especially types 16, 18, 31, 45)
Kaposi's sarcoma, body-cavity lymphomas	HHV-8
T cell leukemia	HTLV-I
Hepatocellular carcinoma	HBV
Tropical spastic paraparesis	HTLV-I
Scabies	*Sarcoptes scabiei*
Pubic lice	*Pthirus pubis*

Abbreviations: CMV, cytomegalovirus; DGI, disseminated gonococcal infection; EBV, Epstein-Barr virus; HBV, hepatitis B virus; HHV-8, human herpesvirus type 8; HPV, human papillomavirus; HSV, herpes simplex virus; HTLV, human T cell lymphotropic virus; LGV, lymphogranuloma venereum.

reflect an STD; decisions on screening or prophylactic/preventive treatment; risk reduction counseling and intervention (e.g., hepatitis B vaccination); and treatment of partners of patients with known infections. Consideration of routine demographic data (e.g., gender, age, area of residence) is a simple first step in STD/HIV risk assessment. For example, national guidelines strongly recommend routine screening of sexually active females ≤25 years of age for *C. trachomatis* infection. **Table 30-3** provides a set of 10 STD/HIV risk-assessment questions that clinicians can pose verbally or that health care systems can adapt (with yes/no responses) into a routine self-administered questionnaire for use in clinics. The initial framing statement gives permission to discuss topics that may be perceived as sensitive or socially unacceptable by providers and patients alike.

Risk assessment is followed by clinical assessment (elicitation of information on specific current symptoms and signs of STDs). Confirmatory diagnostic tests (for persons with symptoms or signs) or screening tests (for those without symptoms or signs) may involve microscopic examination, culture, antigen detection tests, nucleic acid amplification tests (NAATs), or serology. Initial syndrome-based treatment should cover the most likely causes. For certain syndromes, results of rapid tests can narrow the spectrum of this initial therapy (e.g., saline microscopy of vaginal fluid for women with vaginal discharge, Gram's stain of urethral discharge for men with urethral discharge, rapid plasma reagin test for genital ulcer). After the institution of treatment, STD management proceeds to the "4 Cs" of prevention and control: *c*ontact tracing (see "Prevention and Control of STIs," later in chapter), ensuring *c*ompliance with therapy, and *c*ounseling on risk reduction, including *c*ondom promotion and provision.

Consistent with current guidelines, all adults should be screened for infection with HIV-1 at least once and more frequently if they are at risk for acquisition of this infection.

TABLE 30-3

TEN-QUESTION STD/HIV RISK ASSESSMENT

Framing Statement:
In order to provide the best care for you today and to understand your risk for certain infections, it is necessary for us to talk about your sexual behavior.

Screening Questions:
(1) Do you have any reason to think you might have a sexually transmitted infection? If so, what reason?
(2) For all adolescents <18 years old: Have you begun having any kind of sex yet?

STD History:
(3) Have you ever had any sexually transmitted infections or any genital infections? If so, which ones?

Sexual Preference:
(4) Have you had sex with men, women, or both?

Injection Drug Use:
(5) Have you ever injected yourself ("shot up") with drugs? (If yes, have you ever shared needles or injection equipment?)
(6) Have you ever had sex with a gay or bisexual man or with anyone who had ever injected drugs?

Characteristics of Partner(s):
(7) Has your sex partner(s) had any sexually transmitted infections? If so, which ones?
(8) Has your sex partner had other sex partners during the time you've been together?

STD Symptoms Checklist:
(9) Have you recently developed any of these symptoms?

For Men	For Women
(a) Discharge of pus (drip) from the penis	(a) Abnormal vaginal discharge (increased amount, abnormal odor, abnormal yellow color)
(b) Genital sores (ulcers) or rash	(b) Genital sores (ulcers), rash, or itching

Sexual Practices, Past 2 Months (for patients answering yes to any of the above questions, to guide examination and testing):
(10) Now I'd like to ask what parts of your body may have been sexually exposed to an STD (e.g., your penis, mouth, vagina, anus).

Query about Interest in STD Screening Tests (for patients answering no to all of the above questions):
(11) Would you like to be tested for HIV or any other STDs today? (If yes, clinician can explore which STD and why.)

Source: Adapted from JR Curtis, KK Holmes, in KK Holmes et al (eds): *Sexually Transmitted Diseases*, 4th ed. New York, McGraw-Hill, 2008.

URETHRITIS IN MEN

Urethritis in men produces urethral discharge, dysuria, or both, usually without frequency of urination. Causes include *Neisseria gonorrhoeae*, *C. trachomatis*, *Mycoplasma genitalium*, *Ureaplasma urealyticum*, *Trichomonas vaginalis*, HSV, and adenovirus.

Until recently, *C. trachomatis* caused ~30–40% of cases of nongonococcal urethritis (NGU), particularly in heterosexual men; however, the proportion of cases due to this organism has probably declined in some populations served by effective chlamydial-control programs, and older men with urethritis appear less likely to have chlamydial infection. HSV and *T. vaginalis* each cause a small proportion of NGU cases in the United States. Recently, multiple studies have consistently implicated *M. genitalium* as a probable cause of many *Chlamydia*-negative cases. Fewer studies than in the past have implicated *Ureaplasma*; the ureaplasmas have been differentiated into *U. urealyticum* and *U. parvum*, and a few studies suggest that *U. urealyticum*—but not *U. parvum*—is associated with NGU. Coliform bacteria can cause urethritis in men who practice insertive anal intercourse. The initial diagnosis of urethritis in men currently includes specific tests only for *N. gonorrhoeae* and *C. trachomatis*; it does not yet include testing for *Mycoplasma* or *Ureaplasma* species. The following summarizes the approach to the patient with suspected urethritis:

1. *Establish the presence of urethritis.* If proximal-to-distal "milking" of the urethra does not express a purulent or mucopurulent discharge, even after the patient has not voided for several hours (or preferably overnight), a Gram's-stained smear of overt discharge or of an anterior urethral specimen obtained by passage of a small urethrogenital swab 2–3 cm into the urethra usually reveals ≥5 neutrophils per 1000× field in areas containing cells; in gonococcal infection, such a smear usually reveals gram-negative intracellular diplococci as well. Alternatively, the centrifuged sediment of the first 20–30 mL of voided urine—ideally collected as the first morning specimen—can be examined for inflammatory cells, either by microscopy showing ≥10 leukocytes per high-power field or by the leukocyte esterase test. Patients with symptoms who lack objective evidence of urethritis may have functional rather than organic problems and generally do not benefit from repeated courses of antibiotics.
2. *Evaluate for complications or alternative diagnoses.* A brief history and examination will exclude epididymitis and systemic complications, such as disseminated gonococcal infection (DGI) and reactive arthritis. Although digital examination of the prostate gland seldom contributes to the evaluation of sexually active young men with urethritis, men with dysuria who lack evidence of urethritis as well as sexually inactive men with urethritis should undergo prostate palpation, urinalysis, and urine culture to exclude bacterial prostatitis and cystitis.
3. *Evaluate for gonococcal and chlamydial infection.* An absence of typical gram-negative diplococci on Gram's-stained smear of urethral exudate containing inflammatory cells warrants a preliminary diagnosis of NGU, as this test is 98% sensitive for the diagnosis of gonococcal urethral infection. However, an increasing proportion of men with symptoms and/or signs of urethritis are simultaneously assessed for infection with *N. gonorrhoeae* and *C. trachomatis* by "multiplex" NAATs of first-voided urine. The urine specimen tested should comprise the first 10–15 mL of the stream, and patients should not have voided for the prior 2 h, if possible. Culture or NAAT for *N. gonorrhoeae* may be positive when Gram's staining is negative; certain strains of *N. gonorrhoeae* can result in negative urethral Gram's stains in up to 30% of cases of urethritis. Results of tests for gonococcal and chlamydial infection predict the patient's prognosis (with greater risk for recurrent NGU if neither chlamydiae nor gonococci are found than if either is detected) and can guide both the counseling given to the patient and the management of the patient's sexual partner(s).
4. *Treat urethritis promptly while test results are pending.*

TREATMENT Urethritis in Men

Table 30-4 summarizes the steps in management of sexually active men with urethral discharge and/or dysuria.

In practice, if Gram's stain does not reveal gonococci, urethritis is treated with a regimen effective for NGU, such as azithromycin or doxycycline. Both are effective, although azithromycin may give better results in *M. genitalium* infection. If gonococci are demonstrated by Gram's stain or if no diagnostic tests are performed to exclude gonorrhea definitively, treatment should include a single-dose regimen for gonorrhea (Chap. 49) plus azithromycin or doxycycline treatment for *C. trachomatis*, which frequently causes urethral co-infection in men with gonococcal urethritis. Sexual partners should ideally be tested for gonorrhea and chlamydial infection; regardless of whether they are tested for these infections, however, they should receive the same regimen given to the male index case. Patients with confirmed persistence or recurrence of urethritis after treatment should be re-treated with the initial regimen if they did not comply with the original treatment or were reexposed to an untreated partner. Otherwise, an intraurethral swab specimen and a first-voided urine sample should be tested for *T. vaginalis* (currently best done by culture, although NAATs appear to be more sensitive and are likely to become commercially available in the future). If compliance with initial treatment is confirmed and reexposure to an untreated sex partner is deemed unlikely, the recommended treatment is with metronidazole or tinidazole (2 g by mouth in a single dose) plus azithromycin (1 g by mouth in a single dose); the azithromycin component is especially important if this drug has not been given during initial therapy.

TABLE 30-4

MANAGEMENT OF URETHRAL DISCHARGE IN MEN

USUAL CAUSES	USUAL INITIAL EVALUATION
Chlamydia trachomatis *Neisseria gonorrhoeae* *Mycoplasma genitalium* *Ureaplasma urealyticum* *Trichomonas vaginalis* Herpes simplex virus	Demonstration of urethral discharge or pyuria Exclusion of local or systemic complications Urethral Gram's stain to confirm urethritis, detect gram-negative diplococci Test for *N. gonorrhoeae, C. trachomatis*
Initial Treatment for Patient and Partners	
Treat gonorrhea (unless excluded): Ceftriaxone, 250 mg IM; *or* Cefpodoxime, 400 mg PO; *or* Cefixime, 400 mg PO[a]	plus **Treat chlamydial infection:** Azithromycin, 1 g PO; *or* Doxycycline, 100 mg bid PO for 7 days
Management of Recurrence	
Confirm objective evidence of urethritis. If patient was reexposed to untreated or new partner, repeat treatment of patient and partner. If patient was not reexposed, consider infection with *T. vaginalis*[b] or doxycycline-resistant *M. genitalium* or *Ureaplasma*, and consider treatment with metronidazole, azithromycin, or both.	

[a]Updates on the emergence of antimicrobial resistance in *N. gonorrhoeae* can be obtained from the Centers for Disease Control and Prevention at *http://www.cdc.gov/std*.

[b]In men, the diagnosis of *T. vaginalis* infection requires culture (or nucleic acid amplification test, where available) of early-morning first-voided urine sediment or of a urethral swab specimen obtained before voiding.

EPIDIDYMITIS

Acute epididymitis, almost always unilateral, produces pain, swelling, and tenderness of the epididymis, with or without symptoms or signs of urethritis. This condition must be differentiated from testicular torsion, tumor, and trauma. Torsion, a surgical emergency, usually occurs in the second or third decade of life and produces a sudden onset of pain, elevation of the testicle within the scrotal sac, rotation of the epididymis from a posterior to an anterior position, and absence of blood flow on Doppler examination or ^{99m}Tc scan. Persistence of symptoms after a course of therapy for epididymitis suggests the possibility of testicular tumor or of a chronic granulomatous disease, such as tuberculosis. In sexually active men under age 35, acute epididymitis is caused most frequently by *C. trachomatis* and less commonly by *N. gonorrhoeae* and is usually associated with overt or subclinical urethritis. Acute epididymitis occurring in older men or following urinary tract instrumentation is usually caused by urinary pathogens. Similarly, epididymitis in men who have practiced insertive rectal intercourse is often caused by Enterobacteriaceae. These men usually have no urethritis but do have bacteriuria.

TREATMENT **Epididymitis**

Ceftriaxone (250 mg as a single dose IM) followed by doxycycline (100 mg by mouth twice daily for 10 days) constitutes effective treatment for epididymitis caused by *N. gonorrhoeae* or *C. trachomatis*. Fluoroquinolones are no longer recommended for treatment of gonorrhea in the United States because of the emergence of resistant strains of *N. gonorrhoeae,* especially (but not only) among MSM (Fig. 30-1). Oral levofloxacin (500 mg once daily for 10 days) is also effective for syndrome-based

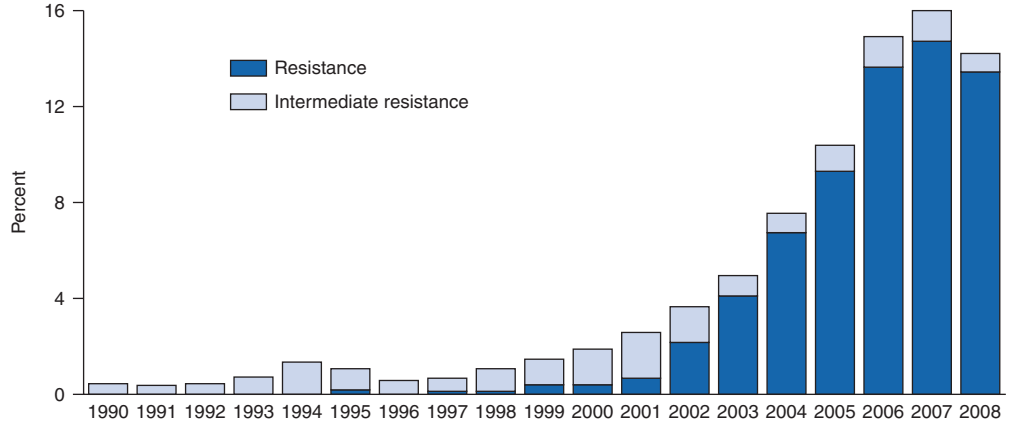


FIGURE 30-1

Percentage of *N. gonorrhoeae* isolates with intermediate resistance or resistance to ciprofloxacin, by year: Gonococcal Isolate Surveillance Project, United States, 1990–2008. Intermediate resistance is defined by ciprofloxacin minimal inhibitory concentrations (MICs) of 0.125–0.5 µg/mL and resistance by MICs of ≥1 µg/mL. (*From the Centers for Disease Control and Prevention: Sexually Transmitted Disease Surveillance, 2008. Atlanta, U.S. Department of Health and Human Services; November 2009.*)

initial treatment of epididymitis when infection with Enterobacteriaceae is suspected; however, this regimen should be combined with effective therapy for possible gonococcal or chlamydial infection unless bacteriuria with Enterobacteriaceae is confirmed.

URETHRITIS AND THE URETHRAL SYNDROME IN WOMEN

C. trachomatis, *N. gonorrhoeae*, and occasionally HSV cause symptomatic urethritis—known as the urethral syndrome in women—that is characterized by "internal" dysuria (usually without urinary urgency or frequency), pyuria, and an absence of *Escherichia coli* and other uropathogens at counts of $\geq 10^2$/mL in urine. In contrast, the dysuria associated with vulvar herpes or vulvovaginal candidiasis (and perhaps with trichomoniasis) is often described as "external," being caused by painful contact of urine with the inflamed or ulcerated labia or introitus. Acute onset, association with urinary urgency or frequency, hematuria, or suprapubic bladder tenderness suggests bacterial cystitis. Among women with symptoms of acute bacterial cystitis, costovertebral pain and tenderness or fever suggests acute pyelonephritis. The management of bacterial urinary tract infection (UTI) is discussed in Chap. 28.

Signs of vulvovaginitis, coupled with symptoms of external dysuria, suggest vulvar infection (e.g., with HSV or *Candida albicans*). Among dysuric women without signs of vulvovaginitis, bacterial UTI must be differentiated from the urethral syndrome by assessment of risk, evaluation of the pattern of symptoms and signs, and specific microbiologic testing. An STI etiology of the urethral syndrome is suggested by young age, more than one current sexual partner, a new partner within the past month, a partner with urethritis, or coexisting mucopurulent cervicitis (see later in chapter). The finding of a single urinary pathogen, such as *E. coli* or *Staphylococcus saprophyticus*, at a concentration of $\geq 10^2$/mL in a properly collected specimen of midstream urine from a dysuric woman with pyuria indicates probable bacterial UTI, whereas pyuria with $<10^2$ conventional uropathogens per milliliter of urine ("sterile" pyuria) suggests acute urethral syndrome due to *C. trachomatis* or *N. gonorrhoeae*. Gonorrhea and chlamydial infection should be sought by specific tests (e.g., NAATs on the first 10 mL of voided urine). Among dysuric women with sterile pyuria caused by infection with *N. gonorrhoeae* or *C. trachomatis*, appropriate treatment alleviates dysuria.

VULVOVAGINAL INFECTIONS

Abnormal vaginal discharge

If directly questioned about vaginal discharge during routine health checkups, many women acknowledge having nonspecific symptoms of vaginal discharge that do not correlate with objective signs of inflammation or with actual infection. However, unsolicited reporting of abnormal vaginal discharge does suggest bacterial vaginosis or trichomoniasis. Specifically, an abnormally increased amount or an abnormal odor of the discharge is associated with one or both of these conditions. Cervical infection with *N. gonorrhoeae* or *C. trachomatis* does not often cause an increased amount or abnormal odor of discharge; however, when these pathogens cause cervicitis, they—like *T. vaginalis*—often result in an increased number of neutrophils in vaginal fluid that thus takes on a yellow color. Vulvar conditions such as genital herpes or vulvovaginal candidiasis can cause vulvar pruritus, burning, irritation, or lesions as well as external dysuria (as urine passes over the inflamed vulva or areas of epithelial disruption) or vulvar dyspareunia.

Certain vulvovaginal infections may have serious sequelae. Trichomoniasis, bacterial vaginosis, and vulvovaginal candidiasis have all been associated with increased risk of acquisition of HIV infection. Vaginal trichomoniasis and bacterial vaginosis early in pregnancy independently predict premature onset of labor. Bacterial vaginosis can also lead to anaerobic bacterial infection of the endometrium and salpinges. Vaginitis may be an early and prominent feature of toxic shock syndrome, and recurrent or chronic vulvovaginal candidiasis develops with increased frequency among women with systemic illnesses, such as diabetes mellitus or HIV-related immunosuppression (although only a very small proportion of women with recurrent vulvovaginal candidiasis in industrialized countries actually have a serious predisposing illness).

Thus vulvovaginal symptoms or signs warrant careful evaluation, including pelvic examination, simple rapid diagnostic tests, and appropriate therapy specific for the anatomic site and type of infection. Unfortunately, a survey in the United States indicated that clinicians seldom perform the tests required to establish the cause of such symptoms. Further, comparison of telephone and office management of vulvovaginal symptoms has documented the inaccuracy of the former, and comparison of evaluations by nurse-midwives with those by physician-practitioners showed that the practitioners' clinical evaluations correlated poorly both with the nurses' evaluations and with diagnostic tests. The diagnosis and treatment of the three most common types of vaginal infection are summarized in **Table 30-5**.

Inspection of the vulva and perineum may reveal tender genital ulcerations or fissures (typically due to HSV infection or vulvovaginal candidiasis) or discharge visible at the introitus before insertion of a speculum (suggestive of bacterial vaginosis or trichomoniasis). Speculum examination permits the clinician to discern whether the discharge in fact looks abnormal and whether any abnormal discharge in the vagina emanates from the cervical os (mucoid and, if abnormal, yellow) or from the vagina (not mucoid, since the vaginal epithelium does not produce mucus). Symptoms or signs of abnormal vaginal discharge should prompt testing of vaginal fluid for pH, for a fishy odor when mixed with 10% KOH, and for certain microscopic features when mixed with saline (motile trichomonads and/or "clue cells") and with 10% KOH (pseudohyphae or hyphae indicative

TABLE 30-5

DIAGNOSTIC FEATURES AND MANAGEMENT OF VAGINAL INFECTION

FEATURE	NORMAL VAGINAL EXAMINATION	VULVOVAGINAL CANDIDIASIS	TRICHOMONAL VAGINITIS	BACTERIAL VAGINOSIS
Etiology	Uninfected; lactobacilli predominant	*Candida albicans*	*Trichomonas vaginalis*	Associated with *Gardnerella vaginalis*, various anaerobic and/or noncultured bacteria, and mycoplasmas
Typical symptoms	None	Vulvar itching and/or irritation	Profuse purulent discharge; vulvar itching	Malodorous, slightly increased discharge
Discharge				
Amount	Variable; usually scant	Scant	Often profuse	Moderate
Color[a]	Clear or translucent	White	White or yellow	White or gray
Consistency	Nonhomogeneous, floccular	Clumped; adherent plaques	Homogeneous	Homogeneous, low viscosity; uniformly coats vaginal walls
Inflammation of vulvar or vaginal epithelium	None	Erythema of vaginal epithelium, introitus; vulvar dermatitis, fissures common	Erythema of vaginal and vulvar epithelium; colpitis macularis	None
pH of vaginal fluid[b]	Usually ≤4.5	Usually ≤4.5	Usually ≥5	Usually >4.5
Amine ("fishy") odor with 10% KOH	None	None	May be present	Present
Microscopy[c]	Normal epithelial cells; lactobacilli predominant	Leukocytes, epithelial cells; mycelia or pseudomycelia in up to 80% of *C. albicans* culture-positive persons with typical symptoms	Leukocytes; motile trichomonads seen in 80–90% of symptomatic patients, less often in the absence of symptoms	Clue cells; few leukocytes; no lactobacilli or only a few outnumbered by profuse mixed microbiota, nearly always including *G. vaginalis* plus anaerobic species on Gram's stain (Nugent's score ≥7)
Other laboratory findings		Isolation of *Candida* spp.	Isolation of T. *vaginalis* or positive NAAT[d]	
Usual treatment	None	Azole cream, tablet, or suppository—e.g., miconazole (100-mg vaginal suppository) or clotrimazole (100-mg vaginal tablet) once daily for 7 days Fluconazole, 150 mg orally (single dose)	Metronidazole or tinidazole, 2 g orally (single dose) Metronidazole, 500 mg PO bid for 7 days	Metronidazole, 500 mg PO bid for 7 days Metronidazole gel, 0.75%, one applicator (5 g) intravaginally once daily for 5 days Clindamycin, 2% cream, one full applicator vaginally each night for 7 days
Usual management of sexual partner	None	None; topical treatment if candidal dermatitis of penis is detected	Examination for STD; treatment with metronidazole, 2 g PO (single dose)	None

[a]Color of discharge is best determined by examination against the white background of a swab.
[b]A pH determination is not useful if blood is present.
[c]To detect fungal elements, vaginal fluid is digested with 10% KOH prior to microscopic examination; to examine for other features, fluid is mixed (1:1) with physiologic saline. Gram's stain is also excellent for detecting yeasts (less predictive of vulvovaginitis) and pseudomycelia or mycelin (strongly predictive of vulvovaginitis) and for distinguishing normal flora from the mixed flora seen in bacterial vaginosis, but it is less sensitive than the saline preparation for detection of *T. vaginalis.*
[d]NAAT, nucleic acid amplification test (where available).
Source: *The Practitioner's Handbook for the Management of Sexually Transmitted Diseases* accessed from *http://depts.washington.edu/nnptc/online_training/std_handbook/pdfs/ch6_vaginitis.pdf.*

of vulvovaginal candidiasis). Additional objective laboratory tests useful for establishing the cause of abnormal vaginal discharge include rapid point-of-care tests for bacterial vaginosis, as described in the Treatment box, and a DNA probe test (the Affirm test) to detect *T. vaginalis* and *C. albicans* as well as the increased concentrations of *Gardnerella vaginalis* associated with bacterial vaginosis. Gram's staining of vaginal fluid can be used to score alterations in the vaginal microbiota but is employed primarily for research purposes and requires some familiarity with the morphotypes and scale involved.

TREATMENT **Vaginal Discharge**

Patterns of treatment for vaginal discharge vary widely. In developing countries, where clinics or pharmacies often dispense treatment based on symptoms alone without examination or testing, oral treatment with metronidazole—particularly with a 7-day regimen—provides reasonable coverage against both trichomoniasis and bacterial vaginosis, the usual causes of symptoms of vaginal discharge; metronidazole treatment of sex partners prevents reinfection of women with trichomoniasis, even though it does not help prevent the recurrence of bacterial vaginosis. Guidelines for syndromic management promulgated by the World Health Organization suggest consideration of treatment for cervical infection and for trichomoniasis, bacterial vaginosis, and vulvovaginal candidiasis in women with symptoms of abnormal vaginal discharge. However, it is important to note that the majority of chlamydial and gonococcal cervical infections produce no symptoms.

In industrialized countries, clinicians treating symptoms and signs of abnormal vaginal discharge should, at a minimum, differentiate between bacterial vaginosis and trichomoniasis, because optimal management of patients and partners differs for these two conditions (as discussed briefly next).

Vaginal trichomoniasis

(See also Chap. 125) Symptomatic trichomoniasis characteristically produces a profuse, yellow, purulent, homogeneous vaginal discharge and vulvar irritation, sometimes with visible inflammation of the vaginal and vulvar epithelium and petechial lesions on the cervix (the so-called strawberry cervix, usually evident only by colposcopy). The pH of vaginal fluid—normally <4.7—usually rises to ≥5. In women with typical symptoms and signs of trichomoniasis, microscopic examination of vaginal discharge mixed with saline reveals motile trichomonads in most culture-positive cases. However, saline microscopy probably detects only one-half of all cases, and, especially in the absence of symptoms or signs, culture is usually required for detection of the organism. NAAT for *T. vaginalis* is as sensitive as or more sensitive than culture, and NAAT of urine has disclosed surprisingly high prevalences of this pathogen among men at several STD clinics in the United States. Treatment of asymptomatic as well as symptomatic cases reduces rates of transmission and prevents later development of symptoms.

TREATMENT **Vaginal Trichomoniasis**

Only nitroimidazoles (e.g., metronidazole and tinidazole) consistently cure trichomoniasis. A single 2-g oral dose of metronidazole is effective and much less expensive than the alternatives. Tinidazole has a longer half-life than metronidazole, causes fewer gastrointestinal symptoms, and is especially useful in treating trichomoniasis that fails to respond to metronidazole. Treatment of sexual partners—facilitated by dispensing metronidazole to the female patient to give to her partner(s), with a warning about avoiding the concurrent use of alcohol—significantly reduces both the risk of reinfection and the reservoir of infection; treating the partner is the standard of care. Intravaginal treatment with 0.75% metronidazole gel is not reliable for vaginal trichomoniasis. Systemic use of metronidazole is recommended throughout pregnancy. In a large randomized trial, metronidazole treatment of trichomoniasis during pregnancy did not reduce—and in fact actually increased—the frequency of perinatal morbidity; thus routine screening of asymptomatic pregnant women for trichomoniasis is not recommended.

Bacterial vaginosis

Bacterial vaginosis (formerly termed *nonspecific vaginitis*, *Haemophilus vaginitis*, *anaerobic vaginitis*, or *Gardnerella-associated vaginal discharge*) is a syndrome of uncertain etiology that is characterized by symptoms of vaginal malodor and a slightly to moderately increased white discharge, which appears homogeneous, is low in viscosity, and evenly coats the vaginal mucosa. Bacterial vaginosis has been associated with increased risk of acquiring several other genital infections, including those caused by HIV, *C. trachomatis*, and *N. gonorrhoeae*. Other risk factors include recent unprotected vaginal intercourse, having a female sex partner, and vaginal douching. Although bacteria associated with bacterial vaginosis have been detected under the foreskin of uncircumcised men, metronidazole treatment of male partners has not reduced the rate of recurrence among affected women.

Among women with bacterial vaginosis, culture of vaginal fluid has shown markedly increased prevalences and concentrations of *G. vaginalis*, *Mycoplasma hominis*, and several anaerobic bacteria [e.g., *Mobiluncus*, *Prevotella* (formerly *Bacteroides*), and some *Peptostreptococcus* species] as well as an absence of hydrogen peroxide–producing *Lactobacillus* spp., that constitute most of the normal vaginal microbiota and help protect against certain cervical and vaginal infections. Broad-range polymerase chain reaction (PCR) amplification of 16S rDNA in vaginal fluid, with subsequent identification of specific bacterial species by various methods, has

documented an even greater and unexpected bacterial diversity, including several unique species not previously cultivated [e.g., three species in the order Clostridiales that appear to be specific for bacterial vaginosis and are associated with metronidazole treatment failure **(Fig. 30-2)**]. Also detected are DNA sequences related to *Atopobium vaginae*, an organism that is strongly associated with bacterial vaginosis, is resistant to metronidazole, and is also associated with recurrent bacterial vaginosis after metronidazole treatment. Other genera newly implicated in bacterial vaginosis include *Megasphaera*, *Leptotrichia*, *Eggerthella*, and *Dialister*.

Bacterial vaginosis is conventionally diagnosed clinically with the Amsel criteria that include any three of the following four clinical abnormalities: (1) objective signs of increased white homogeneous vaginal discharge; (2) a vaginal discharge pH of >4.5; (3) liberation of a distinct fishy odor (attributable to volatile amines such as trimethylamine) immediately after vaginal secretions are mixed with a 10% solution of KOH; and (4) microscopic demonstration of "clue cells" (vaginal epithelial cells coated with coccobacillary organisms, which have a granular appearance and indistinct borders; **Fig. 30-3**) on a wet mount prepared by mixing vaginal secretions with normal saline in a ratio of ~1:1.

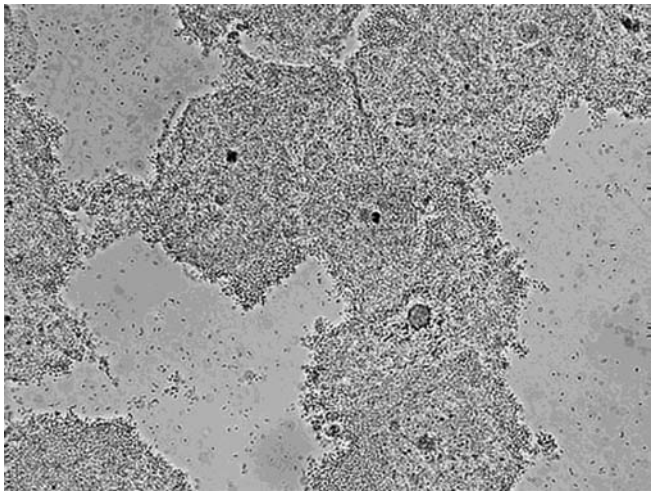


FIGURE 30-3
Wet mount of vaginal fluid showing typical clue cells from a woman with bacterial vaginosis. Note the obscured epithelial cell margins and the granular appearance attributable to many adherent bacteria (×400). (*Photograph provided by Lorna K. Rabe, reprinted with permission from S Hillier et al, in KK Holmes et al (eds). Sexually Transmitted Diseases, 4th ed. New York, McGraw-Hill, 2008.*)

TREATMENT **Bacterial Vaginosis**

The standard dosage of oral metronidazole for the treatment of bacterial vaginosis is 500 mg twice daily for 7 days. The single 2-g oral dose of metronidazole recommended for trichomoniasis produces significantly lower short-term cure rates and should not be used. Intravaginal treatment with 2% clindamycin cream [one full applicator (5 g containing 100 mg of clindamycin phosphate) each night for 7 nights] or with 0.75% metronidazole gel [one full applicator (5 g containing 37.5 mg of metronidazole) twice daily for 5 days] is also approved for use in the United States and does not elicit systemic adverse reactions; the response to both of these treatments is similar to the response to oral metronidazole. Other alternatives include oral clindamycin (300 mg twice daily for 7 days), clindamycin ovules (100 g intravaginally once at bedtime for 3 days), and oral tinidazole (1 g daily for 5 days or 2 g daily for 3 days). Unfortunately, recurrence over the long term (i.e., several months later) is distressingly common after either oral or intravaginal treatment. A randomized trial comparing intravaginal gel containing 37.5 mg of metronidazole with a suppository containing 500 mg of metronidazole plus nystatin (the latter not marketed in the United States) showed significantly higher rates of recurrence with the 37.5-mg regimen; this result suggests that higher metronidazole dosages may be important in topical intravaginal therapy. Recurrences can be significantly lessened with the twice-weekly use of suppressive intravaginal metronidazole gel. As stated earlier, treatment of male partners with metronidazole does not prevent recurrence of bacterial vaginosis.

Efforts to replenish numbers of vaginal lactobacilli that produce hydrogen peroxide and probably sustain vaginal health have been largely unsuccessful. While one randomized trial of orally ingested lactobacilli found reduced rates of recurrent bacterial vaginosis,

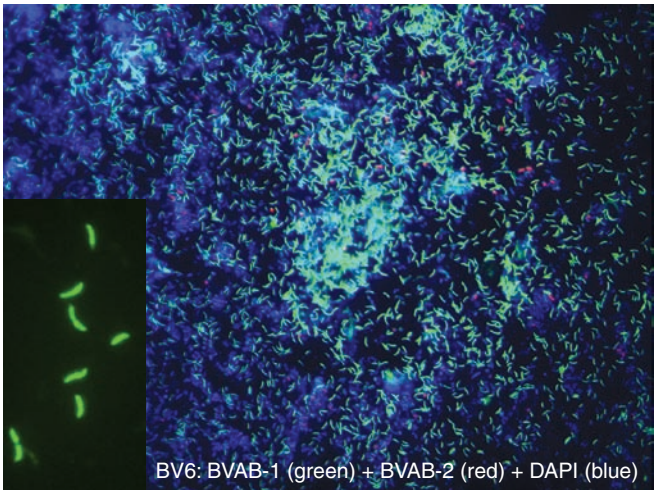


FIGURE 30-2
Broad-range PCR amplification of 16S rDNA in vaginal fluid from a woman with bacterial vaginosis shows a field of bacteria hybridizing with probes for bacterial vaginosis–associated bacterium 1 (BVAB-1, visible as a thin, curved green rod) and for BVAB-2 (red). The inset shows that BVAB-1 has a morphology similar to that of *Mobiluncus* (curved rod). (*Reprinted with permission from DN Fredricks et al*: *N Engl J Med 353:1899, 2005*.)

this result has not yet been either confirmed or refuted, and a randomized multicenter trial in the United States found no benefit of repeated intravaginal inoculation of a vaginal peroxide-producing *Lactobacillus* species following treatment of bacterial vaginosis with metronidazole. A meta-analysis of 18 studies concluded that bacterial vaginosis during pregnancy substantially increased the risk of preterm delivery and of spontaneous abortion. However, most studies of topical intravaginal treatment of bacterial vaginosis with clindamycin during pregnancy have not reduced adverse pregnancy outcomes. Numerous trials of oral metronidazole treatment during pregnancy have given inconsistent results, and a 2007 Cochrane review concluded that antenatal treatment of women with bacterial vaginosis—even those with previous preterm delivery—did not reduce the risk of preterm delivery. The U.S. Preventive Services Task Force thus recommends against routine screening of pregnant women for bacterial vaginosis.

Vulvovaginal pruritus, burning, or irritation

Vulvovaginal candidiasis produces vulvar pruritus, burning, or irritation, generally without symptoms of increased vaginal discharge or malodor. Genital herpes can produce similar symptoms, with lesions sometimes difficult to distinguish from the fissures and inflammation caused by candidiasis. Signs of vulvovaginal candidiasis include vulvar erythema, edema, fissures, and tenderness. With candidiasis, a white scanty vaginal discharge sometimes takes the form of white thrush-like plaques or cottage cheese–like curds adhering loosely to the vaginal mucosa. *C. albicans* accounts for nearly all cases of symptomatic vulvovaginal candidiasis, which probably arise from endogenous strains of *C. albicans* that have colonized the vagina or the intestinal tract. Complicated vulvovaginal candidiasis includes cases that recur four or more times per year; are unusually severe; are caused by non-*albicans Candida* spp.; or occur in women with uncontrolled diabetes, debilitation, immunosuppression, or pregnancy.

In addition to compatible clinical symptoms, the diagnosis of vulvovaginal candidiasis usually involves the demonstration of pseudohyphae or hyphae by microscopic examination of vaginal fluid mixed with saline or 10% KOH or subjected to Gram's staining. Microscopic examination is less sensitive than culture but correlates better with symptoms. Culture is typically reserved for cases that do not respond to standard first-line antimycotic agents and is undertaken to rule out imidazole or azole resistance (often associated with *Candida glabrata*) or before the initiation of suppressive antifungal therapy for recurrent disease.

TREATMENT **Vulvovaginal Pruritus, Burning, or Irritation**

Symptoms and signs of vulvovaginal candidiasis warrant treatment, usually intravaginal administration of any of several imidazole antibiotics (e.g., miconazole or clotrimazole) for 3–7 days or of a single dose of oral fluconazole (Table 30-5). Over-the-counter marketing of such preparations has reduced the cost of care and made treatment more convenient for many women with recurrent yeast vulvovaginitis. However, most women who purchase these preparations do not have vulvovaginal candidiasis, while many do have other vaginal infections that require different treatment. Therefore, only women with classic symptoms of vulvar pruritus and a history of previous episodes of yeast vulvovaginitis documented by an experienced clinician should self-treat. Short-course topical intravaginal azole drugs are effective for the treatment of uncomplicated vulvovaginal candidiasis (e.g., clotrimazole, two 100-mg vaginal tablets daily for 3 days; or miconazole, a 1200-mg vaginal suppository as a single dose). Single-dose oral treatment with fluconazole (150 mg) is also effective and is preferred by many patients. Management of complicated cases (see earlier in chapter) and those that do not respond to the usual intravaginal or single-dose oral therapy often involves prolonged or periodic oral therapy; this situation is discussed extensively in the 2010 CDC STD treatment guidelines *(http://www.cdc.gov/std/treatment)*. Treatment of sexual partners is not routinely indicated.

Other causes of vaginal discharge or vaginitis

In the ulcerative vaginitis associated with staphylococcal toxic shock syndrome, *Staphylococcus aureus* should be promptly identified in vaginal fluid by Gram's stain and by culture. In desquamative inflammatory vaginitis, smears of vaginal fluid reveal neutrophils, massive vaginal epithelial-cell exfoliation with increased numbers of parabasal cells, and gram-positive cocci; this syndrome may respond to treatment with 2% clindamycin cream, often given in combination with topical steroid preparations for several weeks. Additional causes of vaginitis and vulvovaginal symptoms include retained foreign bodies (e.g., tampons), cervical caps, vaginal spermicides, vaginal antiseptic preparations or douches, vaginal epithelial atrophy (in postmenopausal women or during prolonged breast-feeding in the postpartum period), allergic reactions to latex condoms, vaginal aphthae associated with HIV infection or Behçet's syndrome, and vestibulitis (a poorly understood syndrome).

MUCOPURULENT CERVICITIS

Mucopurulent cervicitis (MPC) refers to inflammation of the columnar epithelium and subepithelium of the endocervix and of any contiguous columnar epithelium that lies exposed in an ectopic position on the ectocervix. MPC in women represents the "silent partner" of urethritis in men, being equally common and often caused by the same agents (*N. gonorrhoeae*, *C. trachomatis*, or—as shown by case-control studies—*M. genitalium*); however, MPC is more difficult than urethritis to recognize. As the most common manifestation of these serious bacterial infections

in women, MPC can be a harbinger or sign of upper genital tract infection, also known as *pelvic inflammatory disease* (PID; see later in chapter). In pregnant women, MPC can lead to obstetric complications. In a prospective study in Seattle of 167 consecutive patients with MPC [defined on the basis of yellow endocervical mucopus or ≥30 polymorphonuclear leukocytes (PMNs)/1000× microscopic field] who were seen at STD clinics during the 1980s, slightly more than one-third of cervicovaginal specimens tested for *C. trachomatis*, *N. gonorrhoeae*, *M. genitalium*, HSV, and *T. vaginalis* revealed no identifiable etiology **(Fig. 30-4)**. More recently, a study in Baltimore using NAATs for these pathogens still failed to identify a microbiologic etiology in nearly one-half of the 133 women with MPC.

The diagnosis of MPC rests on the detection of cardinal signs at the cervix, including yellow mucopurulent discharge from the cervical os, endocervical bleeding upon gentle swabbing, and edematous cervical ectopy (see later in chapter); the latter two findings are somewhat more common with MPC due to chlamydial infection, but signs alone do not allow a distinction between the causative pathogens. Unlike the endocervicitis produced by gonococcal or chlamydial infection, cervicitis caused by HSV produces ulcerative lesions on the stratified squamous epithelium of the ectocervix as well as on the columnar epithelium. Yellow cervical mucus on a white swab removed from the endocervix indicates the presence of PMNs. Gram's staining may confirm their presence, although it adds relatively little to the diagnostic value of assessment for cervical signs. The presence of ≥20 PMNs/1000× microscopic field within strands of cervical mucus not contaminated by vaginal squamous epithelial cells or vaginal bacteria indicates endocervicitis. Detection of intracellular gram-negative diplococci in carefully collected endocervical mucus is quite specific but ≤50% sensitive for gonorrhea. Therefore, specific and sensitive tests for *N. gonorrhoeae* as well as for *C. trachomatis* (e.g., NAATs) are always indicated in the evaluation of MPC.

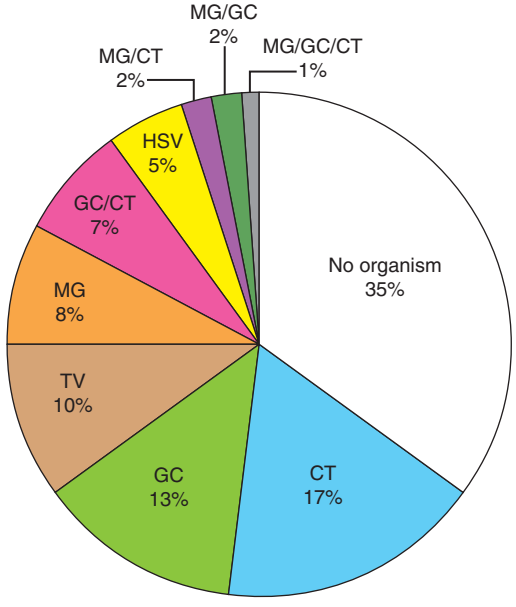


FIGURE 30-4
Organisms detected among female STD clinic patients with mucopurulent cervicitis (n = 167). GC, gonococcus; CT, *Chlamydia trachomatis*; MG, *Mycoplasma genitalium*; TV, *Trichomonas vaginalis*; HSV, herpes simplex virus. (*Courtesy of Dr. Lisa Manhart; with permission.*)

TREATMENT **Mucopurulent Cervicitis**

Although the earlier criteria for MPC are neither highly specific nor highly predictive of gonococcal or chlamydial infection in some settings, the 2010 CDC STD guidelines call for consideration of empirical treatment for MPC, pending test results, in most patients. Presumptive treatment with antibiotics active against *C. trachomatis* should be provided for women at increased risk for this common STI (risk factors: age <25 years, new or multiple sex partners, and unprotected sex), especially if follow-up cannot be ensured. Concurrent therapy for gonorrhea is indicated if the prevalence of this infection is substantial in the relevant patient population (e.g., young adults, a clinic with documented high prevalence). In this situation, therapy should include a single-dose regimen effective for gonorrhea plus treatment for chlamydial infection, as outlined in Table 30-4 for the treatment of urethritis. In settings where gonorrhea is much less common than chlamydial infection, initial therapy for chlamydial infection alone suffices, pending test results for gonorrhea. The etiology and potential benefit of treatment for endocervicitis not associated with gonorrhea or chlamydial infection have not been established. Although the antimicrobial susceptibility of *M. genitalium* is not yet well defined, the organism frequently persists after doxycycline therapy, and it currently seems reasonable to use azithromycin to treat possible *M. genitalium* infection in such cases. The sexual partner(s) of a woman with MPC should be examined and given a regimen similar to that chosen for the woman unless results of tests for gonorrhea or chlamydial infection in either partner warrant different therapy or no therapy.

CERVICAL ECTOPY

Cervical ectopy, often mislabeled "cervical erosion," is easily confused with infectious endocervicitis. Ectopy represents the presence of the one-cell-thick columnar epithelium extending from the endocervix out onto the visible ectocervix. In ectopy, the cervical os may contain clear or slightly cloudy mucus but usually not yellow mucopus. Colposcopy shows intact epithelium. Normally found during adolescence and early adulthood, ectopy gradually recedes through the second and third decades of life, as squamous metaplasia replaces the ectopic columnar epithelium. Oral contraceptive use favors the persistence or reappearance of ectopy, while smoking apparently accelerates squamous metaplasia. Cauterization of ectopy is not warranted. Ectopy may render the cervix

more susceptible to infection with *N. gonorrhoeae*, *C. trachomatis*, or HIV.

PELVIC INFLAMMATORY DISEASE

The term *pelvic inflammatory disease* usually refers to infection that ascends from the cervix or vagina to involve the endometrium and/or fallopian tubes. Infection can extend beyond the reproductive tract to cause pelvic peritonitis, generalized peritonitis, perihepatitis, perisplenitis, or pelvic abscess. Rarely, infection not related to specific sexually transmitted pathogens extends secondarily to the pelvic organs (1) from adjacent foci of inflammation (e.g., appendicitis, regional ileitis, or diverticulitis) or bacterial vaginosis, (2) as a result of hematogenous dissemination (e.g., of tuberculosis or staphylococcal bacteremia), or (3) as a complication of certain tropical diseases (e.g., schistosomiasis). Intrauterine infection can be primary (spontaneously occurring and usually sexually transmitted) or secondary to invasive intrauterine surgical procedures [e.g., dilatation and curettage, termination of pregnancy, insertion of an intrauterine device (IUD), or hysterosalpingography] or to parturition.

Etiology

The agents most often implicated in acute PID include the primary causes of endocervicitis (e.g., *N. gonorrhoeae* and *C. trachomatis*) and organisms that can be regarded as components of an altered vaginal microbiota. In general, PID is most often caused by *N. gonorrhoeae* where there is a high incidence of gonorrhea—e.g., in inner-city populations in the United States. In case-control studies, *M. genitalium* has also been significantly associated with histopathologic diagnoses of endometritis and with salpingitis.

Anaerobic and facultative organisms (especially *Prevotella* species, peptostreptococci, *E. coli*, *Haemophilus influenzae*, and group B streptococci) as well as genital mycoplasmas have been isolated from the peritoneal fluid or fallopian tubes in a varying proportion (typically one-fourth to one-third) of women with PID studied in the United States. The difficulty of determining the exact microbial etiology of an individual case of PID—short of using invasive procedures for specimen collection—has implications for the approach to empirical antimicrobial treatment of this infection.

Epidemiology

In the United States, the estimated annual number of initial visits to physicians' offices for PID by women 15–44 years of age fell from an average of 400,000 during the 1980s to 250,000 in 1999 and then to 104,000 in 2008. Hospitalizations for acute PID in the United States also declined steadily throughout the 1980s and early 1990s but have remained fairly constant at 70,000–100,000 per year since 1995. Important risk factors for acute PID include the presence of endocervical infection or bacterial vaginosis, a history of salpingitis or of recent vaginal douching, and recent insertion of an IUD. Certain other iatrogenic factors, such as dilatation and curettage or cesarean section, can increase the risk of PID, especially among women with endocervical gonococcal or chlamydial infection or bacterial vaginosis. Symptoms of *N. gonorrhoeae*–associated and *C. trachomatis*–associated PID often begin during or soon after the menstrual period; this timing suggests that menstruation is a risk factor for ascending infection from the cervix and vagina. Experimental inoculation of the fallopian tubes of nonhuman primates has shown that repeated exposure to *C. trachomatis* leads to the greatest degree of tissue inflammation and damage; thus, immunopathology probably contributes to the pathogenesis of chlamydial salpingitis. Women using oral contraceptives appear to be at decreased risk of symptomatic PID, and tubal sterilization reduces the risk of salpingitis by preventing intraluminal spread of infection into the tubes.

Clinical manifestations

Endometritis: a clinical pathologic syndrome

A study of women with clinically suspected PID who were undergoing both endometrial biopsy and laparoscopy showed that those with endometritis alone differed from those who also had salpingitis in significantly less often having lower quadrant, adnexal, or cervical motion or abdominal rebound tenderness; fever; or elevated C-reactive protein levels. In addition, women with endometritis alone differed from those with neither endometritis nor salpingitis in more often having gonorrhea, chlamydial infection, and risk factors such as douching or IUD use. Thus, women with endometritis alone were intermediate between those with neither endometritis nor salpingitis and those with salpingitis with respect to risk factors, clinical manifestations, cervical infection prevalence, and elevated C-reactive protein level. Women with endometritis alone are at lower risk of subsequent tubal occlusion and resulting infertility than are those with salpingitis.

Salpingitis

Symptoms of nontuberculous salpingitis classically evolve from a yellow or malodorous vaginal discharge caused by MPC and/or bacterial vaginosis to midline abdominal pain and abnormal vaginal bleeding caused by endometritis and then to bilateral lower abdominal and pelvic pain caused by salpingitis, with nausea, vomiting, and increased abdominal tenderness if peritonitis develops.

The abdominal pain in nontuberculous salpingitis is usually described as dull or aching. In some cases, pain is lacking or atypical, but active inflammatory changes are found in the course of an unrelated evaluation or procedure, such as a laparoscopic evaluation for infertility. Abnormal uterine bleeding precedes or coincides with the onset of pain in ~40% of women with PID, symptoms of urethritis (dysuria) occur in 20%, and symptoms of proctitis (anorectal pain, tenesmus, and rectal discharge or bleeding) are occasionally seen in women with gonococcal or chlamydial infection.

Speculum examination shows evidence of MPC (yellow endocervical discharge, easily induced endocervical bleeding) in the majority of women with gonococcal or chlamydial PID. Cervical motion tenderness is produced by stretching of the adnexal attachments on the side toward which the cervix is pushed. Bimanual examination reveals uterine fundal tenderness due to endometritis and abnormal adnexal tenderness due to salpingitis that is usually, but not necessarily, bilateral. Adnexal swelling is palpable in about one-half of women with acute salpingitis, but evaluation of the adnexae in a patient with marked tenderness is not reliable. The initial temperature is >38°C in only about one-third of patients with acute salpingitis. Laboratory findings include elevation of the erythrocyte sedimentation rate (ESR) in 75% of patients with acute salpingitis and elevation of the peripheral white blood cell count in up to 60%.

Unlike nontuberculous salpingitis, genital tuberculosis often occurs in older women, many of whom are postmenopausal. Presenting symptoms include abnormal vaginal bleeding, pain (including dysmenorrhea), and infertility. About one-quarter of these women have had adnexal masses. Endometrial biopsy shows tuberculous granulomas and provides optimal specimens for culture.

Perihepatitis and periappendicitis

Pleuritic upper abdominal pain and tenderness, usually localized to the right upper quadrant (RUQ), develop in 3–10% of women with acute PID. Symptoms of perihepatitis arise during or after the onset of symptoms of PID and may overshadow lower abdominal symptoms, thereby leading to a mistaken diagnosis of cholecystitis. In perhaps 5% of cases of acute salpingitis, early laparoscopy reveals perihepatic inflammation ranging from edema and erythema of the liver capsule to exudate with fibrinous adhesions between the visceral and parietal peritoneum. When treatment is delayed and laparoscopy is performed late, dense "violin-string" adhesions can be seen over the liver; chronic exertional or positional RUQ pain ensues when traction is placed on the adhesions. Although perihepatitis, also known as the *Fitz-Hugh–Curtis syndrome*, was for many years specifically attributed to gonococcal salpingitis, most cases are now attributed to chlamydial salpingitis. In patients with chlamydial salpingitis, serum titers of microimmunofluorescent antibody to *C. trachomatis* are typically much higher when perihepatitis is present than when it is absent.

Physical findings include RUQ tenderness and usually include adnexal tenderness and cervicitis, even in patients whose symptoms do not suggest salpingitis. Results of liver function tests and RUQ ultrasonography are nearly always normal. The presence of MPC and pelvic tenderness in a young woman with subacute pleuritic RUQ pain and normal ultrasonography of the gallbladder points to a diagnosis of perihepatitis.

Periappendicitis (appendiceal serositis without involvement of the intestinal mucosa) has been found in ~5% of patients undergoing appendectomy for suspected appendicitis and can occur as a complication of gonococcal or chlamydial salpingitis.

Among women with salpingitis, HIV infection is associated with increased severity of salpingitis and with tuboovarian abscess requiring hospitalization and surgical drainage. Nonetheless, among women with HIV infection and salpingitis, the clinical response to conventional antimicrobial therapy (coupled with drainage of tuboovarian abscess, when found) has usually been satisfactory.

Diagnosis

Treatment appropriate for PID must not be withheld from patients who have an equivocal diagnosis; it is better to err on the side of overdiagnosis and overtreatment. On the other hand, it is essential to differentiate between salpingitis and other pelvic pathology, particularly surgical emergencies such as appendicitis and ectopic pregnancy.

Nothing short of laparoscopy definitively identifies salpingitis, but routine laparoscopy to confirm suspected salpingitis is generally impractical. Most patients with acute PID have lower abdominal pain of <3 weeks' duration, pelvic tenderness on bimanual pelvic examination, and evidence of lower genital tract infection (e.g., MPC). Approximately 60% of such patients have salpingitis at laparoscopy, and perhaps 10–20% have endometritis alone. Among the patients with these findings, a rectal temperature >38°C, a palpable adnexal mass, and elevation of the ESR to >15 mm/h also raise the probability of salpingitis, which has been found at laparoscopy in 68% of patients with one of these additional findings, 90% of patients with two, and 96% of patients with three. However, only 17% of all patients with laparoscopy-confirmed salpingitis have had all three additional findings.

In a woman with pelvic pain and tenderness, increased numbers of PMNs (30 per 1000× microscopic field in strands of cervical mucus) or leukocytes outnumbering epithelial cells in vaginal fluid (in the absence of trichomonal vaginitis, which also produces PMNs in vaginal discharge) increase the predictive value of a clinical diagnosis of acute PID, as do onset with menses, history of recent abnormal menstrual bleeding, presence of an IUD, history of salpingitis, and sexual exposure to a male with urethritis. Appendicitis or another disorder of the gut is favored by the early onset of anorexia, nausea, or vomiting; the onset of pain later than day 14 of the menstrual cycle; or unilateral pain limited to the right or left lower quadrant. Whenever the diagnosis of PID is being considered, serum assays for human β-chorionic gonadotropin should be performed; these tests are usually positive with ectopic pregnancy. Ultrasonography and MRI can be useful for the identification of tuboovarian or pelvic abscess. MRI of the tubes can also show increased tubal diameter, intratubal fluid, or tubal wall thickening in cases of salpingitis.

The primary and uncontested value of laparoscopy in women with lower abdominal pain is for the exclusion of other surgical problems. Some of the most common or serious problems that may be confused with salpingitis (e.g., acute appendicitis, ectopic pregnancy, corpus luteum bleeding, ovarian tumor) are unilateral. Unilateral pain

or pelvic mass, although not incompatible with PID, is a strong indication for laparoscopy unless the clinical picture warrants laparotomy instead. Atypical clinical findings such as the absence of lower genital tract infection, a missed menstrual period, a positive pregnancy test, or failure to respond to appropriate therapy, are other common indications for laparoscopy. Endometrial biopsy is relatively sensitive and specific for the diagnosis of endometritis, which correlates well with the presence of salpingitis.

Endocervical swab specimens should be examined by NAATs for *N. gonorrhoeae* and *C. trachomatis*. At a minimum, vaginal fluid should be evaluated for the presence of PMNs, and endocervical secretions ideally should be assessed by Gram's staining for PMNs and gram-negative diplococci that indicate gonococcal infection. The clinical diagnosis of PID made by expert gynecologists is confirmed by laparoscopy or endometrial biopsy in ~90% of women who also have cultures positive for *N. gonorrhoeae* or *C. trachomatis*. Even among women with no symptoms suggestive of acute PID who were attending an STD clinic or a gynecology clinic in Pittsburgh, endometritis was significantly associated with endocervical gonorrhea or chlamydial infection or with bacterial vaginosis, being detected in 26%, 27%, and 15% of women with these conditions, respectively.

TREATMENT Pelvic Inflammatory Disease

The 2010 CDC guidelines recommend initiation of empirical treatment for PID in sexually active young women and other women at risk for PID if they are experiencing pelvic or lower abdominal pain, if no other cause for the pain can be identified, and if pelvic examination reveals one or more of the following criteria for PID: cervical motion tenderness, uterine tenderness, or adnexal tenderness. Women with suspected PID can be treated as either outpatients or inpatients. In the multicenter Pelvic Inflammatory Disease Evaluation and Clinical Health (PEACH) trial, 831 women with mild to moderately severe symptoms and signs of PID were randomized to receive either inpatient treatment with IV cefoxitin and doxycycline or outpatient treatment with a single IM dose of cefoxitin plus oral doxycycline. Short-term clinical and microbiologic outcomes and long-term outcomes were equivalent in the two groups. Nonetheless, hospitalization should be considered when (1) the diagnosis is uncertain and surgical emergencies such as appendicitis and ectopic pregnancy cannot be excluded, (2) the patient is pregnant, (3) pelvic abscess is suspected, (4) severe illness or nausea and vomiting preclude outpatient management, (5) the patient has HIV infection, (6) the patient is assessed as unable to follow or tolerate an outpatient regimen, or (7) the patient has failed to respond to outpatient therapy. Some experts also prefer to hospitalize adolescents with PID for initial therapy, although younger women do as well as older women on outpatient therapy.

Recommended combination regimens for ambulatory or parenteral management of PID are presented in Table 30-6. Women managed as outpatients should receive a combined regimen with broad activity, such as ceftriaxone (to cover possible gonococcal infection) followed by doxycycline (to cover possible chlamydial infection). Metronidazole can be added, if tolerated, to enhance activity against anaerobes; this addition should be strongly considered if bacterial vaginosis is documented. Although few methodologically sound clinical trials (especially with prolonged follow-up) have been conducted, one meta-analysis suggested a benefit of providing good coverage against anaerobes.

Neither doxycycline nor the fluoroquinolones provide reliable coverage for gonococcal infection today. Thus, adequate oral treatment of women with serious intolerance to cephalosporins is a challenge. If penicillins are an option, amoxicillin/clavulanic acid combined with doxycycline has effected short-term clinical response in one clinical trial. If fluoroquinolones are the only option and if the community prevalence and individual risk for gonorrhea are known to be low, oral levofloxacin (500 mg once daily) or ofloxacin (400 mg twice daily) for 14 days, with or without metronidazole, may be considered. In this case, it is imperative to perform a sensitive diagnostic test for gonorrhea (ideally, culture to test for antimicrobial

TABLE 30-6

COMBINATION ANTIMICROBIAL REGIMENS RECOMMENDED FOR OUTPATIENT TREATMENT OR FOR PARENTERAL TREATMENT OF PID

Outpatient Regimens[a]	Parenteral Regimens
Ceftriaxone (250 mg IM once) *plus* Doxycycline (100 mg PO bid for 14 days) *plus*[b] Metronidazole (500 mg PO bid for 14 days)	Initiate parenteral therapy with either of the following regimens; continue parenteral therapy until 48 h after clinical improvement; then change to outpatient therapy, as described in the text. **Regimen A** Cefotetan (2 g IV q12h) *or* Cefoxitin (2 g IV q6h) *plus* Doxycycline (100 mg IV or PO q12h) **Regimen B** Clindamycin (900 mg IV q8h) *plus* Gentamicin (loading dose of 2 mg/kg IV or IM, then maintenance dose of 1.5 mg/kg q8h)

[a]See text for discussion of options in the patient who is intolerant of cephalosporins.

[b]The addition of metronidazole is recommended by some experts, particularly if bacterial vaginosis is present.

Source: Adapted from Centers for Disease Control and Prevention: MMWR Recomm Rep 59 (RR-12):1, 2010.

susceptibility) before initiating therapy. For those women whose PID involves quinolone-resistant gonorrhea, treatment is uncertain but could include parenteral gentamicin or oral azithromycin, although the latter agent has not been studied for this purpose.

For hospitalized patients, the following two parenteral regimens have given nearly identical results in a multicenter randomized trial:

1. Doxycycline (100 mg twice daily, given IV or PO) plus cefotetan (2 g IV every 12 h) or cefoxitin (2 g IV every 6 h): Administration of these drugs should be continued by the IV route for at least 48 h after the patient's condition improves and then followed with oral doxycycline (100 mg twice daily) to complete 14 days of therapy.
2. Clindamycin (900 mg IV every 8 h) plus gentamicin (2 mg/kg IV or IM, followed by 1.5 mg/kg every 8 h) in patients with normal renal function: Once-daily dosing of gentamicin (with combination of the total daily dose into a single daily dose) has not been evaluated in PID but has been efficacious in other serious infections and could be substituted. Treatment with these drugs should be continued for at least 48 h after the patient's condition improves and then followed with oral doxycycline (100 mg twice daily) or clindamycin (450 mg four times daily) to complete 14 days of therapy. In cases with tuboovarian abscess, clindamycin rather than doxycycline for continued therapy provides better coverage for anaerobic infection.

FOLLOW-UP Hospitalized patients should show substantial clinical improvement within 3–5 days. Women treated as outpatients should be clinically reevaluated within 72 h. A follow-up telephone survey of women seen in an emergency department and given a prescription for 10 days of oral doxycycline for PID found that 28% never filled the prescription and 41% stopped taking the medication early (after an average of 4.1 days), often because of persistent symptoms, lack of symptoms, or side effects. Women not responding favorably to ambulatory therapy should be hospitalized for parenteral therapy and further diagnostic evaluations, including a consideration of laparoscopy. Male sex partners should be evaluated and treated empirically for gonorrhea and chlamydial infection. After completion of treatment, tests for persistent or recurrent infection with *N. gonorrhoeae* or *C. trachomatis* should be performed if symptoms persist or recur or if the patient has not complied with therapy or has been reexposed to an untreated sex partner.

SURGERY Surgery is necessary for the treatment of salpingitis only in the face of life-threatening infection (such as rupture or threatened rupture of a tuboovarian abscess) or for drainage of an abscess. Conservative surgical procedures are usually sufficient. Pelvic abscesses can often be drained by posterior colpotomy, and peritoneal lavage can be used for generalized peritonitis.

Prognosis

Late sequelae include infertility due to bilateral tubal occlusion, ectopic pregnancy due to tubal scarring without occlusion, chronic pelvic pain, and recurrent salpingitis. The overall postsalpingitis risk of infertility due to tubal occlusion in a large study in Sweden was 11% after one episode of salpingitis, 23% after two episodes, and 54% after three or more episodes. A University of Washington study found a sevenfold increase in the risk of ectopic pregnancy and an eightfold increase in the rate of hysterectomy after PID.

Prevention

A randomized controlled trial designed to determine whether selective screening for chlamydial infection reduces the risk of subsequent PID showed that women randomized to undergo screening had a 56% lower rate of PID over the following year than did women receiving the usual care without screening. This report helped prompt U.S. national guidelines for risk-based chlamydial screening of young women to reduce the incidence of PID and the prevalence of post-PID sequelae, while also reducing sexual transmission of *C. trachomatis*. The CDC and the U.S. Preventive Services Task Force recommend that sexually active women ≤25 years of age be screened for genital chlamydial infection annually. Despite this recommendation, screening coverage in many primary care settings remains low.

ULCERATIVE GENITAL OR PERIANAL LESIONS

Genital ulceration reflects a set of important STIs, most of which sharply increase the risk of sexual acquisition and shedding of HIV. In a 1996 study of genital ulcers in 10 of the U.S. cities with the highest rates of primary syphilis, PCR testing of ulcer specimens demonstrated HSV in 62% of patients, *Treponema pallidum* (the agent of syphilis) in 13%, and *Haemophilus ducreyi* (the agent of chancroid) in 12–20%. Today, genital herpes represents an even higher proportion of genital ulcers in the United States and other industrialized countries.

In Asia and Africa, chancroid **(Fig. 30-5)** was once considered the most common type of genital ulcer, followed in frequency by primary syphilis and then genital herpes **(Fig.30-6)**. With increased efforts to control chancroid and syphilis and widespread use of broad-spectrum antibiotics to treat STI-related syndromes, together with more frequent recurrences or persistence of genital herpes attributable to HIV infection, PCR testing of genital ulcers now clearly implicates genital herpes as the most common cause of genital ulceration in some developing countries. LGV caused by *C. trachomatis*; **(Fig. 30-7)** and donovanosis (granuloma inguinale, caused by *Klebsiella granulomatis*; see Fig. 66-1) continue to cause genital ulceration in developing countries. LGV virtually disappeared in industrialized countries during the first 20 years of the HIV pandemic, but outbreaks are again occurring in Europe

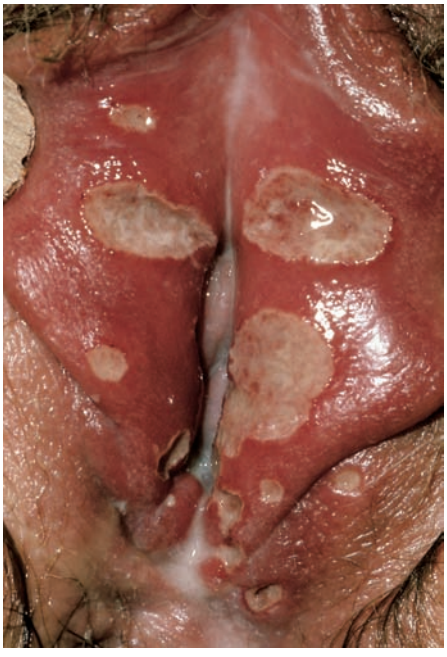


FIGURE 30-5
Chancroid: multiple, painful, punched-out ulcers with undermined borders on the labia occurring after autoinoculation.

(including the United Kingdom), in North America, and in Australia. In these outbreaks, LGV typically presents as proctitis in men who report unprotected receptive anal intercourse, very often in association with HIV and/or hepatitis C virus infection; the latter may be an acute infection acquired through the same exposure. Other causes of genital ulcers include (1) candidiasis and traumatized genital warts—both readily recognized; (2) lesions due to genital involvement by more widespread dermatoses; (3) cutaneous manifestations of systemic diseases such as genital mucosal ulceration in Stevens-Johnson syndrome or

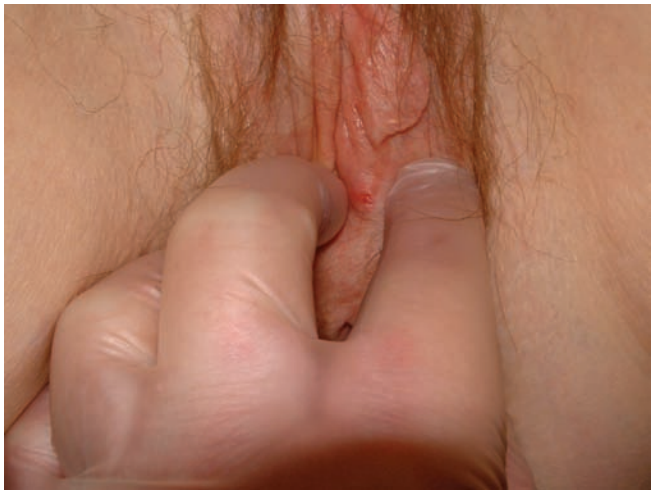


FIGURE 30-6
Genital herpes. A relatively mild, superficial ulcer is typically seen in episodic outbreaks. (*Courtesy of Michael Remington, University of Washington Virology Research Clinic.*)

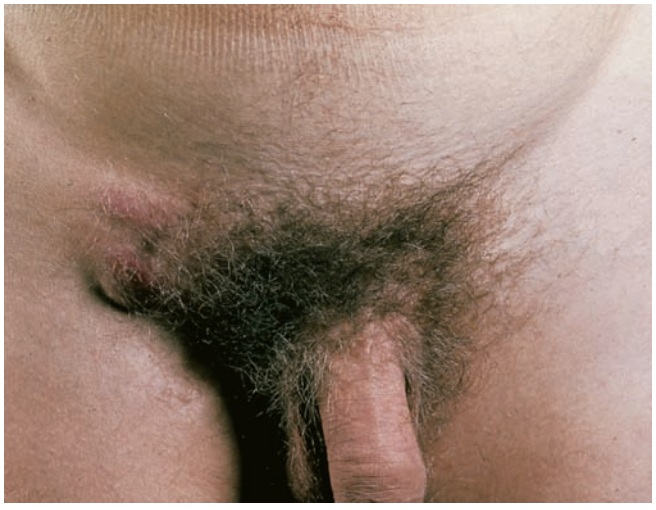


FIGURE 30-7
Lymphogranuloma venereum: striking tender lymphadenopathy occurring at the femoral and inguinal lymph nodes, separated by a groove made by Poupart's ligament. This "sign-of-the-groove" is not considered specific for LGV; for example, lymphomas may present with this sign.

Behçet's disease; (4) superinfections of lesions that may originally have been sexually acquired such as methicillin-resistant *S. aureus* complicating a genital ulcer due to HSV-2; and (5) localized drug reactions, such as the ulcers occasionally seen with topical paromomycin cream or boric acid preparations.

Diagnosis

Although most genital ulcerations cannot be diagnosed confidently on clinical grounds alone, clinical findings and epidemiologic considerations **(Table 30-7)** can usually guide initial management **(Table 30-8)** pending results of further tests. Clinicians should order a rapid serologic test for syphilis in all cases of genital ulcer. To evaluate lesions except those highly characteristic of infection with HSV (i.e., those with herpetic vesicles), dark-field microscopy, direct immunofluorescence, and PCR for *T. pallidum* can be useful but are rarely available today in the United States. It is important to note that 30% of syphilitic chancres—the primary ulcer of syphilis—are associated with a nonreactive syphilis serology. All patients presenting with genital ulceration should be counseled and tested for HIV infection.

Typical vesicles or pustules or a cluster of painful ulcers preceded by vesiculopustular lesions suggests genital herpes. These typical clinical manifestations make detection of the virus optional; however, many patients want confirmation of the diagnosis, and differentiation of HSV-1 from HSV-2 has prognostic implications, since the latter causes more frequent genital recurrences.

Painless, nontender, indurated ulcers with firm, nontender inguinal adenopathy suggest primary syphilis. If results of dark-field examination and a rapid serologic

TABLE 30-7

CLINICAL FEATURES OF GENITAL ULCERS

FEATURE	SYPHILIS	HERPES	CHANCROID	LYMPHOGRANULOMA VENEREUM	DONOVANOSIS
Incubation period	9–90 days	2–7 days	1–14 days	3 days–6 weeks	1–4 weeks (up to 6 months)
Early primary lesions	Papule	Vesicle	Pustule	Papule, pustule, or vesicle	Papule
No. of lesions	Usually one	Multiple	Usually multiple, may coalesce	Usually one; often not detected, despite lymphadenopathy	Variable
Diameter	5–15 mm	1–2 mm	Variable	2–10 mm	Variable
Edges	Sharply demarcated, elevated, round, or oval	Erythematous	Undermined, ragged, irregular	Elevated, round, or oval	Elevated, irregular
Depth	Superficial or deep	Superficial	Excavated	Superficial or deep	Elevated
Base	Smooth, nonpurulent, relatively nonvascular	Serous, erythematous, nonvascular	Purulent, bleeds easily	Variable, nonvascular	Red and velvety, bleeds readily
Induration	Firm	None	Soft	Occasionally firm	Firm
Pain	Uncommon	Frequently tender	Usually very tender	Variable	Uncommon
Lymphadenopathy	Firm, nontender, bilateral	Firm, tender, often bilateral with initial episode	Tender, may suppurate, loculated, usually unilateral	Tender, may suppurate, loculated, usually unilateral	None; pseudobuboes

Source: From RM Ballard, in KK Holmes et al (eds): *Sexually Transmitted Diseases*, 4th ed. New York, McGraw-Hill, 2008.

test for syphilis are initially negative, presumptive therapy should be provided on the basis of the individual's risk. For example, with increasing rates of syphilis among MSM in the United States, most experts would not withhold therapy for this infection pending watchful waiting and/or subsequent detection of seroconversion. Repeated serologic testing for syphilis 1 or 2 weeks after treatment of seronegative primary syphilis usually demonstrates seroconversion.

"Atypical" or clinically trivial ulcers may be more common manifestations of genital herpes than classic vesiculopustular lesions. Specific tests for HSV in such lesions are therefore indicated (Chap. 84). Commercially available type-specific serologic tests for serum antibody to HSV-2 may give negative results, especially when patients present early with the initial episode of genital herpes or when HSV-1 is the cause of genital herpes (as is often the case today). Furthermore, a positive test for antibody to HSV-2 does not prove that the current lesions are herpetic, since nearly one-fifth of the general population of the United States (and no doubt a higher proportion of those at risk for other STIs) becomes seropositive for HSV-2 during early adulthood. Although even "type-specific" tests for HSV-2 that are commercially available in the United States are not 100% specific, a positive HSV-2 serology does enable the clinician to tell the patient that he or she has probably had genital herpes, should learn to recognize symptoms, should avoid sex during recurrences, and should consider use of condoms or suppressive antiviral therapy, both of which can reduce the risk of transmission to a sexual partner.

Demonstration of *H. ducreyi* by culture (or by PCR, when available) is most useful when ulcers are painful and purulent, especially if inguinal lymphadenopathy with fluctuance or overlying erythema is noted; if chancroid is prevalent in the community; or if the patient has recently had a sexual exposure elsewhere in a chancroid-endemic area (e.g., a developing country). Enlarged, fluctuant lymph nodes should be aspirated for culture or PCR to detect *H. ducreyi* as well as for Gram's staining and culture to rule out the presence of other pyogenic bacteria.

When genital ulcers persist beyond the natural history of initial episodes of herpes (2–3 weeks) or of chancroid or syphilis (up to 6 weeks) and do not resolve with syndrome-based antimicrobial therapy, then—in addition to the usual tests for herpes, syphilis, and chancroid—biopsy is indicated to exclude donovanosis, carcinoma, and other nonvenereal dermatoses. If not performed previously, HIV serology should be standard, since chronic, persistent genital herpes is common in AIDS.

TABLE 30-8

INITIAL MANAGEMENT OF GENITAL OR PERIANAL ULCER

Usual Causes
Herpes simplex virus (HSV) *Treponema pallidum* (primary syphilis) *Haemophilus ducreyi* (chancroid)
Usual Initial Laboratory Evaluation
Dark-field exam (if available), direct FA, or PCR for *T. pallidum;* RPR, VDRL, or EIA test for syphilis (if negative but primary syphilis suspected, treat presumptively when indicated by epidemiologic and sexual risk assessment; repeat in 1 week); culture, direct FA, ELISA, or PCR for HSV; consider HSV-2-specific serology. In chancroid-endemic area: PCR or culture for *H. ducreyi*
Initial Treatment
Herpes confirmed or suspected (history or sign of vesicles): Treat for genital herpes with acyclovir, valacyclovir, or famciclovir
Syphilis confirmed (dark-field, FA, or PCR showing *T. pallidum*, or RPR reactive): Benzathine penicillin [2.4 million units IM once to patient, recent (e.g., within 3 months) seronegative partner(s), and all seropositive partners]
Chancroid confirmed or suspected (diagnostic test positive, or HSV and syphilis excluded, and persistent lesion): Ciprofloxacin (500 mg PO as single dose) *or* Ceftriaxone (250 mg IM as single dose) *or* Azithromycin (1 g PO as single dose)

Abbreviations: FA, fluorescent antibody; PCR, polymerase chain reaction; RPR, rapid plasma reagin; EIA, enzyme immunoassay; ELISA, enzyme-linked immunosorbent assay; HSV, herpes simplex virus; VDRL, Venereal Disease Research Laboratory.

TREATMENT Ulcerative Genital or Perianal Lesions

Immediate syndrome-based treatment for acute genital ulcerations (after collection of all necessary diagnostic specimens at the first visit) is often appropriate before all test results become available, because patients with typical initial or recurrent episodes of genital or anorectal herpes can benefit from prompt oral antiviral therapy (Chap. 84); because early treatment of sexually transmitted causes of genital ulcers decreases further transmission; and because many patients do not return for test results and treatment. A thorough assessment of the patient's sexual-risk profile and medical history is critical in determining the course of initial management. The patient who has risk factors consistent with exposure to syphilis (e.g., a male patient who reports sex with other men or who has HIV infection) should generally receive initial treatment for syphilis. Empirical therapy for chancroid should be considered if there has been an exposure in an area of the world where chancroid occurs or if regional lymph node suppuration is evident. In resource-poor settings lacking ready access to diagnostic tests, this approach to syndromic treatment for syphilis and chancroid has helped bring these two diseases under control. Finally, empirical antimicrobial therapy may be indicated if ulcers persist and the diagnosis remains unclear after a week of observation despite attempts to diagnose herpes, syphilis, and chancroid.

PROCTITIS, PROCTOCOLITIS, ENTEROCOLITIS, AND ENTERITIS

Sexually acquired *proctitis*, with inflammation limited to the rectal mucosa (the distal 10–12 cm), results from direct rectal inoculation of typical STD pathogens. In contrast, inflammation extending from the rectum to the colon (*proctocolitis*), involving both the small and the large bowel (*enterocolitis*), or involving the small bowel alone (*enteritis*) can result from ingestion of typical intestinal pathogens through oral-anal exposure during sexual contact. Anorectal pain and mucopurulent, bloody rectal discharge suggest proctitis or protocolitis. Proctitis commonly produces tenesmus (causing frequent attempts to defecate, but not true diarrhea) and constipation, whereas proctocolitis and enterocolitis more often cause true diarrhea. In all three conditions, anoscopy usually shows mucosal exudate and easily induced mucosal bleeding (i.e., a positive "wipe test"), sometimes with petechiae or mucosal ulcers. Exudate should be sampled for Gram's staining and other microbiologic studies. Sigmoidoscopy or colonoscopy shows inflammation limited to the rectum in proctitis or disease extending at least up into the sigmoid colon in proctocolitis.

The AIDS era brought an extraordinary shift in the clinical and etiologic spectrum of intestinal infections among MSM. The number of cases of the acute intestinal STIs described earlier fell as high-risk sexual behaviors became less common in this group. At the same time, the number of AIDS-related opportunistic intestinal infections increased rapidly, many associated with chronic or recurrent symptoms. The incidence of these infections has since fallen with increasingly effective antiretroviral therapy. Two species initially isolated in association with intestinal symptoms in MSM are now known as *Helicobacter cinaedi* and *Helicobacter fennelliae*, and both have subsequently been isolated from the blood of HIV-infected men and other immunosuppressed persons, often in association with a syndrome of multifocal dermatitis and arthritis.

Acquisition of HSV, *N. gonorrhoeae*, or *C. trachomatis* (including LGV strains of *C. trachomatis*) during receptive anorectal intercourse causes most cases of infectious proctitis in women and MSM. Primary and secondary syphilis can also produce anal or anorectal lesions, with or without symptoms. Gonococcal or chlamydial proctitis typically involves the most distal rectal mucosa and the anal crypts and is clinically mild, without systemic manifestations. In contrast, primary proctitis

due to HSV and proctocolitis due to the strains of *C. trachomatis* that cause LGV usually produce severe anorectal pain and often cause fever. Perianal ulcers and inguinal lymphadenopathy, most commonly due to HSV, can also occur in LGV or syphilis. Sacral nerve root radiculopathies, usually presenting as urinary retention, laxity of the anal sphincter, or constipation, may complicate primary herpetic proctitis. In LGV, rectal biopsy typically shows crypt abscesses, granulomas, and giant cells—findings resembling those in Crohn's disease; such findings should always prompt rectal culture and serology for LGV, which is a curable infection. Syphilis can also produce rectal granulomas, usually in association with infiltration by plasma cells or other mononuclear cells. Syphilis, LGV, and HSV infection involving the rectum can produce perirectal adenopathy that is sometimes mistaken for malignancy; syphilis, LGV, HSV infection, and chancroid involving the anus can produce inguinal adenopathy, because anal lymphatics drain to inguinal lymph nodes.

Diarrhea and abdominal bloating or cramping pain without anorectal symptoms and with normal findings on anoscopy and sigmoidoscopy occur with inflammation of the small intestine (enteritis) or with proximal colitis. In MSM without HIV infection, enteritis is often attributable to *Giardia lamblia*. Sexually acquired proctocolitis is most often due to *Campylobacter* or *Shigella* species.

TREATMENT **Proctitis, Proctocolitis, Enterocolitis, and Enteritis**

Acute proctitis in persons who have practiced receptive anorectal intercourse is usually sexually acquired. Such patients should undergo anoscopy to detect rectal ulcers or vesicles and petechiae after swabbing of the rectal mucosa; to examine rectal exudates for PMNs and gram-negative diplococci; and to obtain rectal swab specimens for testing for rectal gonorrhea, chlamydial infection, herpes, and syphilis. Pending test results, patients with proctitis should receive empirical syndromic treatment—e.g., with ceftriaxone (a single IM dose of 125 mg for gonorrhea) plus doxycycline (100 mg by mouth twice daily for 7 days for possible chlamydial infection) plus treatment for herpes or syphilis if indicated.

PREVENTION AND CONTROL OF STIs

Prevention and control of STIs require the following:

1. Reduction of the average rate of sexual exposure to STIs through alteration of sexual risk behaviors and behavioral norms among both susceptible and infected persons in all population groups. The necessary changes include reduction in the total number of sexual partners and the number of concurrent sexual partners.
2. Reduction of the efficiency of transmission through the promotion of safer sexual practices, the use of condoms during casual or commercial sex, vaccination against HBV and HPV infection, male circumcision (which reduces risk of acquisition of HIV, chancroid, and perhaps other STIs), and a growing number of other approaches (e.g., early detection and treatment of other STIs to reduce the efficiency of sexual transmission of HIV). Longitudinal studies have shown that consistent condom use is associated with significant protection of both males and females against all STIs that have been examined, including HIV, HPV, and HSV infections as well as gonorrhea and chlamydial infection. The only exceptions are probably sexually transmitted *Pthirus pubis* and *Sarcoptes scabiei* infestations.
3. Shortening of the duration of infectivity of STIs through early detection and curative or suppressive treatment of patients and their sexual partners.

Financial and time constraints imposed by many clinical practices, along with the reluctance of some clinicians to ask questions about stigmatized sexual behaviors, often curtail screening and prevention services. As outlined in **Fig. 30-8**, the success of clinicians' efforts to detect and treat STIs depends in part on societal efforts to teach young people how to recognize symptoms of STIs; to motivate individuals with symptoms to seek care promptly; to educate persons who are at risk but have no symptoms about what tests they should undergo routinely; and to make high-quality, appropriate care accessible, affordable, and acceptable, especially to the young indigent patients most likely to acquire an STI.

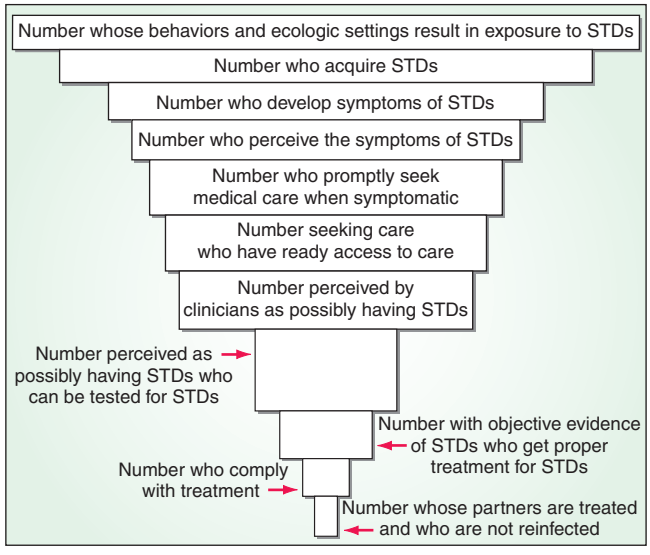


FIGURE 30-8
Critical control points for preventive and clinical interventions against sexually transmitted diseases (STDs). (*Adapted from HT Waller and MA Piot: Bull World Health Organ 41:75, 1969 and 43:1, 1970; and from "Resource allocation model for public health planning—a case study of tuberculosis control," Bull World Health Organ 48 (Suppl), 1973.*)

Since many infected individuals develop no symptoms or fail to recognize and report symptoms, clinicians should routinely perform an STI risk assessment for teenagers and young adults as a guide to selective screening. As stated earlier, U.S. Preventive Services Task Force Guidelines recommend screening sexually active female patients ≤25 years of age for *C. trachomatis* whenever they present for health care (at least once a year); older women should be tested if they have more than one sexual partner, have begun a new sexual relationship since the previous test, or have another STI diagnosed. In women 25–29 years of age, chlamydial infection is uncommon but still may reach a prevalence of 3–5% in some settings; information on a sex partner's concurrency provided by women in this age group (i.e., whether a male partner has had another sex partner during the time they have been together) is helpful in identifying women at increased risk. In the United States, widespread selective screening of young women for cervical *C. trachomatis* infection in some regions has been associated with a 50–60% drop in prevalence, and such screening also protects the individual woman from PID. Sensitive urine-based genetic amplification tests permit expansion of screening to men, teenage boys, and girls in settings where examination is not planned or is impractical (e.g., during pre-participation sports examinations or during initial medical evaluation of adolescent girls). Vaginal swabs—collected either by the health care provider at a pelvic examination or by the woman herself—are highly sensitive and specific for the diagnosis of chlamydial and gonococcal infection; they are now the preferred type of specimen for screening and diagnosis of these infections.

Although gonorrhea is now substantially less common than chlamydial infection in industrialized countries, screening tests for *N. gonorrhoeae* are still appropriate for women and teenage girls attending STD clinics and for sexually active teens and young women from areas of high gonorrhea prevalence. Multiplex NAATs that combine screening for *N. gonorrhoeae* and *C. trachomatis* in a single low-cost assay now facilitate the prevention and control of both infections in populations at high risk.

All patients with newly detected STIs or at high risk for STIs according to routine risk assessment as well as all pregnant women should be encouraged to undergo serologic testing for syphilis and HIV infection, with appropriate HIV counseling before and after testing. Randomized trials have shown that risk-reduction counseling of patients with STIs significantly lowers subsequent risk of acquiring an STI; such counseling should now be considered a standard component of STI management. Preimmunization serologic testing for antibody to HBV is indicated for unvaccinated persons who are known to be at high risk, such as homosexually active men and injection drug users. In most young persons, however, it is more cost-effective to vaccinate against HBV without serologic screening. It is important to recognize that, while immunization against HBV has contributed to marked reductions in the incidence of infection with this virus, the majority of new cases that do occur are acquired through sex. In 2006, the Advisory Committee on Immunization Practices (ACIP) of the CDC recommended the following: (1) Universal hepatitis B vaccination should be implemented for all unvaccinated adults in settings in which a high proportion of adults have risk factors for HBV infection (e.g., STD clinics, HIV testing and treatment facilities, drug-abuse treatment and prevention settings, health care settings targeting services to injection drug users or MSM, and correctional facilities). (2) In other primary care and specialty medical settings in which adults at risk for HBV infection receive care, health care providers should inform all patients about the health benefits of vaccination, the risk factors for HBV infection, and the persons for whom vaccination is recommended and should vaccinate adults who report risk factors for HBV infection as well as any adult who requests protection from HBV infection. To promote vaccination in all settings, health care providers should implement standing orders to identify adults recommended for hepatitis B vaccination, should administer hepatitis B vaccine as part of routine clinical services, should not require acknowledgment of an HBV infection risk factor for adult vaccination, and should use available reimbursement mechanisms to remove financial barriers to hepatitis B vaccination.

In 2007, the ACIP recommended routine immunization of 9- to 26-year-old girls and women with the quadrivalent HPV vaccine (against HPV types 6, 11, 16, and 18) approved by the U.S. Food and Drug Administration; the optimal age for recommended vaccination is 11–12 years because of the very high risk of HPV infection after sexual debut. In 2009, the ACIP added bivalent HPV vaccine (against types 6 and 11) as an option and expanded the groups in which immunization (with either quadrivalent or bivalent vaccine) is safe and effective to include boys and men 9–26 years old. HPV vaccines offering broader protection against additional oncogenic HPV types are anticipated.

Partner notification is the process of identifying and informing partners of infected patients about possible exposure to an STI and of examining, testing, and treating partners as appropriate. In a series of 22 reports concerning partner notification during the 1990s, index patients with gonorrhea or chlamydial infection named a mean of 0.75–1.6 partners, of whom one-fourth to one-third were infected; those with syphilis named 1.8–6.3 partners, with one-third to one-half infected; and those with HIV infection named 0.76–5.31 partners, with up to one-fourth infected. Persons who transmit infection or who have recently been infected and are still in the incubation period usually have no symptoms or only mild symptoms and seek medical attention only when notified of their exposure. Therefore, the clinician must encourage patients to participate in partner notification, must ensure that exposed persons are notified and treated, and must guarantee confidentiality to all involved. In the United States, local health departments often offer assistance in partner notification, treatment, and/or counseling. It seems both feasible and most useful to notify those partners exposed within the patient's likely period of infectiousness, which is often considered the preceding 1 month for gonorrhea,

1–2 months for chlamydial infection, and up to 3 months for early syphilis.

Persons with a new-onset STI always have a *source* contact who gave them the infection; in addition, they may have a *secondary* (*spread* or *exposed*) contact with whom they had sex after becoming infected. The identification and treatment of these two types of contacts have different objectives. Treatment of the source contact (often a casual contact) benefits the community by preventing further transmission; treatment of the recently exposed secondary contact (typically a spouse or another steady sexual partner) prevents both the development of serious complications (such as PID) in the partner and reinfection of the index patient. A survey of a random sample of U.S. physicians found that most instructed patients to abstain from sex during treatment, to use condoms, and to inform their sex partners after being diagnosed with gonorrhea, chlamydial infection, or syphilis; physicians sometimes gave the patients drugs for their partners. However, follow-up of the partners by physicians was infrequent. A randomized trial compared patients' delivery of therapy to partners exposed to gonorrhea or chlamydial infection with conventional notification and advice to partners to seek evaluation for STD; patients' delivery of partners' therapy (PDPT), also known as *expedited partner therapy* (EPT), significantly reduced combined rates of reinfection of the index patient with *N. gonorrhoeae* or *C. trachomatis*. State-by-state variations in regulations governing this approach have not been well defined, but the 2010 CDC STD treatment guidelines and the EPT final report of 2006 (*http://www.cdc.gov/std/treatment/EPTFinalReport2006.pdf*) describe its potential use. Currently, EPT is commonly used by many practicing physicians. Its legal status varies by state, but EPT is now permissible in 22 states and potentially allowable in another 20. (Updated information on the legal status of EPT is available at *http://www.cdc.gov/std/ept*.)

In summary, clinicians and public health agencies share responsibility for the prevention and control of STIs. In the current health care environment, the role of primary care clinicians has become increasingly important in STI prevention as well as in diagnosis and treatment, and the resurgence of bacterial STIs like syphilis and LGV among MSM—particularly those co-infected with HIV—emphasizes the need for risk assessment and routine screening.

CHAPTER 31

MENINGITIS, ENCEPHALITIS, BRAIN ABSCESS, AND EMPYEMA

Karen L. Roos ■ Kenneth L. Tyler

Acute infections of the nervous system are among the most important problems in medicine because early recognition, efficient decision-making, and rapid institution of therapy can be lifesaving. These distinct clinical syndromes include acute bacterial meningitis, viral meningitis, encephalitis, focal infections such as brain abscess and subdural empyema, and infectious thrombophlebitis. Each may present with a nonspecific prodrome of fever and headache, which in a previously healthy individual may initially be thought to be benign, until (with the exception of viral meningitis) altered consciousness, focal neurologic signs, or seizures appear. Key goals of early management are to emergently distinguish between these conditions, identify the responsible pathogen, and initiate appropriate antimicrobial therapy.

APPROACH TO THE PATIENT: Meningitis, Encephalitis, Brain Abscess, and Empyema

(Fig. 31-1) The first task is to identify whether an infection predominantly involves the subarachnoid space (*meningitis*) or whether there is evidence of either generalized or focal involvement of brain tissue in the cerebral hemispheres, cerebellum, or *brainstem*. When brain tissue is directly injured by a viral infection, the disease

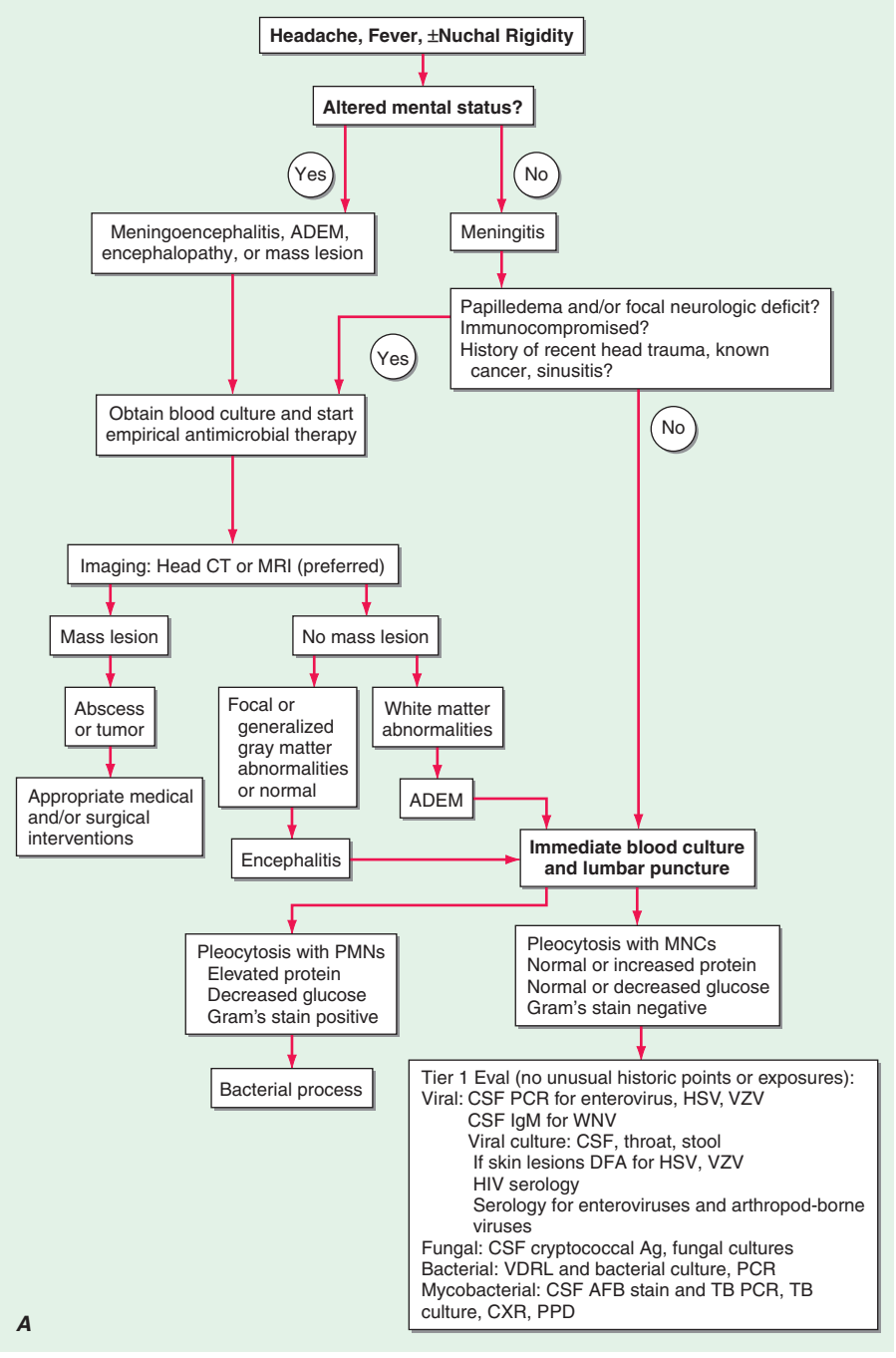


FIGURE 31-1

The management of patients with suspected CNS infection. ADEM, acute disseminated encephalomyelitis; AFB, acid-fast bacillus; Ag, antigen; CSF, cerebrospinal fluid; CT, computed tomography; CTFV, Colorado tick fever virus; CXR, chest x-ray; DFA, direct fluorescent antibody; EBV, Epstein-Barr virus; HHV, human herpesvirus; HSV, herpes simplex virus; LCMV, lymphocytic choriomeningitis virus; MNCs, mononuclear cells; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; PMNs, polymorphonuclear leukocytes; PPD, purified protein derivative; TB, tuberculosis; VDRL, Venereal Disease Research Laboratory; VZV, varicella-zoster virus; WNV, West Nile virus.

is referred to as *encephalitis*, whereas focal infections involving brain tissue are classified as either *cerebritis* or *abscess*, depending on the presence or absence of a capsule.

Nuchal rigidity ("stiff neck") is the pathognomonic sign of meningeal irritation and is present when the neck resists passive flexion. Kernig's and Brudzinski's signs are also classic signs of meningeal irritation. *Kernig's sign* is elicited with the patient in the supine position. The thigh is flexed on the abdomen, with the knee flexed; attempts to passively extend the knee elicit pain when meningeal irritation is present. *Brudzinski's sign* is elicited with the patient in the supine position and is positive when

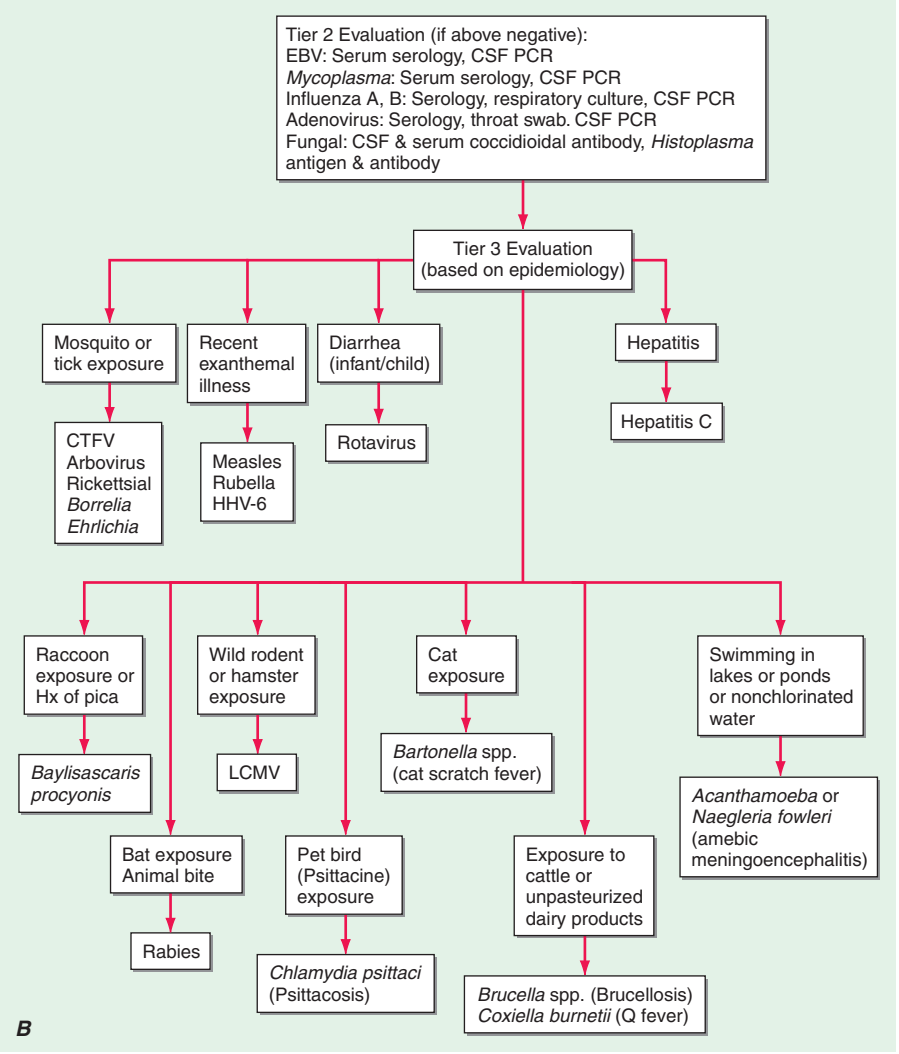


FIGURE 31-1 (***Continued***)

passive flexion of the neck results in spontaneous flexion of the hips and knees. Although commonly tested on physical examinations, the sensitivity and specificity of Kernig's and Brudzinski's signs are uncertain. Both may be absent or reduced in very young or elderly patients, immunocompromised individuals, or patients with a severely depressed mental status. The high prevalence of cervical spine disease in older individuals may result in false-positive tests for nuchal rigidity.

Initial management can be guided by several considerations: (1) Empirical therapy should be initiated promptly whenever bacterial meningitis is a significant diagnostic consideration. (2) All patients who have had recent head trauma, are immunocompromised, have known malignant lesions or central nervous system (CNS) neoplasms, or have focal neurologic findings, papilledema or a depressed level of consciousness should undergo CT or MRI of the brain prior to lumbar puncture (LP). In these cases empirical antibiotic therapy should not be delayed pending test results but should be administered prior to neuroimaging and LP. (3) A significantly depressed level of consciousness (e.g., somnolence, coma), seizures, or focal neurologic deficits do not occur in viral meningitis; patients with these symptoms should be hospitalized for further evaluation and treated empirically for bacterial and viral meningoencephalitis. (4) Immunocompetent patients with a normal level of consciousness, no prior antimicrobial treatment, and a cerebrospinal fluid (CSF) profile consistent with viral meningitis (lymphocytic pleocytosis and a normal glucose concentration) can often be treated as outpatients if appropriate contact and monitoring can be ensured. Failure of a patient with suspected viral meningitis to improve within 48 h should prompt a reevaluation including follow-up neurologic and general medical examination and repeat imaging and laboratory studies, often including a second LP.

ACUTE BACTERIAL MENINGITIS

DEFINITION

Bacterial meningitis is an acute purulent infection within the subarachnoid space. It is associated with a CNS

inflammatory reaction that may result in decreased consciousness, seizures, raised intracranial pressure (ICP), and stroke. The meninges, the subarachnoid space, and the brain parenchyma are all frequently involved in the inflammatory reaction (*meningoencephalitis*).

EPIDEMIOLOGY

Bacterial meningitis is the most common form of suppurative CNS infection, with an annual incidence in the United States of >2.5 cases/100,000 population. The organisms most often responsible for community-acquired bacterial meningitis are *Streptococcus pneumoniae* (~50%), *Neisseria meningitidis* (~25%), group B streptococci (~15%), and *Listeria monocytogenes* (~10%). *Haemophilus influenzae* type b accounts for <10% of cases of bacterial meningitis in most series. *N. meningitidis* is the causative organism of recurring epidemics of meningitis every 8 to 12 years.

ETIOLOGY

S. pneumoniae (Chap. 39) is the most common cause of meningitis in adults >20 years of age, accounting for nearly half the reported cases (1.1 per 100,000 persons per year). There are a number of predisposing conditions that increase the risk of pneumococcal meningitis, the most important of which is pneumococcal pneumonia. Additional risk factors include coexisting acute or chronic pneumococcal sinusitis or otitis media, alcoholism, diabetes, splenectomy, hypogammaglobulinemia, complement deficiency, and head trauma with basilar skull fracture and CSF rhinorrhea. The mortality rate remains ~20% despite antibiotic therapy.

The incidence of meningitis due to *N. meningitidis* (Chap. 48) has decreased with the routine immunization of 11- to 18-year-olds with the tetravalent (serogroups A, C, W-135, and Y) meningococcal glycoconjugate vaccine. The vaccine does not contain serogroup B, which is responsible for one-third of cases of meningococcal disease. The presence of petechial or purpuric skin lesions can provide an important clue to the diagnosis of meningococcal infection. In some patients the disease is fulminant, progressing to death within hours of symptom onset. Infection may be initiated by nasopharyngeal colonization, which can result in either an asymptomatic carrier state or invasive meningococcal disease. The risk of invasive disease following nasopharyngeal colonization depends on both bacterial virulence factors and host immune defense mechanisms, including the host's capacity to produce antimeningococcal antibodies and to lyse meningococci by both classic and alternative complement pathways. Individuals with deficiencies of any of the complement components, including properdin, are highly susceptible to meningococcal infections.

Enteric gram-negative bacilli cause meningitis in individuals with chronic and debilitating diseases such as diabetes, cirrhosis, or alcoholism and in those with chronic urinary tract infections. Gram-negative meningitis can also complicate neurosurgical procedures, particularly craniotomy.

Otitis, mastoiditis, and sinusitis are predisposing and associated conditions for meningitis due to *Streptococcus* spp., gram-negative anaerobes, *S. aureus, Haemophilus* spp., and Enterobacteriaceae. Meningitis complicating endocarditis may be due to viridans streptococci, *S. aureus, S. bovis,* the HACEK group (*Haemophilus* spp., *Aggregatibacter actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, Kingella kingae*), or enterococci.

Group B *Streptococcus*, or *S. agalactiae* (Chap. 39), was previously responsible for meningitis predominantly in neonates, but it has been reported with increasing frequency in individuals >50 years of age, particularly those with underlying diseases.

L. monocytogenes (Chap. 43) is an increasingly important cause of meningitis in neonates (<1 month of age), pregnant women, individuals >60 years old, and immunocompromised individuals of all ages. Infection is acquired by ingesting foods contaminated by *Listeria*. Foodborne human listerial infection has been reported from contaminated coleslaw, milk, soft cheeses, and several types of "ready-to-eat" foods, including delicatessen meat and uncooked hotdogs.

The frequency of *H. influenzae* type b (Chap. 50) meningitis in children has declined dramatically since the introduction of the Hib conjugate vaccine, although rare cases of Hib meningitis in vaccinated children have been reported. More frequently, *H. influenzae* causes meningitis in unvaccinated children and older adults, and non-b *H. influenzae* is an emerging pathogen.

Staphylococcus aureus and coagulase-negative staphylococci (Chap. 38) are important causes of meningitis that occurs following invasive neurosurgical procedures, particularly shunting procedures for hydrocephalus, or as a complication of the use of subcutaneous Ommaya reservoirs for administration of intrathecal chemotherapy.

PATHOPHYSIOLOGY

The most common bacteria that cause meningitis, *S. pneumoniae* and *N. meningitidis*, initially colonize the nasopharynx by attaching to nasopharyngeal epithelial cells. Bacteria are transported across epithelial cells in membrane-bound vacuoles to the intravascular space or invade the intravascular space by creating separations in the apical tight junctions of columnar epithelial cells. Once in the bloodstream, bacteria are able to avoid phagocytosis by neutrophils and classic complement-mediated bactericidal activity because of the presence of a polysaccharide capsule. Bloodborne bacteria can reach the intraventricular choroid plexus, directly infect choroid plexus epithelial cells, and gain access to the CSF. Some bacteria, such as *S. pneumoniae*, can adhere to cerebral capillary endothelial cells and subsequently migrate through or between these cells to reach the CSF. Bacteria are able to multiply rapidly within CSF because of the absence of effective host immune defenses. Normal CSF contains few white

blood cells (WBCs) and relatively small amounts of complement proteins and immunoglobulins. The paucity of the latter two prevents effective opsonization of bacteria, an essential prerequisite for bacterial phagocytosis by neutrophils. Phagocytosis of bacteria is further impaired by the fluid nature of CSF, which is less conducive to phagocytosis than a solid tissue substrate.

A critical event in the pathogenesis of bacterial meningitis is the inflammatory reaction induced by the invading bacteria. Many of the neurologic manifestations and complications of bacterial meningitis result from the immune response to the invading pathogen rather than from direct bacteria-induced tissue injury. As a result, neurologic injury can progress even after the CSF has been sterilized by antibiotic therapy.

The lysis of bacteria with the subsequent release of cell-wall components into the subarachnoid space is the initial step in the induction of the inflammatory response and the formation of a purulent exudate in the subarachnoid space **(Fig. 31-2)**. Bacterial cell-wall components, such as the lipopolysaccharide (LPS) molecules of gram-negative bacteria and teichoic acid and peptidoglycans of *S. pneumoniae*, induce meningeal inflammation by stimulating the production of inflammatory cytokines and chemokines by microglia, astrocytes, monocytes, microvascular endothelial cells, and CSF leukocytes. In experimental models of meningitis, cytokines including tumor necrosis factor alpha (TNF-α) and interleukin 1 β (IL-1β) are present in CSF within 1–2 h of intracisternal inoculation of LPS. This cytokine response is quickly followed by an increase in CSF protein concentration and leukocytosis. Chemokines (cytokines that induce chemotactic migration in leukocytes) and a variety of other proinflammatory cytokines are also produced and secreted by leukocytes and tissue cells that are stimulated by IL-1β and TNF-α. In addition, bacteremia and the inflammatory cytokines induce the production of excitatory amino acids, reactive

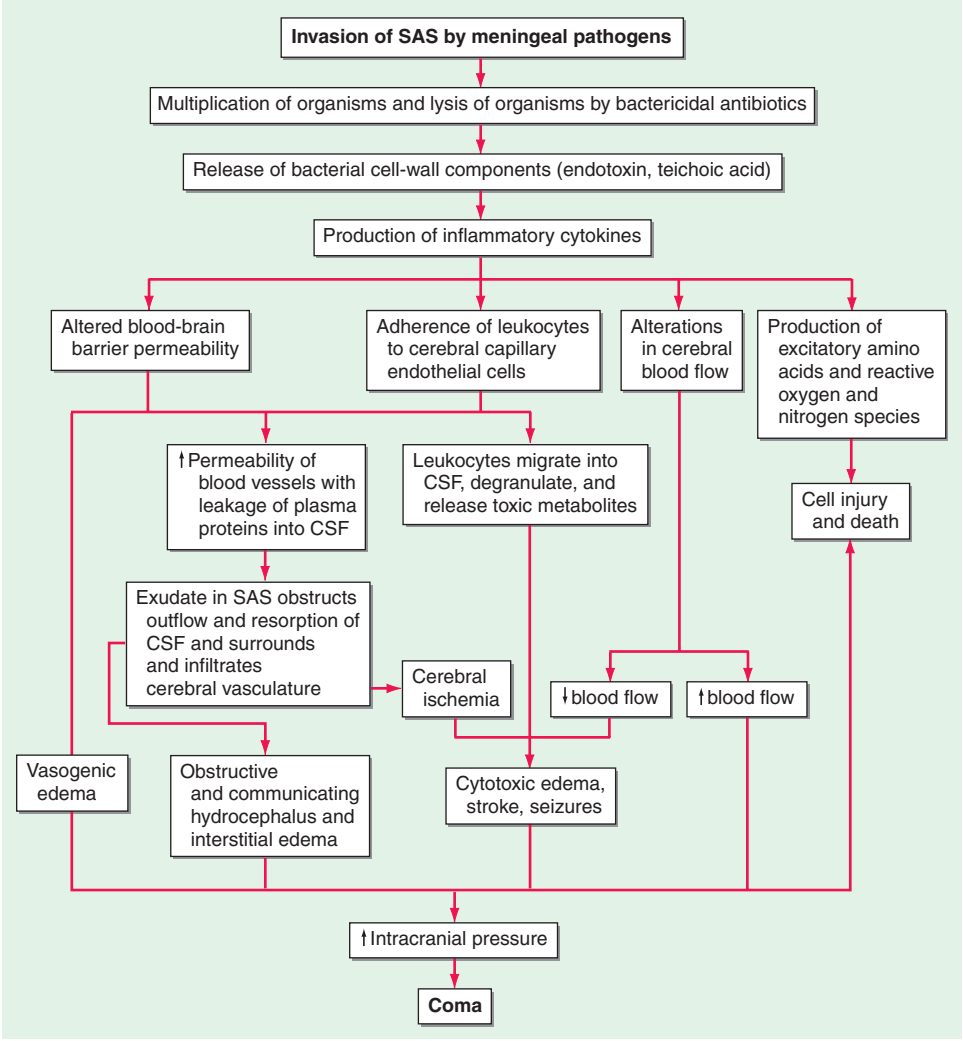


FIGURE 31-2
The pathophysiology of the neurologic complications of bacterial meningitis. CSF, cerebrospinal fluid; SAS, subarachnoid space.

oxygen and nitrogen species (free oxygen radicals, nitric oxide, and peroxynitrite), and other mediators that can induce death of brain cells, especially in the dentate gyrus of the hippocampus.

Much of the pathophysiology of bacterial meningitis is a direct consequence of elevated levels of CSF cytokines and chemokines. TNF-α and IL-1β act synergistically to increase the permeability of the blood-brain barrier, resulting in induction of vasogenic edema and the leakage of serum proteins into the subarachnoid space (Fig. 31-2). The subarachnoid exudate of proteinaceous material and leukocytes obstructs the flow of CSF through the ventricular system and diminishes the resorptive capacity of the arachnoid granulations in the dural sinuses, leading to obstructive and communicating hydrocephalus and concomitant interstitial edema.

Inflammatory cytokines upregulate the expression of selectins on cerebral capillary endothelial cells and leukocytes, promoting leukocyte adherence to vascular endothelial cells and subsequent migration into the CSF. The adherence of leukocytes to capillary endothelial cells increases the permeability of blood vessels, allowing for the leakage of plasma proteins into the CSF, which adds to the inflammatory exudate. Neutrophil degranulation results in the release of toxic metabolites that contribute to cytotoxic edema, cell injury, and death. Contrary to previous beliefs, CSF leukocytes probably do little to contribute to the clearance of CSF bacterial infection.

During the very early stages of meningitis, there is an increase in cerebral blood flow, soon followed by a decrease in cerebral blood flow and a loss of cerebrovascular autoregulation. Narrowing of the large arteries at the base of the brain due to encroachment by the purulent exudate in the subarachnoid space and infiltration of the arterial wall by inflammatory cells with intimal thickening (*vasculitis*) also occur and may result in ischemia and infarction, obstruction of branches of the middle cerebral artery by thrombosis, thrombosis of the major cerebral venous sinuses, and thrombophlebitis of the cerebral cortical veins. The combination of interstitial, vasogenic, and cytotoxic edema leads to raised ICP and coma. Cerebral herniation usually results from the effects of cerebral edema, either focal or generalized; hydrocephalus and dural sinus or cortical vein thrombosis may also play a role.

CLINICAL PRESENTATION

Meningitis can present as either an acute fulminant illness that progresses rapidly in a few hours or as a subacute infection that progressively worsens over several days. The classic clinical triad of meningitis is fever, headache, and nuchal rigidity, but the classic triad may not be present. A decreased level of consciousness occurs in >75% of patients and can vary from lethargy to coma. Fever and either headache, stiff neck, or an altered level of consciousness will be present in nearly every patient with bacterial meningitis. Nausea, vomiting, and photophobia are also common complaints.

Seizures occur as part of the initial presentation of bacterial meningitis or during the course of the illness in 20–40% of patients. Focal seizures are usually due to focal arterial ischemia or infarction, cortical venous thrombosis with hemorrhage, or focal edema. Generalized seizure activity and status epilepticus may be due to hyponatremia, cerebral anoxia, or, less commonly, the toxic effects of antimicrobial agents such as high-dose penicillin.

Raised ICP is an expected complication of bacterial meningitis and the major cause of obtundation and coma in this disease. More than 90% of patients will have a CSF opening pressure >180 mmH_2O, and 20% have opening pressures >400 mmH_2O. Signs of increased ICP include a deteriorating or reduced level of consciousness, papilledema, dilated poorly reactive pupils, sixth nerve palsies, decerebrate posturing, and the Cushing reflex (bradycardia, hypertension, and irregular respirations). The most disastrous complication of increased ICP is cerebral herniation. The incidence of herniation in patients with bacterial meningitis has been reported to range from as low as 1% to as high as 8%.

Specific clinical features may provide clues to the diagnosis of individual organisms and are discussed in more detail in specific chapters devoted to individual pathogens. The most important of these clues is the rash of meningococcemia, which begins as a diffuse erythematous maculopapular rash resembling a viral exanthem; however, the skin lesions of meningococcemia rapidly become petechial. Petechiae are found on the trunk and lower extremities, in the mucous membranes and conjunctiva, and occasionally on the palms and soles.

DIAGNOSIS

When bacterial meningitis is suspected, blood cultures should be immediately obtained and empirical antimicrobial and adjunctive dexamethasone therapy initiated without delay **(Table 31-1)**. The diagnosis of bacterial meningitis is made by examination of the CSF **(Table 31-2)**. The need to obtain neuroimaging studies (CT or MRI) prior to LP requires clinical judgment. In an immunocompetent patient with no known history of recent head trauma, a normal level of consciousness, and no evidence of papilledema or focal neurologic deficits, it is considered safe to perform LP without prior neuroimaging studies. If LP is delayed in order to obtain neuroimaging studies, empirical antibiotic therapy should be initiated after blood cultures are obtained. Antibiotic therapy initiated a few hours prior to LP will not significantly alter the CSF WBC count or glucose concentration, nor is it likely to prevent visualization of organisms by Gram's stain or detection of bacterial nucleic acid by polymerase chain reaction (PCR) assay.

The classic CSF abnormalities in bacterial meningitis (Table 31-2) are (1) polymorphonuclear (PMN) leukocytosis (>100 cells/μL in 90%), (2) decreased glucose concentration [<2.2 mmol/L (<40 mg/dL) and/or CSF/serum glucose ratio of <0.4 in ~60%], (3) increased protein concentration [>0.45 g/L (>45 mg/dL) in 90%], and (4) increased opening pressure (>180 mmH_2O in 90%).

TABLE 31-1

ANTIBIOTICS USED IN EMPIRICAL THERAPY OF BACTERIAL MENINGITIS AND FOCAL CNS INFECTIONS[a]

INDICATION	ANTIBIOTIC
Preterm infants to infants <1 month	Ampicillin + cefotaxime
Infants 1–3 mo	Ampicillin + cefotaxime or ceftriaxone
Immunocompetent children >3 mo and adults <55	Cefotaxime, ceftriaxone or cefepime + vancomycin
Adults >55 and adults of any age with alcoholism or other debilitating illnesses	Ampicillin + cefotaxime, ceftriaxone or cefepime + vancomycin
Hospital-acquired meningitis, posttraumatic or postneurosurgery meningitis, neutropenic patients, or patients with impaired cell-mediated immunity	Ampicillin + ceftazidime or meropenem + vancomycin

	TOTAL DAILY DOSE AND DOSING INTERVAL	
ANTIMICROBIAL AGENT	**CHILD (>1 MONTH)**	**ADULT**
Ampicillin	200 (mg/kg)/d, q4h	12 g/d, q4h
Cefepime	150 (mg/kg)/d, q8h	6 g/d, q8h
Cefotaxime	200 (mg/kg)/d, q6h	12 g/d, q4h
Ceftriaxone	100 (mg/kg)/d, q12h	4 g/d, q12h
Ceftazidime	150 (mg/kg)/d, q8h	6 g/d, q8h
Gentamicin	7.5 (mg/kg)/d, q8h[b]	7.5 (mg/kg)/d, q8h
Meropenem	120 (mg/kg)/d, q8h	3 g/d, q8h
Metronidazole	30 (mg/kg)/d, q6h	1500–2000 mg/d, q6h
Nafcillin	100–200 (mg/kg)/d, q6h	9–12 g/d, q4h
Penicillin G	400,000 (U/kg)/d, q4h	20–24 million U/d, q4h
Vancomycin	60 (mg/kg)/d, q6h	2 g/d, q12h[b]

[a]All antibiotics are administered intravenously; doses indicated assume normal renal and hepatic function.
[b]Doses should be adjusted based on serum peak and trough levels: gentamicin therapeutic level: peak: 5–8 μg/mL; trough: <2 μg/mL; vancomycin therapeutic level: peak: 25–40 μg/mL; trough: 5–15 μg/mL.

CSF bacterial cultures are positive in >80% of patients, and CSF Gram's stain demonstrates organisms in >60%.

CSF glucose concentrations <2.2 mmol/L (<40 mg/dL) are abnormal, and a CSF glucose concentration of zero can be seen in bacterial meningitis. Use of the CSF/serum glucose ratio corrects for hyperglycemia that may mask a relative decrease in the CSF glucose concentration. The CSF glucose concentration is low when the CSF/serum glucose ratio is <0.6. A CSF/serum glucose ratio <0.4 is highly suggestive of bacterial meningitis, but may also be seen in other conditions, including fungal, tuberculous, and carcinomatous meningitis. It takes from 30 min to several hours for the concentration of CSF glucose to reach equilibrium with blood glucose levels; therefore, administration of 50 mL of 50% glucose (D50) prior to LP, as commonly occurs in emergency room settings, is unlikely to alter CSF glucose concentration significantly unless more than a few hours have elapsed between glucose administration and LP.

A 16S rRNA conserved sequence broad-based bacterial PCR can detect small numbers of viable and nonviable organisms in CSF and is expected to be useful for making a diagnosis of bacterial meningitis in patients who have been pretreated with oral or parenteral antibiotics and in whom Gram's stain and CSF culture are negative. When the broad-range PCR is positive, a PCR that uses specific bacterial primers to detect the nucleic acid of *S. pneumoniae, N. meningitidis, Escherichia coli, L. monocytogenes, H. influenzae*, and *S. agalactiae* can be obtained

TABLE 31-2

CEREBROSPINAL FLUID (CSF) ABNORMALITIES IN BACTERIAL MENINGITIS

Opening pressure	>180 mmH_2O
White blood cells	10/μL to 10,000/μL; neutrophils predominate
Red blood cells	Absent in nontraumatic tap
Glucose	<2.2 mmol/L (<40 mg/dL)
CSF/serum glucose	<0.4
Protein	>0.45 g/L (>45 mg/dL)
Gram's stain	Positive in >60%
Culture	Positive in >80%
Latex agglutination	May be positive in patients with meningitis due to *S. pneumoniae*, *N. meningitidis*, *H. influenzae* type b, *E. coli*, group B streptococci
Limulus lysate	Positive in cases of gram-negative meningitis
PCR	Detects bacterial DNA

Abbreviation: PCR, polymerase chain reaction.

based on the clinical suspicion of the meningeal pathogen. The latex agglutination (LA) test for the detection of bacterial antigens of *S. pneumoniae*, *N. meningitidis*, *H. influenzae* type b, group B *Streptococcus*, and *E. coli* K1 strains in the CSF has been useful for making a diagnosis of bacterial meningitis but is being replaced by the CSF bacterial PCR assay. The CSF LA test has a *specificity* of 95–100% for *S. pneumoniae* and *N. meningitidis*, so a positive test is virtually diagnostic of bacterial meningitis caused by these organisms. However, the *sensitivity* of the CSF LA test is only 70–100% for detection of *S. pneumoniae* and 33–70% for detection of *N. meningitidis* antigens, so a negative test does not exclude infection by these organisms. The Limulus amebocyte lysate assay is a rapid diagnostic test for the detection of gram-negative endotoxin in CSF and thus for making a diagnosis of gram-negative bacterial meningitis. The test has a specificity of 85–100% and a sensitivity approaching 100%. Thus, a positive Limulus amebocyte lysate assay occurs in virtually all patients with gram-negative bacterial meningitis, but false positives may occur.

Almost all patients with bacterial meningitis will have neuroimaging studies performed during the course of their illness. MRI is preferred over CT because of its superiority in demonstrating areas of cerebral edema and ischemia. In patients with bacterial meningitis, diffuse meningeal enhancement is often seen after the administration of gadolinium. Meningeal enhancement is not diagnostic of meningitis but occurs in any CNS disease associated with increased blood-brain barrier permeability.

Petechial skin lesions, if present, should be biopsied. The rash of meningococcemia results from the dermal seeding of organisms with vascular endothelial damage, and biopsy may reveal the organism on Gram's stain.

DIFFERENTIAL DIAGNOSIS

Viral meningoencephalitis, and particularly herpes simplex virus (HSV) encephalitis, can mimic the clinical presentation of bacterial meningitis (see "Viral Encephalitis," later in chapter). HSV encephalitis typically presents with headache, fever, altered consciousness, focal neurologic deficits (e.g., dysphasia, hemiparesis), and focal or generalized seizures. The findings on CSF studies, neuroimaging, and electroencephalogram (EEG) distinguish HSV encephalitis from bacterial meningitis. The typical CSF profile with viral CNS infections is a lymphocytic pleocytosis with a normal glucose concentration, in contrast to PMN pleocytosis and hypoglycorrhachia characteristic of bacterial meningitis. MRI abnormalities (other than meningeal enhancement) are not seen in uncomplicated bacterial meningitis. By contrast, in HSV encephalitis, on T2-weighted and fluid-attenuated inversion recovery (FLAIR) MRI images, high signal intensity lesions are seen in the orbitofrontal, anterior, and medial temporal lobes in the majority of patients within 48 h of symptom onset. Some patients with HSV encephalitis have a distinctive periodic pattern on EEG (see later).

Rickettsial disease can resemble bacterial meningitis (Chap. 79). Rocky Mountain spotted fever (RMSF) is transmitted by a tick bite and caused by the bacteria *Rickettsia rickettsii*. The disease may present acutely with high fever, prostration, myalgia, headache, nausea, and vomiting. Most patients develop a characteristic rash within 96 h of the onset of symptoms. The rash is initially a diffuse erythematous maculopapular rash that may be difficult to distinguish from that of meningococcemia. It progresses to a petechial rash, then to a purpuric rash and, if untreated, to skin necrosis or gangrene. The color of the lesions changes from bright red to very dark red, then yellowish-green to black. The rash typically begins in the wrist and ankles and then spreads distally and proximally within a matter of a few hours, involving the palms and soles. Diagnosis is made by immunofluorescent staining of skin biopsy specimens. Ehrlichioses are also transmitted by a tick bite. Two species of these small gram-negative coccobacilli cause human disease: *Anaplasma phagocytophilum* causes human granulocytic ehrlichiosis (anaplasmosis), and *Ehrlichia chaffeensis* causes human monocytic ehrlichiosis. The clinical and laboratory manifestations of the infections are similar. Patients present with fever, headache, nausea, and vomiting. Twenty percent of patients have a maculopapular or petechial rash. There is laboratory evidence of leukopenia, thrombocytopenia, and anemia, and there are mild to moderate elevations in alanine aminotransferases, alkaline phosphatase, and lactate dehydrogenase. Patients with RMSF and those with ehrlichial infections may have an altered level of consciousness ranging from mild lethargy to coma, confusion, focal neurologic signs, cranial nerve palsies, hyperreflexia, and seizures.

Focal suppurative CNS infections (see next), including subdural and epidural empyema and brain abscess, should also be considered, especially when focal neurologic findings are present. MRI should be performed promptly in all patients with suspected meningitis who have focal features, both to detect the intracranial infection and to search for associated areas of infection in the sinuses or mastoid bones.

A number of noninfectious CNS disorders can mimic bacterial meningitis. Subarachnoid hemorrhage (SAH) is generally the major consideration. Other possibilities include chemical meningitis due to rupture of tumor contents into the CSF (e.g., from a cystic glioma or craniopharyngioma epidermoid or dermoid cyst); drug-induced hypersensitivity meningitis; carcinomatous or lymphomatous meningitis; meningitis associated with inflammatory disorders such as sarcoid, systemic lupus erythematosus (SLE), and Behçet's syndrome; pituitary apoplexy; and uveomeningitic syndromes (Vogt-Koyanagi-Harada syndrome).

On occasion, subacutely evolving meningitis (Chap. 32) may be considered in the differential diagnosis of acute meningitis. The principal causes include *Mycobacterium tuberculosis* (Chap. 70), *Cryptococcus neoformans* (Chap. 109), *Histoplasma capsulatum* (Chap. 106), *Coccidioides immitis* (Chap. 107), and *Treponema pallidum* (Chap. 74).

TREATMENT Acute Bacterial Meningitis

EMPIRICAL ANTIMICROBIAL THERAPY

(Table 31-1) Bacterial meningitis is a medical emergency. The goal is to begin antibiotic therapy within 60 min of a patient's arrival in the emergency room. Empirical antimicrobial therapy is initiated in patients with suspected bacterial meningitis before the results of CSF Gram's stain and culture are known. *S. pneumoniae* (Chap. 37) and *N. meningitidis* (Chap. 48) are the most common etiologic organisms of community-acquired bacterial meningitis. Due to the emergence of penicillin- and cephalosporin-resistant *S. pneumoniae*, empirical therapy of suspected community-acquired bacterial meningitis in children and adults should include a combination of dexamethasone, a third- or fourth-generation cephalosporin (e.g., ceftriaxone, cefotaxime, or cefepime), and vancomycin as well as acyclovir, as HSV encephalitis is the leading disease in the differential diagnosis, and doxycycline during tick season to treat tick-borne bacterial infections. Ceftriaxone or cefotaxime provide good coverage for susceptible *S. pneumoniae*, group B streptococci, and *H. influenzae* and adequate coverage for *N. meningitidis*. Cefepime is a broad-spectrum fourth-generation cephalosporin with in vitro activity similar to that of cefotaxime or ceftriaxone against *S. pneumoniae* and *N. meningitidis* and greater activity against *Enterobacter* species and *Pseudomonas aeruginosa*. In clinical trials, cefepime has been demonstrated to be equivalent to cefotaxime in the treatment of penicillin-sensitive pneumococcal and meningococcal meningitis, and it has been used successfully in some patients with meningitis due to *Enterobacter* species and *P. aeruginosa*. Ampicillin should be added to the empirical regimen for coverage of *L. monocytogenes* in individuals <3 months of age, those >55, or those with suspected impaired cell-mediated immunity because of chronic illness, organ transplantation, pregnancy, malignancy, or immunosuppressive therapy. Metronidazole is added to the empirical regimen to cover gram-negative anaerobes in patients with otitis, sinusitis, or mastoiditis. In hospital-acquired meningitis, and particularly meningitis following neurosurgical procedures, staphylococci and gram-negative organisms including *P. aeruginosa* are the most common etiologic organisms. In these patients, empirical therapy should include a combination of vancomycin and ceftazidime, cefepime, or meropenem. Ceftazidime, cefepime, or meropenem should be substituted for ceftriaxone or cefotaxime in neurosurgical patients and in neutropenic patients, as ceftriaxone and cefotaxime do not provide adequate activity against CNS infection with *P. aeruginosa*. Meropenem is a carbapenem antibiotic that is highly active in vitro against *L. monocytogenes*, has been demonstrated to be effective in cases of meningitis caused by *P. aeruginosa*, and shows good activity against penicillin-resistant pneumococci. In experimental pneumococcal meningitis, meropenem was comparable to ceftriaxone and inferior to vancomycin in sterilizing CSF cultures. The number of patients with bacterial meningitis enrolled in clinical trials of meropenem has not been sufficient to definitively assess the efficacy of this antibiotic.

SPECIFIC ANTIMICROBIAL THERAPY

Meningococcal Meningitis (Table 31-3) Although ceftriaxone and cefotaxime provide adequate empirical coverage for *N. meningitidis*, penicillin G remains the antibiotic of choice for meningococcal meningitis caused by susceptible strains. Isolates of *N. meningitidis* with moderate resistance to penicillin have been identified, but patients infected with these strains have still been successfully treated with penicillin. CSF isolates of *N. meningitidis* should be tested for penicillin and ampicillin susceptibility, and if resistance is found, cefotaxime or ceftriaxone should be substituted for penicillin. A 7-day course of intravenous antibiotic therapy is adequate for uncomplicated meningococcal meningitis. The index case and all close contacts should receive chemoprophylaxis with a 2-day regimen of rifampin (600 mg every 12 h for 2 days in adults and 10 mg/kg every 12 h for 2 days in children >1 year). Rifampin is not recommended in pregnant women. Alternatively, adults can be treated with one dose of azithromycin (500 mg) or one intramuscular dose of ceftriaxone (250 mg). Close contacts are defined as those individuals who have had contact with oropharyngeal secretions, either through kissing or by sharing toys, beverages, or cigarettes.

Pneumococcal Meningitis Antimicrobial therapy of pneumococcal meningitis is initiated with a cephalosporin (ceftriaxone, cefotaxime, or cefepime) and vancomycin. All CSF isolates of *S. pneumoniae* should be tested

TABLE 31-3

ANTIMICROBIAL THERAPY OF CNS BACTERIAL INFECTIONS BASED ON PATHOGEN[a]

ORGANISM	ANTIBIOTIC
Neisseria meningitidis	
Penicillin-sensitive	Penicillin G or ampicillin
Penicillin-resistant	Ceftriaxone or cefotaxime
Streptococcus pneumoniae	
Penicillin-sensitive	Penicillin G
Penicillin-intermediate	Ceftriaxone or cefotaxime or cefepime
Penicillin-resistant	(Ceftriaxone or cefotaxime or cefepime) + vancomycin
Gram-negative bacilli (except *Pseudomonas* spp.)	Ceftriaxone or cefotaxime
Pseudomonas aeruginosa	Ceftazidime or cefepime or meropenem
Staphylococcus spp.	
Methicillin-sensitive	Nafcillin
Methicillin-resistant	Vancomycin
Listeria monocytogenes	Ampicillin + gentamicin
Haemophilus influenzae	Ceftriaxone or cefotaxime or cefepime
Streptococcus agalactiae	Penicillin G or ampicillin
Bacteroides fragilis	Metronidazole
Fusobacterium spp.	Metronidazole

[a]Doses are as indicated in Table 31-1.

for sensitivity to penicillin and the cephalosporins. Once the results of antimicrobial susceptibility tests are known, therapy can be modified accordingly (Table 31-3). For *S. pneumoniae* meningitis, an isolate of *S. pneumoniae* is considered to be susceptible to penicillin with a minimal inhibitory concentration (MIC) <0.06 μg/mL, to have intermediate resistance when the MIC is 0.1–1.0 μg/mL, and to be highly resistant when the MIC >1.0 μg/mL. Isolates of *S. pneumoniae* that have cephalosporin MICs ≤0.5 μg/mL are considered sensitive to the cephalosporins (cefotaxime, ceftriaxone, cefepime). Those with MICs of 1 μg/mL are considered to have intermediate resistance, and those with MICs ≥2 μg/mL are considered resistant. For meningitis due to pneumococci with cefotaxime or ceftriaxone MICs ≤0.5 μg/mL, treatment with cefotaxime or ceftriaxone is usually adequate; with an MIC >1 μg/mL, vancomycin is the antibiotic of choice. Rifampin can be added to vancomycin for its synergistic effect but is inadequate as monotherapy because resistance develops rapidly when it is used alone.

A 2-week course of intravenous antimicrobial therapy is recommended for pneumococcal meningitis.

Patients with *S. pneumoniae* meningitis should have a repeat LP performed 24–36 h after the initiation of antimicrobial therapy to document sterilization of the CSF. Failure to sterilize the CSF after 24–36 h of antibiotic therapy should be considered presumptive evidence of antibiotic resistance. Patients with penicillin- and cephalosporin-resistant strains of *S. pneumoniae* who do not respond to intravenous vancomycin alone may benefit from the addition of intraventricular vancomycin. The intraventricular route of administration is preferred over the intrathecal route because adequate concentrations of vancomycin in the cerebral ventricles are not always achieved with intrathecal administration.

Listerial Meningitis Meningitis due to *L. monocytogenes* is treated with ampicillin for at least 3 weeks (Table 31-3). Gentamicin is added in critically ill patients (2 mg/kg loading dose, then 7.5 mg/kg per day given every 8 h and adjusted for serum levels and renal function). The combination of trimethoprim (10–20 mg/kg per day) and sulfamethoxazole (50–100 mg/kg per day) given every 6 h may provide an alternative in penicillin-allergic patients.

Staphylococcal Meningitis Meningitis due to susceptible strains of *S. aureus* or coagulase-negative staphylococci is treated with nafcillin (Table 31-3). Vancomycin is the drug of choice for methicillin-resistant staphylococci and for patients allergic to penicillin. In these patients, the CSF should be monitored during therapy. If the CSF is not sterilized after 48 h of intravenous vancomycin therapy, then either intraventricular or intrathecal vancomycin, 20 mg once daily, can be added.

Gram-Negative Bacillary Meningitis The third-generation cephalosporins—cefotaxime, ceftriaxone, and ceftazidime—are equally efficacious for the treatment of gram-negative bacillary meningitis, with the exception of meningitis due to *P. aeruginosa*, which should be treated with ceftazidime, cefepime, or meropenem(Table 31-3). A 3-week course of intravenous antibiotic therapy is recommended for meningitis due to gram-negative bacilli.

ADJUNCTIVE THERAPY The release of bacterial cell-wall components by bactericidal antibiotics leads to the production of the inflammatory cytokines IL-1β and TNF-α in the subarachnoid space. Dexamethasone exerts its beneficial effect by inhibiting the synthesis of IL-1β and TNF-α at the level of mRNA, decreasing CSF outflow resistance, and stabilizing the blood-brain barrier. The rationale for giving dexamethasone 20 min before antibiotic therapy is that dexamethasone inhibits the production of TNF-α by macrophages and microglia only if it is administered before these cells are activated by endotoxin. Dexamethasone does not alter TNF-α production once it has been induced. The results of clinical trials of dexamethasone therapy in children, predominantly with meningitis due to *H. influenzae* and *S. pneumoniae*, have demonstrated its efficacy in decreasing meningeal inflammation and neurologic sequelae such as the incidence of sensorineural hearing loss.

A prospective European trial of adjunctive therapy for acute bacterial meningitis in 301 adults found that dexamethasone reduced the number of unfavorable outcomes (15 vs. 25%, $p = 0.03$), including death (7 vs. 15%, $p = 0.04$). The benefits were most striking in patients with pneumococcal meningitis. Dexamethasone (10 mg intravenously) was administered 15–20 min before the first dose of an antimicrobial agent, and the same dose was repeated every 6 h for 4 days. These results were confirmed in a second trial of dexamethasone in adults with pneumococcal meningitis. Therapy with dexamethasone should ideally be started 20 min before, or not later than concurrent with, the first dose of antibiotics. It is unlikely to be of significant benefit if started >6 h after antimicrobial therapy has been initiated. Dexamethasone may decrease the penetration of vancomycin into CSF, and it delays the sterilization of CSF in experimental models of *S. pneumoniae* meningitis. As a result, its potential benefit should be carefully weighed when vancomycin is the antibiotic of choice. Alternatively, vancomycin can be administered by the intraventricular route.

One of the concerns for using dexamethasone in adults with bacterial meningitis is that in experimental models of meningitis, dexamethasone therapy increased hippocampal cell injury and reduced learning capacity. This has not been the case in clinical series. The efficacy of dexamethasone therapy in preventing neurologic sequelae is different between high- and low-income countries. Three large randomized trials in low-income countries (sub-Saharan Africa, Southeast Asia) failed to show benefit in subgroups of patients. The lack of efficacy of dexamethasone in these trials has been attributed to late presentation to the hospital with more advanced disease, antibiotic pretreatment, malnutrition, infection with HIV, and treatment of patients with probable, but not microbiologically proven, bacterial meningitis. The results of these clinical trials suggest that

patients in sub-Saharan Africa and those in low-income countries with negative CSF Gram's stain and culture should not be treated with dexamethasone.

INCREASED INTRACRANIAL PRESSURE Emergency treatment of increased ICP includes elevation of the patient's head to 30–45°, intubation and hyperventilation (Pa_{co_2} 25–30 mm Hg), and mannitol. Patients with increased ICP should be managed in an intensive care unit; accurate ICP measurements are best obtained with an ICP monitoring device.

PROGNOSIS

Mortality rates are 3–7% for meningitis caused by *H. influenzae*, *N. meningitidis*, or group B streptococci; 15% for that due to *L. monocytogenes*; and 20% for *S. pneumoniae*. In general, the risk of death from bacterial meningitis increases with (1) decreased level of consciousness on admission, (2) onset of seizures within 24 h of admission, (3) signs of increased ICP, (4) young age (infancy) and age >50, (5) the presence of comorbid conditions including shock and/or the need for mechanical ventilation, and (6) delay in the initiation of treatment. Decreased CSF glucose concentration [<2.2 mmol/L (<40 mg/dL)] and markedly increased CSF protein concentration [>3 g/L (>300 mg/dL)] have been predictive of increased mortality and poorer outcomes in some series. Moderate or severe sequelae occur in ~25% of survivors, although the exact incidence varies with the infecting organism. Common sequelae include decreased intellectual function, memory impairment, seizures, hearing loss and dizziness, and gait disturbances.

ACUTE VIRAL MENINGITIS

CLINICAL MANIFESTATIONS

Immunocompetent adult patients with viral meningitis usually present with headache, fever, and signs of meningeal irritation coupled with an inflammatory CSF profile (see later in chapter). Headache is almost invariably present, is often characterized as frontal or retro-orbital, and is frequently associated with photophobia and pain on moving the eyes. Nuchal rigidity is present in most cases but may be mild and present only near the limit of neck anteflexion. Constitutional signs can include malaise, myalgia, anorexia, nausea and vomiting, abdominal pain, and/or diarrhea. Patients often have mild lethargy or drowsiness; however, profound alterations in consciousness, such as stupor, coma, or marked confusion do not occur in viral meningitis and suggest the presence of encephalitis or other alternative diagnoses. Similarly, seizures or focal neurologic signs or symptoms or neuroimaging abnormalities indicative of brain parenchymal involvement are not typical of viral meningitis and suggest the presence of encephalitis or another CNS infectious or inflammatory process.

ETIOLOGY

Using a variety of diagnostic techniques, including CSF PCR, culture, and serology, a specific viral cause can be found in 75–90% of cases of viral meningitis. The most important agents are enteroviruses (including echoviruses and coxsackieviruses in addition to numbered enteroviruses), HSV type 2 (HSV-2), HIV, and arboviruses **(Table 31-4)**. CSF cultures are positive in 30–70% of patients, the frequency of isolation depending on the specific viral agent. Approximately two-thirds of culture-negative cases of "aseptic" meningitis have a specific viral etiology identified by CSF PCR testing (see later).

EPIDEMIOLOGY

Viral meningitis is not a nationally reportable disease; however, it has been estimated that the incidence is ~75,000 cases per year. In temperate climates, there is a substantial increase in cases during the summer and early fall months, reflecting the seasonal predominance of enterovirus and arthropod-borne virus (arbovirus) infections, with a peak monthly incidence of about 1 reported case per 100,000 population.

LABORATORY DIAGNOSIS

CSF examination

The most important laboratory test in the diagnosis of viral meningitis is examination of the CSF. The typical profile is a lymphocytic pleocytosis (25–500 cells/μL),

TABLE 31-4

VIRUSES CAUSING ACUTE MENINGITIS AND ENCEPHALITIS IN NORTH AMERICA

ACUTE MENINGITIS

Common	Less Common
Enteroviruses (coxsackieviruses, echoviruses, and human enteroviruses 68–71)	Varicella-zoster virus
Herpes simplex virus 2	Epstein-Barr virus
Arthropod-borne viruses	Lymphocytic choriomeningitis virus
HIV	

ACUTE ENCEPHALITIS

Common	Less Common
Herpesviruses	Rabies virus
Herpes simplex virus 1	Eastern equine encephalitis virus
Varicella-zoster virus	Western equine encephalitis virus
Epstein-Barr virus	Powassan virus
Arthropod-borne viruses	Cytomegalovirus[a]
La Crosse virus	Enteroviruses[a]
West Nile virus	Colorado tick fever virus
St. Louis encephalitis virus	Mumps virus

[a]Immunocompromised host.

a normal or slightly elevated protein concentration [0.2–0.8 g/L (20–80 mg/dL)], a normal glucose concentration, and a normal or mildly elevated opening pressure (100–350 mmH_2O). Organisms are *not* seen on Gram's stain of CSF. Rarely, PMNs may predominate in the first 48 h of illness, especially with infections due to echovirus 9, West Nile virus, eastern equine encephalitis (EEE) virus, or mumps. A pleocytosis of polymorphonuclear neutrophils occurs in 45% of patients with West Nile virus (WNV) meningitis and can persist for a week or longer before shifting to a lymphocytic pleocytosis. Despite these exceptions, the presence of a CSF PMN pleocytosis in a patient with suspected viral meningitis in whom a specific diagnosis has not been established should prompt consideration of alternative diagnoses, including bacterial meningitis or parameningeal infections. The total CSF cell count in viral meningitis is typically 25–500/μL, although cell counts of several thousand/μL are occasionally seen, especially with infections due to lymphocytic choriomeningitis virus (LCMV) and mumps virus. The CSF glucose concentration is typically normal in viral infections, although it may be decreased in 10–30% of cases due to mumps virus or LCMV. Rare instances of decreased CSF glucose concentration occur in cases of meningitis due to echoviruses and other enteroviruses, HSV-2, and varicella-zoster virus (VZV). As a rule, a lymphocytic pleocytosis with a low glucose concentration should suggest fungal or tuberculous meningitis, *Listeria* meningoencephalitis, or noninfectious disorders (e.g., sarcoid, neoplastic meningitis).

A number of tests measuring levels of various CSF proteins, enzymes, and mediators—including C-reactive protein, lactic acid, lactate dehydrogenase, neopterin, quinolinate, IL-1β, IL-6, soluble IL-2 receptor, β_2-microglobulin, and TNF—have been proposed as potential discriminators between viral and bacterial meningitis or as markers of specific types of viral infection (e.g., infection with HIV), but they remain of uncertain sensitivity and specificity and are not widely used for diagnostic purposes.

Polymerase chain reaction amplification of viral nucleic acid

Amplification of viral-specific DNA or RNA from CSF by PCR has become the single most important method for diagnosing CNS viral infections. In both enteroviral and HSV infections of the CNS, PCR has become the diagnostic procedure of choice and is substantially more sensitive than viral cultures. HSV PCR is also an important diagnostic test in patients with recurrent episodes of "aseptic" meningitis, many of whom have amplifiable HSV DNA in CSF despite negative viral cultures. CSF PCR is also used routinely to diagnose CNS viral infections caused by cytomegalovirus (CMV), Epstein-Barr virus (EBV), VZV, and human herpesvirus 6 (HHV-6). CSF PCR tests are available for WNV but are not as sensitive as detection of WNV-specific CSF IgM. PCR is also useful in the diagnosis of CNS infection caused by *Mycoplasma pneumoniae,* which can mimic viral meningitis and encephalitis.

Viral culture

The sensitivity of CSF cultures for the diagnosis of viral meningitis and encephalitis, in contrast to its utility in bacterial infections, is generally poor. In addition to CSF, specific viruses may also be isolated from throat swabs, stool, blood, and urine. Enteroviruses and adenoviruses may be found in feces; arboviruses, some enteroviruses, and LCMV in blood; mumps virus and CMV in urine; and enteroviruses, mumps virus, and adenoviruses in throat washings. During enteroviral infections, viral shedding in stool may persist for several weeks. The presence of enterovirus in stool is not diagnostic and may result from residual shedding from a previous enteroviral infection; it also occurs in some asymptomatic individuals during enteroviral epidemics.

Serologic studies

For some viruses, including many arboviruses such as WNV, serologic studies remain a crucial diagnostic tool. Serum antibody determination is less useful for viruses with high seroprevalence rates in the general population, such as HSV, VZV, CMV, and EBV. For viruses with low seroprevalence rates, diagnosis of acute viral infection can be made by documenting seroconversion between acute-phase and convalescent sera (the latter typically obtained after 2–4 weeks) or by demonstrating the presence of virus-specific IgM antibodies. Documentation of synthesis of virus-specific antibodies in CSF, as shown by an increased IgG index or the presence of CSF IgM antibodies, is more useful than serum serology alone and can provide presumptive evidence of CNS infection. Although serum and CSF IgM antibodies generally persist for only a few months after acute infection, there are exceptions to this rule. For example, WNV IgM has been shown to persist in some patients for >1 year following acute infection. Unfortunately, the delay between onset of infection and the host's generation of a virus-specific antibody response often means that serologic data are useful mainly for the retrospective establishment of a specific diagnosis, rather than in aiding acute diagnosis or management.

CSF oligoclonal gamma globulin bands occur in association with a number of viral infections. The associated antibodies are often directed against viral proteins. Oligoclonal bands also occur commonly in certain noninfectious neurologic diseases (e.g., multiple sclerosis) and may be found in nonviral infections (e.g., neurosyphilis, Lyme neuroborreliosis).

Other laboratory studies

All patients with suspected viral meningitis should have a complete blood count and differential, liver and renal function tests, erythrocyte sedimentation rate (ESR), and C-reactive protein, electrolytes, glucose, creatine

kinase, aldolase, amylase, and lipase. Neuroimaging studies (MRI, CT) are not necessary in patients with uncomplicated viral meningitis but should be performed in patients with altered consciousness, seizures, focal neurologic signs or symptoms, or atypical CSF profiles.

DIFFERENTIAL DIAGNOSIS

The most important issue in the differential diagnosis of viral meningitis is to consider diseases that can mimic viral meningitis, including (1) untreated or partially treated bacterial meningitis; (2) early stages of meningitis caused by fungi, mycobacteria, or *Treponema pallidum* (neurosyphilis), in which a lymphocytic pleocytosis is common, cultures may be slow growing or negative, and hypoglycorrhachia may not be present early; (3) meningitis caused by agents such as *Mycoplasma*, *Listeria* spp., *Brucella* spp., *Coxiella* spp., *Leptospira* spp., and *Rickettsia* spp.; (4) parameningeal infections; (5) neoplastic meningitis; and (6) meningitis secondary to noninfectious inflammatory diseases, including hypersensitivity meningitis, SLE and other rheumatologic diseases, sarcoidosis, Behçet's syndrome, and the uveomeningitic syndromes. Studies in children >28 days of age suggest that the presence of CSF protein at >0.5 g/L (sensitivity 89%, specificity 78%) and elevated serum procalcitonin levels >0.5 ng/mL; (sensitivity 89%, specificity 89%) were clues to the presence of bacterial as opposed to "aseptic" meningitis. A variety of clinical algorithms for differentiating bacterial from aseptic meningitis have been promulgated, although none have been widely validated. One such prospectively validated system, the *bacterial meningitis score*, suggests that the probability of bacterial meningitis is 0.1% or less (negative predictive value 99.9%, 95% CI 99.6–100%) in children with CSF pleocytosis who have: (1) a negative CSF Gram's stain, (2) CSF neutrophil count <1000 cells/μL, (3) CSF protein <80 mg/dL, (4) peripheral absolute neutrophil count of <10,000 cells/μL, and (5) no prior history or current presence of seizures.

SPECIFIC VIRAL ETIOLOGIES

Enteroviruses (EV) (Chap. 97) are the most common cause of viral meningitis, accounting for >85% of cases in which a specific etiology can be identified. Cases may either be sporadic or occur in clusters. Recent outbreaks of EV meningitis in the United States have been associated with coxsackievirus B5 and echovirus strains 6, 9, and 30. Coxsackievirus strains A9, B3, and B4 are more commonly associated with individual cases. EV71 has produced large epidemics of neurologic disease outside the United States, especially in Southeast Asia, but most recently reported cases in the United States have been sporadic. Enteroviruses are the most likely cause of viral meningitis in the summer and fall months, especially in children (<15 years), although cases occur at reduced frequency year round. Although the incidence of enteroviral meningitis declines with increasing age, some outbreaks have preferentially affected older children and adults. Meningitis outside the neonatal period is usually benign. Patients present with sudden onset of fever; headache; nuchal rigidity; and often constitutional signs, including vomiting, anorexia, diarrhea, cough, pharyngitis, and myalgias. The physical examination should include a careful search for stigmata of enterovirus infection, including exanthems, hand-foot-and-mouth disease, herpangina, pleurodynia, myopericarditis, and hemorrhagic conjunctivitis. The CSF profile is typically a lymphocytic pleocytosis (100–1000 cells/μL) with normal glucose and normal or mildly elevated protein concentration. However, up to 15% of patients, most commonly young infants rather than older children or adults, have a normal CSF leukocyte count. In rare cases, PMNs may predominate during the first 48 h of illness. CSF reverse transcriptase PCR (RT-PCR) is the diagnostic procedure of choice and is both sensitive (>95%) and specific (>100%). CSF PCR has the highest sensitivity if performed within 48 h of symptom onset, with sensitivity declining rapidly after day 5 of symptoms. Treatment is supportive, and patients usually recover without sequelae. Chronic and severe infections can occur in neonates and in individuals with hypo- or agammaglobulinemia.

Arbovirus infections (Chap. 102) occur predominantly in the summer and early fall. Arboviral meningitis should be considered when clusters of meningitis and encephalitis cases occur in a restricted geographic region during the summer or early fall. In the United States the most important causes of arboviral meningitis and encephalitis are West Nile virus, St. Louis encephalitis virus, and the California encephalitis group of viruses. In WNV epidemics, avian deaths may serve as sentinel infections for subsequent human disease. A history of tick exposure or travel or residence in the appropriate geographic area should suggest the possibility of Colorado tick fever virus or Powassan virus infection, although nonviral tick-borne diseases, including RMSF and Lyme neuroborreliosis, may present similarly. Arbovirus meningoencephalitis is typically associated with a CSF lymphocytic pleocytosis, normal glucose concentration, and normal or mildly elevated protein concentration. However, 40–45% of patients with WNV meningoencephalitis have CSF neutrophilia, which can persist for a week or more. The rarity of hypoglycorrhachia in WNV infection as well as the absence of positive Gram's stains and the negative cultures help distinguish these patients from those with bacterial meningitis. The presence of increased numbers of plasmacytoid cells or Mollaret-like large mononuclear cells in the CSF may be a clue to the diagnosis of WNV infection. Definitive diagnosis of arboviral meningoencephalitis is based on demonstration of viral-specific IgM in CSF or seroconversion. CSF PCR tests are available for some viruses in selected diagnostic laboratories and at the Centers for Disease Control and Prevention (CDC), but in the case of WNV, sensitivity (~70%) of CSF PCR is less than that of CSF serology.

HSV-2 meningitis (Chap. 84) has been increasingly recognized as a major cause of viral meningitis in adults,

and overall it is probably second in importance to enteroviruses as a cause of viral meningitis, accounting for 5% of total cases overall and undoubtedly a higher frequency of those cases occurring in adults and/or outside of the summer-fall period when enterovirus infections are increasingly common. HSV meningitis occurs in ~25-35% of women and ~10-15% of men at the time of an initial (primary) episode of genital herpes. Of these patients, 20% go on to have recurrent attacks of meningitis. Diagnosis of HSV meningitis is usually by HSV CSF PCR as cultures may be negative, especially in patients with recurrent meningitis. Demonstration of intrathecal synthesis of HSV-specific antibody may also be useful in diagnosis, although antibody tests are less sensitive and less specific than PCR and may not become positive until after the first week of infection. In contrast to HSV encephalitis in adults, in whom >90% of cases are due to HSV-1, the overwhelming majority of HSV meningitis cases are due to HSV-2. Although a history of or the presence of HSV genital lesions is an important diagnostic clue, many patients with HSV meningitis give no history and have no evidence of active genital herpes at the time of presentation. Most cases of recurrent viral or "aseptic" meningitis, including cases previously diagnosed as Mollaret's meningitis, are likely due to HSV.

VZV meningitis (Chap. 85) should be suspected in the presence of concurrent chickenpox or shingles. However, it is important to recognize that in some series, up to 40% of VZV meningitis cases have been reported to occur in the absence of rash. The frequency of VZV as a cause of meningitis is extremely variable, ranging from as low as 3% to as high as 20% in different series. Diagnosis is usually based on CSF PCR, although the sensitivity of this test may not be as high as for the other herpesviruses. In patients with negative CSF PCR results, the diagnosis of VZV CNS infection can be made by the demonstration of VZV-specific intrathecal antibody synthesis and/or the presence of VZV CSF IgM antibodies, or by positive CSF cultures.

EBV infections (Chap. 86) may also produce aseptic meningitis, with or without associated infectious mononucleosis. The presence of atypical lymphocytes in the CSF or peripheral blood is suggestive of EBV infection but may occasionally be seen with other viral infections. EBV is almost never cultured from CSF. Serum and CSF serology can help establish the presence of acute infection, which is characterized by IgM viral capsid antibodies (VCAs), antibodies to early antigens (EAs), and the absence of antibodies to EBV-associated nuclear antigen (EBNA). CSF PCR is another important diagnostic test, although positive results may reflect viral reactivation associated with other infectious or inflammatory processes.

HIV meningitis should be suspected in any patient presenting with a viral meningitis with known or suspected risk factors for HIV infection. Meningitis may occur following primary infection with HIV in 5–10% of cases and less commonly at later stages of illness. Cranial nerve palsies, most commonly involving cranial nerves V, VII, or VIII, are more common in HIV meningitis than in other viral infections. Diagnosis can be confirmed by detection of HIV genome in blood or CSF. Seroconversion may be delayed, and patients with negative HIV serologies who are suspected of having HIV meningitis should be monitored for delayed seroconversion. For further discussion of HIV infection, see Chap. 93.

Mumps (Chap. 100) should be considered when meningitis occurs in the late winter or early spring, especially in males (male/female ratio 3:1). With the widespread use of the live attenuated mumps vaccine in the United States since 1967, the incidence of mumps meningitis has fallen by >95%; however, mumps remains a potential source of infection in nonimmunized individuals and populations. Rare cases (10–100:100,000 vaccinated individuals) of vaccine-associated mumps meningitis have been described, with onset typically 2–4 weeks after vaccination. The presence of parotitis, orchitis, oophoritis, pancreatitis, or elevations in serum lipase and amylase is suggestive of mumps meningitis; however, the absence of these abnormalities does not exclude the diagnosis. Clinical meningitis was previously estimated to occur in 10–30% of patients with mumps parotitis; however, in a recent U.S. outbreak of nearly 2600 cases of mumps, only 11 cases of meningitis were identified, suggesting that the incidence may be lower than previously suspected. Mumps infection confers lifelong immunity, so a documented history of previous infection excludes this diagnosis. Patients with meningitis have a CSF pleocytosis that can exceed 1000 cells/μL in 25%. Lymphocytes predominate in 75%, although CSF neutrophilia occurs in 25%. Hypoglycorrhachia, occurs in 10–30% of patients and may be a clue to the diagnosis when present. Diagnosis is typically made by culture of virus from CSF or by detecting IgM antibodies or seroconversion. CSF PCR is available in some diagnostic and research laboratories.

LCMV infection (Chap. 102) should be considered when aseptic meningitis occurs in the late fall or winter and in individuals with a history of exposure to house mice (*Mus musculus*), pet or laboratory rodents (e.g., hamsters, rats, mice), or their excreta. Some patients have an associated rash, pulmonary infiltrates, alopecia, parotitis, orchitis, or myopericarditis. Laboratory clues to the diagnosis of LCMV, in addition to the clinical findings noted earlier, may include the presence of leukopenia, thrombocytopenia, or abnormal liver function tests. Some cases present with a marked CSF pleocytosis (>1000 cells/μL) and hypoglycorrhachia (<30%). Diagnosis is based on serology and/or culture of virus from CSF.

TREATMENT Acute Viral Meningitis

Treatment of almost all cases of viral meningitis is primarily symptomatic and includes use of analgesics, antipyretics, and antiemetics. Fluid and electrolyte

status should be monitored. Patients with suspected bacterial meningitis should receive appropriate empirical therapy pending culture results (see earlier in chapter). Hospitalization may not be required in immunocompetent patients with presumed viral meningitis and no focal signs or symptoms, no significant alteration in consciousness, and a classic CSF profile (lymphocytic pleocytosis, normal glucose, negative Gram's stain) if adequate provision for monitoring at home and medical follow-up can be ensured. Immunocompromised patients; patients with significant alteration in consciousness, seizures, or the presence of focal signs and symptoms suggesting the possibility of encephalitis or parenchymal brain involvement; and those patients who have an atypical CSF profile should be hospitalized. Oral or intravenous acyclovir may be of benefit in patients with meningitis caused by HSV-1 or -2 and in cases of severe EBV or VZV infection. Data concerning treatment of HSV, EBV, and VZV meningitis are extremely limited. Seriously ill patients should probably receive intravenous acyclovir (15–30 mg/kg per day in three divided doses), which can be followed by an oral drug such as acyclovir (800 mg, five times daily), famciclovir (500 mg tid), or valacyclovir (1000 mg tid) for a total course of 7–14 days. Patients who are less ill can be treated with oral drugs alone. Patients with HIV meningitis should receive highly active antiretroviral therapy (Chap. 93).

Patients with viral meningitis who are known to have deficient humoral immunity (e.g., X-linked agammaglobulinemia) and who are not already receiving either intramuscular gamma globulin or intravenous immunoglobulin (IVIg) should be treated with these agents. Intraventricular administration of immunoglobulin through an Ommaya reservoir has been tried in some patients with chronic enteroviral meningitis who have not responded to intramuscular or intravenous immunoglobulin.

An investigational drug, pleconaril, has shown efficacy against a variety of enteroviral infections and has good oral bioavailability and excellent CNS penetration. Clinical trials in patients with enteroviral meningitis indicated that pleconaril decreased the duration of symptoms compared to placebo; however, the drug is not likely to be marketed and is not generally available due to its modest benefit in trials of non-CNS EV infections.

Vaccination is an effective method of preventing the development of meningitis and other neurologic complications associated with poliovirus, mumps, and measles infection. A live attenuated VZV vaccine (Varivax) is available in the United States. Clinical studies indicate an effectiveness rate of 70–90% for this vaccine, but a booster may be required to maintain immunity. An inactivated varicella vaccine is available for transplant recipients.

PROGNOSIS

In adults, the prognosis for full recovery from viral meningitis is excellent. Rare patients complain of persisting headache, mild mental impairment, incoordination, or generalized asthenia for weeks to months. The outcome in infants and neonates (<1 year) is less certain; intellectual impairment, learning disabilities, hearing loss, and other lasting sequelae have been reported in some studies.

VIRAL ENCEPHALITIS

DEFINITION

In contrast to viral meningitis, where the infectious process and associated inflammatory response are limited largely to the meninges, in encephalitis the brain parenchyma is also involved. Many patients with encephalitis also have evidence of associated meningitis (meningoencephalitis) and, in some cases, involvement of the spinal cord or nerve roots (encephalomyelitis, encephalomyeloradiculitis).

CLINICAL MANIFESTATIONS

In addition to the acute febrile illness with evidence of meningeal involvement characteristic of meningitis, the patient with encephalitis commonly has an altered level of consciousness (confusion, behavioral abnormalities), or a depressed level of consciousness ranging from mild lethargy to coma, and evidence of either focal or diffuse neurologic signs and symptoms. Patients with encephalitis may have hallucinations, agitation, personality change, behavioral disorders, and, at times, a frankly psychotic state. Focal or generalized seizures occur in many patients with encephalitis. Virtually every possible type of focal neurologic disturbance has been reported in viral encephalitis; the signs and symptoms reflect the sites of infection and inflammation. The most commonly encountered focal findings are aphasia, ataxia, upper or lower motor neuron patterns of weakness, involuntary movements (e.g., myoclonic jerks, tremor), and cranial nerve deficits (e.g., ocular palsies, facial weakness). Involvement of the hypothalamic-pituitary axis may result in temperature dysregulation, diabetes insipidus, or the development of the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). Even though neurotropic viruses typically cause pathologic injury in distinct regions of the CNS, variations in clinical presentations make it impossible to reliably establish the etiology of a specific case of encephalitis on clinical grounds alone (see "Differential Diagnosis," later in the chapter).

ETIOLOGY

In the United States, there are ~20,000 reported cases of encephalitis per year, although the actual number of cases is likely to be significantly larger. Despite comprehensive diagnostic efforts, the majority of cases of acute encephalitis of suspected viral etiology remain of unknown cause. Hundreds of viruses are capable of causing encephalitis, although only a limited subset is responsible for most cases in which a specific cause is identified (Table 31-4). The most commonly identified viruses causing sporadic cases of acute encephalitis in immunocompetent adults are herpesviruses (HSV,

VZV, EBV). Epidemics of encephalitis are caused by arboviruses that belong to several different viral taxonomic groups, including *Alphaviruses* (e.g., EEE virus, western equine encephalitis virus), *Flaviviruses* (e.g., WNV, St. Louis encephalitis virus, Japanese encephalitis virus, Powassan virus), and *Bunyaviruses* (e.g., California encephalitis virus serogroup, LaCrosse virus). Historically, the largest number of cases of arbovirus encephalitis in the United States has been due to St. Louis encephalitis virus and the California encephalitis virus serogroup. However, since 2002, WNV has been responsible for the majority of arbovirus meningitis and encephalitis cases in the United States. The 2003 epidemic was the largest epidemic of arboviral neuroinvasive disease (encephalitis + meningitis) ever recorded in the United States, with 2866 cases and 264 deaths. In 2004–2007, WNV accounted for between 1142 and 1459 confirmed cases of neuroinvasive disease per year in the United States and 100–177 deaths. In 2008 and 2009 there was an unexpected and dramatic decline in both the number of WNV neuroinvasive cases (2008 = 687, 2009 = 335) and the number of deaths (2008 = 44, 2009 = 30). New causes of viral CNS infections are constantly appearing, as evidenced by the recent outbreak of cases of encephalitis in Southeast Asia caused by Nipah virus, a newly identified member of the Paramyxoviridae family; of meningitis in Europe caused by Toscana virus, an arbovirus belonging to the Bunyavirus family; and of neurologic disorders associated with major epidemics of chikungunya virus, a togavirus, in Africa, India, and Southeast Asia.

LABORATORY DIAGNOSIS

CSF examination

CSF examination should be performed in all patients with suspected viral encephalitis unless contraindicated by the presence of severely increased ICP. The characteristic CSF profile is indistinguishable from that of viral meningitis and typically consists of a lymphocytic pleocytosis, a mildly elevated protein concentration, and a normal glucose concentration. A CSF pleocytosis (>5 cells/μL) occurs in >95% of immunocompetent patients with documented viral encephalitis. In rare cases, a pleocytosis may be absent on the initial LP but present on subsequent LPs. Patients who are severely immunocompromised by HIV infection, glucocorticoid or other immunosuppressant drugs, chemotherapy, or lymphoreticular malignancies may fail to mount a CSF inflammatory response. CSF cell counts exceed 500/μL in only about 10% of patients with encephalitis. Infections with certain arboviruses (e.g., EEE virus or California encephalitis virus), mumps virus, and LCMV may occasionally result in cell counts >1000/μL, but this degree of pleocytosis should suggest the possibility of nonviral infections or other inflammatory processes. Atypical lymphocytes in the CSF may be seen in EBV infection and less commonly with other viruses, including CMV, HSV, and enteroviruses. Increased numbers of plasmacytoid or Mollaret-like large mononuclear cells have been reported in WNV encephalitis. Polymorphonuclear pleocytosis occurs in ~45% of patients with WNV encephalitis and is also a common feature in CMV myeloradiculitis in immunocompromised patients. Large numbers of CSF PMNs may be present in patients with encephalitis due to EEE virus, echovirus 9, and, more rarely, other enteroviruses. However, persisting CSF neutrophilia should prompt consideration of bacterial infection, leptospirosis, amebic infection, and noninfectious processes such as acute hemorrhagic leukoencephalitis. About 20% of patients with encephalitis will have a significant number of red blood cells (>500/μL) in the CSF in a nontraumatic tap. The pathologic correlate of this finding may be a hemorrhagic encephalitis of the type seen with HSV; however, CSF red blood cells occur with similar frequency and in similar numbers in patients with nonherpetic focal encephalitides. A decreased CSF glucose concentration is distinctly unusual in viral encephalitis and should suggest the possibility of bacterial, fungal, tuberculous, parasitic, leptospiral, syphilitic, sarcoid, or neoplastic meningitis. Rare patients with mumps virus, LCMV, or advanced HSV encephalitis and many patients with CMV myeloradiculitis have low CSF glucose concentrations.

CSF PCR

CSF PCR has become the primary diagnostic test for CNS infections caused by CMV, EBV, HHV-6, and enteroviruses (see "Viral Meningitis," earlier in chapter). In the case of VZV CNS infection, CSF PCR and detection of virus-specific IgM or intrathecal antibody synthesis both provide important aids to diagnosis. The sensitivity and specificity of CSF PCRs varies with the virus being tested. In sensitivity (~96%) and specificity (~99%), HSV CSF PCR is equivalent or superior to brain biopsy. It is important to recognize that HSV CSF PCR results need to be interpreted after considering the likelihood of disease in the patient being tested, the timing of the test in relationship to onset of symptoms, and the prior use of antiviral therapy. A negative HSV CSF PCR test performed by a qualified laboratory at the appropriate time during illness in a patient with a high likelihood of HSV encephalitis based on clinical and laboratory abnormalities significantly reduces the likelihood of HSV encephalitis but does not exclude it. For example, in a patient with a pretest probability of 35% of having HSV encephalitis, a negative HSV CSF PCR reduces the posttest probability to ~2%, and for a patient with a pretest probability of 60%, a negative test reduces the posttest probability to ~6%. In both situations a positive test makes the diagnosis almost certain (98–99%). There have been several recent reports of initially negative HSV CSF PCR tests that were obtained early (≤72 h) following symptom onset and that became positive when repeated 1–3 days later. The frequency of positive HSV CSF PCRs in patients with herpes encephalitis also decreases as a function of the duration of illness, with only ~20% of cases remaining

positive after ≥14 days. PCR results are generally not affected by ≤1 week of antiviral therapy. In one study, 98% of CSF specimens remained PCR-positive during the first week of initiation of antiviral therapy, but the numbers fell to ~50% by 8–14 days and to ~21% by >15 days after initiation of antiviral therapy.

The sensitivity and specificity of CSF PCR tests for viruses other than herpes simplex have not been definitively characterized. Enteroviral CSF PCR appears to have a sensitivity and specificity of >95%. The specificity of EBV CSF PCR has not been established. Positive EBV CSF PCRs associated with positive tests for other pathogens have been reported and may reflect reactivation of EBV latent in lymphocytes that enter the CNS as a result of an unrelated infectious or inflammatory process. In patients with CNS infection due to VZV, CSF antibody and PCR studies should be considered complementary, as patients may have evidence of intrathecal synthesis of VZV-specific antibodies and negative CSF PCRs. In the case of WNV infection, CSF PCR appears to be less sensitive (~70% sensitivity) than detection of WNV-specific CSF IgM, although PCR testing remains useful in immunocompromised patients who may not mount an effective antibody response to WNV.

CSF culture

CSF culture is generally of limited utility in the diagnosis of acute viral encephalitis. Culture may be insensitive (e.g., >95% of patients with HSV encephalitis have negative CSF cultures as do virtually all patients with EBV-associated CNS disease) and often takes too long to significantly affect immediate therapy.

Serologic studies and antigen detection

The basic approach to the serodiagnosis of viral encephalitis is identical to that discussed earlier for viral meningitis. Demonstration of WNV IgM antibodies is diagnostic of WNV encephalitis as IgM antibodies do not cross the blood-brain barrier, and their presence in CSF is therefore indicative of intrathecal synthesis. Timing of antibody collection may be important as the rate of CSF WNV IgM seropositivity increases by ~10% per day during the first week after illness onset, reaching 80% or higher on day 7 after symptom onset. In patients with HSV encephalitis, both antibodies to HSV-1 glycoproteins and glycoprotein antigens have been detected in the CSF. Optimal detection of both HSV antibodies and antigen typically occurs after the first week of illness, limiting the utility of these tests in acute diagnosis. Nonetheless, HSV CSF antibody testing is of value in selected patients whose illness is >1 week in duration and who are CSF PCR–negative for HSV. In the case of VZV infection, CSF antibody tests may be positive when PCR fails to detect viral DNA, and both tests should be considered complementary rather than mutually exclusive.

MRI, CT, EEG

Patients with suspected encephalitis almost invariably undergo neuroimaging studies and often EEG. These tests help identify or exclude alternative diagnoses and assist in the differentiation between a focal, as opposed to a diffuse, encephalitic process. Focal findings in a patient with encephalitis should always raise the possibility of HSV encephalitis. Examples of focal findings include: (1) areas of increased signal intensity in the frontotemporal, cingulate, or insular regions of the brain on T2-weighted, FLAIR, or diffusion-weighted MRI **(Fig. 31-3)**; (2) focal areas of low absorption, mass effect, and contrast enhancement on CT; or (3) periodic focal temporal lobe spikes on a background of slow or low-amplitude ("flattened") activity on EEG. Approximately 10% of patients with PCR-documented HSV encephalitis will have a normal MRI, although nearly 80% will have abnormalities in the temporal lobe and an additional 10% in extratemporal regions. The lesions are typically hyperintense on T2-weighted images. The addition of FLAIR and diffusion-weighted images to the standard MRI sequences enhances sensitivity. Children with HSV encephalitis may have atypical patterns of MRI lesions and often show involvement of brain regions outside the frontotemporal areas. CT is less sensitive than MRI and is normal in up to 20–35% of patients. EEG abnormalities occur in >75% of PCR-documented cases of HSV encephalitis; they typically involve the temporal lobes but are often nonspecific. Some patients with HSV encephalitis have a distinctive EEG pattern consisting of periodic, stereotyped,

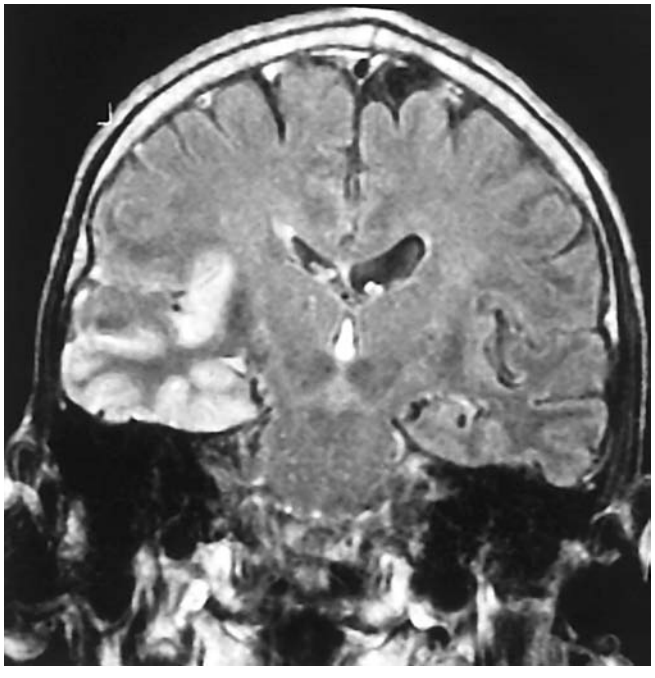


FIGURE 31-3
Coronal FLAIR magnetic resonance image from a patient with herpes simplex encephalitis. Note the area of increased signal in the right temporal lobe (*left side of image*) confined predominantly to the gray matter. This patient had predominantly unilateral disease; bilateral lesions are more common but may be quite asymmetric in their intensity.

sharp-and-slow complexes originating in one or both temporal lobes and repeating at regular intervals of 2–3 s. The periodic complexes are typically noted between days 2 and 15 of the illness and are present in two-thirds of pathologically proven cases of HSV encephalitis.

Significant MRI abnormalities are found in only ~two-thirds of patients with WNV encephalitis, a frequency less than that with HSV encephalitis. When present, abnormalities often involve deep brain structures, including the thalamus, basal ganglia, and brainstem, rather than the cortex and may only be apparent on FLAIR images. EEGs in patients with WNV encephalitis typically show generalized slowing that may be more anteriorly prominent rather than the temporally predominant pattern of sharp or periodic discharges more characteristic of HSV encephalitis. Patients with VZV encephalitis may show multifocal areas of hemorrhagic and ischemic infarction, reflecting the tendency of this virus to produce a CNS vasculopathy rather than a true encephalitis. Immunocompromised adult patients with CMV often have enlarged ventricles with areas of increased T2 signal on MRI outlining the ventricles and subependymal enhancement on T1-weighted post-contrast images. **Table 31-5** highlights specific diagnostic test results in encephalitis that can be useful in clinical decision-making.

Brain biopsy

Brain biopsy is now generally reserved for patients in whom CSF PCR studies fail to lead to a specific diagnosis, who have focal abnormalities on MRI, and who continue to show progressive clinical deterioration despite treatment with acyclovir and supportive therapy.

DIFFERENTIAL DIAGNOSIS

Infection by a variety of other organisms can mimic viral encephalitis. In studies of biopsy-proven HSV encephalitis, common infectious mimics of focal viral encephalitis included mycobacteria, fungi, rickettsiae, *Listeria, Mycoplasma,* and other bacteria (including *Bartonella* spp.).

Infection caused by the ameba *Naegleria fowleri* can also cause acute meningoencephalitis (primary amebic meningoencephalitis), whereas that caused by *Acanthamoeba* and *Balamuthia* more typically produces subacute or chronic granulomatous amebic meningoencephalitis. *Naegleria* thrive in warm, iron-rich pools of water, including those found in drains, canals, and both natural and human-made outdoor pools. Infection has typically occurred in immunocompetent children with a history of swimming in potentially infected water. The CSF, in contrast to the typical profile seen in viral encephalitis, often resembles that of bacterial meningitis with a neutrophilic pleocytosis and hypoglycorrhachia. Motile trophozoites can be seen in a wet mount of warm, fresh CSF. There have been an increasing number of cases of *Balamuthia mandrillaris* amebic encephalitis mimicking acute viral encephalitis in children and immunocompetent adults. This organism has also been associated with encephalitis in recipients of transplanted organs from a donor with unrecognized infection. No effective treatment has been identified, and mortality approaches 100%.

Encephalitis can be caused by the raccoon pinworm *Baylisascaris procyonis*. Clues to the diagnosis include a history of raccoon exposure, especially of playing in or

TABLE 31-5

USE OF DIAGNOSTIC TESTS IN ENCEPHALITIS

The best test for WNV encephalitis is the *CSF IgM antibody test*. The prevalence of positive CSF IgM tests increases by about 10% per day after illness onset and reaches 70–80% by the end of the first week. Serum WNV IgM can provide evidence for recent WNV infection, but in the absence of other findings does not establish the diagnosis of neuroinvasive disease (meningitis, encephalitis, acute flaccid paralysis).
Approximately 80% of patients with proven HSV encephalitis have *MRI* abnormalities involving the temporal lobes. This percentage likely increases to >90% when FLAIR and DWI MR sequences are also utilized. The absence of temporal lobe lesions on MR reduces the likelihood of HSV encephalitis and should prompt consideration of other diagnostic possibilities.
The *CSF HSV PCR* test may be negative in the first 72 h of symptoms of HSV encephalitis. A repeat study should be considered in patients with an initial early negative PCR in whom diagnostic suspicion of HSV encephalitis remains high and no alternative diagnosis has yet been established.
Detection of *intrathecal synthesis* (increased CSF/serum HSV antibody ratio corrected for breakdown of the blood-brain barrier) of *HSV-specific antibody* may be useful in diagnosis of HSV encephalitis in patients in whom only late (>1 week post-onset) CSF specimens are available and PCR studies are negative. Serum serology alone is of no value in diagnosis of HSV encephalitis due to the high seroprevalence rate in the general population.
Negative *CSF viral cultures* are of no value in excluding the diagnosis of HSV or EBV encephalitis.
VZV CSF IgM antibodies may be present in patients with a negative VZV CSF PCR. Both tests should be performed in patients with suspected VZV CNS disease.
The specificity of *EBV CSF PCR* for diagnosis of CNS infection is unknown. Positive tests may occur in patients with a CSF pleocytosis due to other causes. Detection of EBV CSF IgM or intrathecal synthesis of antibody to VCA supports the diagnosis of EBV encephalitis. *Serological studies* consistent with acute EBV infection (e.g., IgM VCA, presence of antibodies to EA, but not to EBNA) can help support the diagnosis.

Abbreviations: CNS, central nervous system; CSF, cerebrospinal fluid; DWI, diffusion-weighted imaging; EA, early antigen; EBNA, EBV-associated nuclear antigen; EBV, Epstein-Barr virus; FLAIR, fluid-attenuated inversion recovery; HSV, herpes simplex virus; IgM, immunoglobulin M; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; VCA, viral capsid antibody; VZV, varicella-zoster virus; WNV, West Nile virus.

eating dirt potentially contaminated with raccoon feces. Most patients are children, and many have an associated eosinophilia.

Once nonviral causes of encephalitis have been excluded, the major diagnostic challenge is to distinguish HSV from other viruses that cause encephalitis. This distinction is particularly important because in virtually every other instance the therapy is supportive, whereas specific and effective antiviral therapy is available for HSV, and its efficacy is enhanced when it is instituted early in the course of infection. HSV encephalitis should be considered when clinical features suggesting involvement of the inferomedial frontotemporal regions of the brain are present, including prominent olfactory or gustatory hallucinations, anosmia, unusual or bizarre behavior or personality alterations, or memory disturbance. HSV encephalitis should always be suspected in patients with signs and symptoms consistent with acute encephalitis with focal findings on clinical examination, neuroimaging studies, or EEG. The diagnostic procedure of choice in these patients is CSF PCR analysis for HSV. A positive CSF PCR establishes the diagnosis, and a negative test dramatically reduces the likelihood of HSV encephalitis (see earlier).

The anatomic distribution of lesions may provide an additional clue to diagnosis. Patients with rapidly progressive encephalitis and prominent brainstem signs, symptoms, or neuroimaging abnormalities may be infected by flaviviruses (WNV, St. Louis encephalitis virus, Japanese encephalitis virus), HSV, rabies virus, or *L. monocytogenes*. Significant involvement of deep gray matter structures, including the basal ganglia and thalamus, should also suggest possible flavivirus infection. These patients may present clinically with prominent movement disorders (tremor, myoclonus) or parkinsonian features. Patients with WNV infection can also present with a poliomyelitis-like acute flaccid paralysis, as can patients infected with enterovirus 71 and, less commonly, other enteroviruses. Acute flaccid paralysis is characterized by the acute onset of a lower motor neuron type of weakness with flaccid tone, reduced or absent reflexes, and relatively preserved sensation. Despite an aggressive World Health Organization poliovirus eradication initiative, 1733 cases of wild-type poliovirus-induced poliomyelitis were reported worldwide in 2009, with 73% occurring in India and Nigeria. There have been recent small outbreaks of poliomyelitis associated with vaccine strains of virus that have reverted to virulence through mutation or recombination with circulating wild-type enteroviruses in Hispaniola, China, the Philippines, Indonesia, Nigeria, and Madagascar.

Epidemiologic factors may provide important clues to the diagnosis of viral meningitis or encephalitis. Particular attention should be paid to the season of the year; the geographic location and travel history; and possible exposure to animal bites or scratches, rodents, and ticks. Although transmission from the bite of an infected dog remains the most common cause of rabies worldwide, in the United States very few cases of dog rabies occur, and the most common risk factor is exposure to bats—although a clear history of a bite or scratch is often lacking. The classic clinical presentation of encephalitic (furious) rabies is of fever, fluctuating consciousness, and autonomic hyperactivity. Phobic spasms of the larynx, pharynx, neck muscles, and diaphragm can be triggered by attempts to swallow water (*hydrophobia*) or by inspiration (*aerophobia*). Patients may also present with paralytic (dumb) rabies characterized by acute ascending paralysis. Rabies due to the bite of a bat has a different clinical presentation than classic rabies due to a dog or wolf bite. Patients present with focal neurologic deficits, myoclonus, seizures, and hallucinations; phobic spasms are not a typical feature. Patients with rabies have a CSF lymphocytic pleocytosis and may show areas of increased T2 signal abnormality in the brainstem, hippocampus, and hypothalamus. Diagnosis can be made by finding rabies virus antigen in brain tissue or in the neural innervation of hair follicles at the nape of the neck. PCR amplification of viral nucleic acid from CSF and saliva or tears may also enable diagnosis. Serology is frequently negative in both serum and CSF in the first week after onset of infection, which limits its acute diagnostic utility. No specific therapy is available, and cases are almost invariably fatal, with isolated survivors having devastating neurologic sequelae.

State public health authorities provide a valuable resource concerning isolation of particular agents in individual regions. Regular updates concerning the number, type, and distribution of cases of arboviral encephalitis can be found on the CDC and U.S. Geological Survey (USGS) websites (*http://www.cdc.gov* and *http://diseasemaps.usgs.gov*).

The major noninfectious etiologies that should be included in the differential diagnosis of acute encephalitis are nonvasculitic autoimmune inflammatory meningoencephalitis, which is frequently associated with serum antithyroid microsomal and antithyroglobulin antibodies (Hashimoto's encephalopathy); paraneoplastic and non-paraneoplastic encephalitis associated with antineuronal antibodies; acute disseminated encephalomyelitis and related fulminant demyelinating disorders); and lymphoma. Finally, Creutzfeldt-Jakob disease (Chap. 104) can rarely present in an explosive fashion mimicking viral encephalitis.

TREATMENT **Viral Encephalitis**

Specific antiviral therapy should be initiated when appropriate. Vital functions, including respiration and blood pressure, should be monitored continuously and supported as required. In the initial stages of encephalitis, many patients will require care in an intensive care unit. Basic management and supportive therapy should include careful monitoring of ICP, fluid restriction, avoidance of hypotonic intravenous solutions, and suppression of fever. Seizures should be treated with standard anticonvulsant regimens, and prophylactic therapy

should be considered in view of the high frequency of seizures in severe cases of encephalitis. As with all seriously ill, immobilized patients with altered levels of consciousness, encephalitis patients are at risk for aspiration pneumonia, stasis ulcers and decubiti, contractures, deep venous thrombosis and its complications, and infections of indwelling lines and catheters.

Acyclovir is of benefit in the treatment of HSV and should be started empirically in patients with suspected viral encephalitis, especially if focal features are present, while awaiting viral diagnostic studies. Treatment should be discontinued in patients found not to have HSV encephalitis, with the possible exception of patients with severe encephalitis due to VZV or EBV. HSV, VZV, and EBV all encode an enzyme, deoxypyrimidine (thymidine) kinase, that phosphorylates acyclovir to produce acyclovir-5′-monophosphate. Host cell enzymes then phosphorylate this compound to form a triphosphate derivative. It is the triphosphate that acts as an antiviral agent by inhibiting viral DNA polymerase and by causing premature termination of nascent viral DNA chains. The specificity of action depends on the fact that uninfected cells do not phosphorylate significant amounts of acyclovir to acyclovir-5′-monophosphate. A second level of specificity is provided by the fact that the acyclovir triphosphate is a more potent inhibitor of viral DNA polymerase than of the analogous host cell enzymes.

Adults should receive a dose of 10 mg/kg of acyclovir intravenously every 8 h (30 mg/kg per day total dose) for 14–21 days. CSF PCR can be repeated at the completion of this course, with PCR-positive patients receiving additional treatment followed by a repeat CSF PCR test. Neonatal HSV CNS infection is less responsive to acyclovir therapy than HSV encephalitis in adults; it is recommended that neonates with HSV encephalitis receive 20 mg/kg of acyclovir every 8 h (60 mg/kg per day, total dose) for a minimum of 21 days.

Prior to intravenous administration, acyclovir should be diluted to a concentration ≤7 mg/mL. (A 70-kg person would receive a dose of 700 mg, which would be diluted in a volume of 100 mL.) Each dose should be infused slowly over 1 h, rather than by rapid or bolus infusion, to minimize the risk of renal dysfunction. Care should be taken to avoid extravasation or intramuscular or subcutaneous administration. The alkaline pH of acyclovir can cause local inflammation and phlebitis (9%). Dose adjustment is required in patients with impaired renal glomerular filtration. Penetration into CSF is excellent, with average drug levels ~50% of serum levels. Complications of therapy include elevations in blood urea nitrogen and creatinine levels (5%), thrombocytopenia (6%), gastrointestinal toxicity (nausea, vomiting, diarrhea) (7%), and neurotoxicity (lethargy or obtundation, disorientation, confusion, agitation, hallucinations, tremors, seizures) (1%). Acyclovir resistance may be mediated by changes in either the viral deoxypyrimidine kinase or DNA polymerase. To date, acyclovir-resistant isolates have not been a significant clinical problem in immunocompetent individuals. However, there have been reports of clinically virulent acyclovir-resistant HSV isolates from sites outside the CNS in immunocompromised individuals, including those with AIDS.

Oral antiviral drugs with efficacy against HSV, VZV, and EBV, including acyclovir, famciclovir, and valacyclovir, have not been evaluated in the treatment of encephalitis either as primary therapy or as supplemental therapy following completion of a course of parenteral acyclovir. A National Institute of Allergy and Infectious Diseases (NIAID)/National Institute of Neurological Disorders and Stroke–sponsored phase III trial of supplemental oral valacyclovir therapy (2 g tid for 3 months) following the initial 14- to 21-day course of therapy with parenteral acyclovir is ongoing in patients with HSV encephalitis (*www.clinicaltrials.gov*, identifier NCT00031486); this may help clarify the role of extended oral antiviral therapy.

Ganciclovir and foscarnet, either alone or in combination, are often utilized in the treatment of CMV-related CNS infections, although their efficacy remains unproven. Cidofovir (see later) may provide an alternative in patients who fail to respond to ganciclovir and foscarnet, although data concerning its use in CMV CNS infections are extremely limited.

Ganciclovir is a synthetic nucleoside analogue of 2′-deoxyguanosine. The drug is preferentially phosphorylated by virus-induced cellular kinases. Ganciclovir triphosphate acts as a competitive inhibitor of the CMV DNA polymerase, and its incorporation into nascent viral DNA results in premature chain termination. Following intravenous administration, CSF concentrations of ganciclovir are 25–70% of coincident plasma levels. The usual dose for treatment of severe neurologic illnesses is 5 mg/kg every 12 h given intravenously at a constant rate over 1 h. Induction therapy is followed by maintenance therapy of 5 mg/kg every day for an indefinite period. Induction therapy should be continued until patients show a decline in CSF pleocytosis and a reduction in CSF CMV DNA copy number on quantitative PCR testing (where available). Doses should be adjusted in patients with renal insufficiency. Treatment is often limited by the development of granulocytopenia and thrombocytopenia (20–25%), which may require reduction in or discontinuation of therapy. Gastrointestinal side effects, including nausea, vomiting, diarrhea, and abdominal pain, occur in ~20% of patients. Some patients treated with ganciclovir for CMV retinitis have developed retinal detachment, but the causal relationship to ganciclovir treatment is unclear. Valganciclovir is an orally bioavailable prodrug that can generate high serum levels of ganciclovir, although studies of its efficacy in treating CMV CNS infections are limited.

Foscarnet is a pyrophosphate analogue that inhibits viral DNA polymerases by binding to the pyrophosphate-binding site. Following intravenous infusion, CSF concentrations range from 15 to 100% of coincident plasma levels. The usual dose for serious CMV-related

neurologic illness is 60 mg/kg every 8 h administered by constant infusion over 1 h. Induction therapy for 14–21 days is followed by maintenance therapy (60–120 mg/kg per day). Induction therapy may need to be extended in patients who fail to show a decline in CSF pleocytosis and a reduction in CSF CMV DNA copy number on quantitative PCR tests (where available). Approximately one-third of patients develop renal impairment during treatment, which is reversible following discontinuation of therapy in most, but not all, cases. This is often associated with elevations in serum creatinine and proteinuria and is less frequent in patients who are adequately hydrated. Many patients experience fatigue and nausea. Reduction in serum calcium, magnesium, and potassium occur in ~15% of patients and may be associated with tetany, cardiac rhythm disturbances, or seizures.

Cidofovir is a nucleotide analogue that is effective in treating CMV retinitis and equivalent to or better than ganciclovir in some experimental models of murine CMV encephalitis, although data concerning its efficacy in human CMV CNS disease are limited. The usual dose is 5 mg/kg intravenously once weekly for 2 weeks, then biweekly for two or more additional doses, depending on clinical response. Patients must be prehydrated with normal saline (e.g., 1 L over 1–2 h) prior to each dose and treated with probenecid (e.g., 1 g 3 h before cidofovir and 1 g 2 and 8 h after cidofovir). Nephrotoxicity is common; the dose should be reduced if renal function deteriorates.

Intravenous ribavirin (15–25 mg/kg per day in divided doses given every 8 h) has been reported to be of benefit in isolated cases of severe encephalitis due to California encephalitis (LaCrosse) virus. Ribavirin might be of benefit for the rare patients, typically infants or young children, with severe adenovirus or rotavirus encephalitis and for patients with encephalitis due to LCMV or other arenaviruses. However, clinical trials are lacking. Hemolysis, with resulting anemia, has been the major side effect limiting therapy.

No specific antiviral therapy of proven efficacy is currently available for treatment of WNV encephalitis. Patients have been treated with α-interferon, ribavirin, WNV-specific antisense oligonucleotides (*ClinicalTrials.gov*, identifier NCT0091845), an Israeli IVIg preparation that contains high-titer antibody to WNV (Omr-IgG-am) (*ClinicalTrials.gov*, identifier NCT00069316 and 0068055), and humanized monoclonal antibodies directed against the viral envelope glycoprotein (*ClinicalTrials.gov*, identifier NCT00927953 and 00515385). WNV chimeric vaccines, in which WNV envelope and premembrane proteins are inserted into the background of another flavivirus, are already undergoing human clinical testing for safety and immunogenicity (*ClinicalTrials.gov*, identifier NCT00746798 and 00442169). Both chimeric and killed inactivated WNV vaccines have been found to be safe and effective in preventing equine WNV infection, and several effective flavivirus vaccines are already in human use, creating optimism that a safe and effective human WNV vaccine can also be developed.

SEQUELAE

There is considerable variation in the incidence and severity of sequelae in patients surviving viral encephalitis. In the case of EEE virus infection, nearly 80% of survivors have severe neurologic sequelae. At the other extreme are infections due to EBV, California encephalitis virus, and Venezuelan equine encephalitis virus, where severe sequelae are unusual. For example, approximately 5–15% of children infected with LaCrosse virus have a residual seizure disorder, and 1% have persistent hemiparesis. Detailed information about sequelae in patients with HSV encephalitis treated with acyclovir is available from the NIAID-Collaborative Antiviral Study Group (CASG) trials. Of 32 acyclovir-treated patients, 26 survived (81%). Of the 26 survivors, 12 (46%) had no or only minor sequelae, 3 (12%) were moderately impaired (gainfully employed but not functioning at their previous level), and 11 (42%) were severely impaired (requiring continuous supportive care). The incidence and severity of sequelae were directly related to the age of the patient and the level of consciousness at the time of initiation of therapy. Patients with severe neurologic impairment (Glasgow coma score 6) at initiation of therapy either died or survived with severe sequelae. Young patients (<30 years) with good neurologic function at initiation of therapy did substantially better (100% survival, 62% with no or mild sequelae) compared with their older counterparts (>30 years; 64% survival, 57% no or mild sequelae). Some recent studies using quantitative HSV CSF PCR tests indicate that clinical outcome following treatment also correlates with the amount of HSV DNA present in CSF at the time of presentation. Many patients with WNV infection have sequelae, including cognitive impairment; weakness; and hyper- or hypokinetic movement disorders, including tremor, myoclonus, and parkinsonism. In a large longitudinal study of prognosis in 156 patients with WNV infection, the mean time to achieve recovery (defined as 95% of maximal predicted score on specific validated tests) was 112–148 days for fatigue, 121–175 days for physical function, 131–139 days for mood, and 302–455 days for mental function (the longer interval in each case representing patients with neuroinvasive disease).

SUBACUTE MENINGITIS

CLINICAL MANIFESTATIONS

Patients with subacute meningitis typically have an unrelenting headache, stiff neck, low-grade fever, and lethargy for days to several weeks before they present for evaluation. Cranial nerve abnormalities and night sweats may be present. This syndrome overlaps that of chronic meningitis, discussed in detail in Chap. 32.

ETIOLOGY

Common causative organisms include *M. tuberculosis*, *C. neoformans*, *H. capsulatum*, *C. immitis*, and *T. pallidum*. Initial infection with *M. tuberculosis* is acquired

by inhalation of aerosolized droplet nuclei. Tuberculous meningitis in adults does not develop acutely from hematogenous spread of tubercle bacilli to the meninges. Rather, millet seed–sized (miliary) tubercles form in the parenchyma of the brain during hematogenous dissemination of tubercle bacilli in the course of primary infection. These tubercles enlarge and are usually caseating. The propensity for a caseous lesion to produce meningitis is determined by its proximity to the subarachnoid space (SAS) and the rate at which fibrous encapsulation develops. Subependymal caseous foci cause meningitis via discharge of bacilli and tuberculous antigens into the SAS. Mycobacterial antigens produce an intense inflammatory reaction that leads to the production of a thick exudate that fills the basilar cisterns and surrounds the cranial nerves and major blood vessels at the base of the brain.

Fungal infections are typically acquired by the inhalation of airborne fungal spores. The initial pulmonary infection may be asymptomatic or present with fever, cough, sputum production, and chest pain. The pulmonary infection is often self-limited. A localized pulmonary fungal infection can then remain dormant in the lungs until there is an abnormality in cell-mediated immunity that allows the fungus to reactivate and disseminate to the CNS. The most common pathogen causing fungal meningitis is *C. neoformans*. This fungus is found worldwide in soil and bird excreta. *H. capsulatum* is endemic to the Ohio and Mississippi River valleys of the central United States and to parts of Central and South America. *C. immitis* is endemic to the desert areas of the southwest United States, northern Mexico, and Argentina.

Syphilis is a sexually transmitted disease that is manifest by the appearance of a painless chancre at the site of inoculation. *T. pallidum* invades the CNS early in the course of syphilis. Cranial nerves VII and VIII are most frequently involved.

LABORATORY DIAGNOSIS

The classic CSF abnormalities in tuberculous meningitis are as follows: (1) elevated opening pressure, (2) lymphocytic pleocytosis (10–500 cells/μL), (3) elevated protein concentration in the range of 1–5 g/L, and (4) decreased glucose concentration in the range of 1.1–2.2 mmol/L (20–40 mg/dL). *The combination of unrelenting headache, stiff neck, fatigue, night sweats, and fever with a CSF lymphocytic pleocytosis and a mildly decreased glucose concentration is highly suspicious for tuberculous meningitis.* The last tube of fluid collected at LP is the best tube to send for a smear for acid-fast bacilli (AFB). If there is a pellicle in the CSF or a cobweb-like clot on the surface of the fluid, AFB can best be demonstrated in a smear of the clot or pellicle. Positive smears are typically reported in only 10–40% of cases of tuberculous meningitis in adults. Cultures of CSF take 4–8 weeks to identify the organism and are positive in ~50% of adults. Culture remains the gold standard to make the diagnosis of tuberculous meningitis. PCR for the detection of *M. tuberculosis* DNA should be sent on CSF if available, but the sensitivity and specificity on CSF have not been defined. The Centers for Disease Control and Prevention recommend the use of nucleic acid amplification tests for the diagnosis of pulmonary tuberculosis.

The characteristic CSF abnormalities in fungal meningitis are a mononuclear or lymphocytic pleocytosis, an increased protein concentration, and a decreased glucose concentration. There may be eosinophils in the CSF in *C. immitis* meningitis. Large volumes of CSF are often required to demonstrate the organism on india ink smear or grow the organism in culture. If spinal fluid examined by LP on two separate occasions fails to yield an organism, CSF should be obtained by high-cervical or cisternal puncture.

The cryptococcal polysaccharide antigen test is a highly sensitive and specific test for cryptococcal meningitis. A reactive CSF cryptococcal antigen test establishes the diagnosis. The detection of the *Histoplasma* polysaccharide antigen in CSF establishes the diagnosis of a fungal meningitis, but is not specific for meningitis due to *H. capsulatum*. It may be falsely positive in coccidioidal meningitis. The CSF complement fixation antibody test is reported to have a specificity of 100% and a sensitivity of 75% for coccidioidal meningitis.

The diagnosis of syphilitic meningitis is made when a reactive serum treponemal test [fluorescent treponemal antibody absorption test (FTA-ABS) or microhemagglutination assay–*T. pallidum* (MHA-TP)] is associated with a CSF lymphocytic or mononuclear pleocytosis and an elevated protein concentration or when the CSF Venereal Disease Research Laboratory (VDRL) is positive. A reactive CSF FTA-ABS is not definitive evidence of neurosyphilis. The CSF FTA-ABS can be falsely positive from blood contamination. A negative CSF VDRL does not rule out neurosyphilis. A negative CSF FTA-ABS or MHA-TP rules out neurosyphilis.

TREATMENT Subacute Meningitis

Empirical therapy of tuberculous meningitis is often initiated on the basis of a high index of suspicion without adequate laboratory support. Initial therapy is a combination of isoniazid (300 mg/d), rifampin (10 mg/kg per day), pyrazinamide (30 mg/kg per day in divided doses), ethambutol (15–25 mg/kg per day in divided doses), and pyridoxine (50 mg/d). When the antimicrobial sensitivity of the *M. tuberculosis* isolate is known, ethambutol can be discontinued. If the clinical response is good, pyrazinamide can be discontinued after 8 weeks and isoniazid and rifampin continued alone for the next 6–12 months. A 6-month course of therapy is acceptable, but therapy should be prolonged for 9–12 months in patients who have an inadequate resolution of symptoms of meningitis or who have positive mycobacterial cultures of CSF during the course of therapy. Dexamethasone therapy is recommended for HIV-negative patients with tuberculous meningitis. The dose is 12–16 mg per day for 3 weeks, then tapered over 3 weeks.

Meningitis due to *C. neoformans* in non-HIV, nontransplant patients is treated with induction therapy with amphotericin B (AmB) (0.7 mg/kg IV per day) plus flucytosine (100 mg/kg per day in four divided doses) for at least 4 weeks if CSF culture results are negative after 2 weeks of treatment. Therapy should be extended for a total of 6 weeks in the patient with neurologic complications. Induction therapy is followed by consolidation therapy with fluconazole (400 mg per day) for 8 weeks. Organ transplant recipients are treated with liposomal AmB (3–4 mg/kg per day) or AmB lipid complex (ABLC) (5 mg/kg per day) plus flucytosine (100 mg/kg per day in four divided doses) for at least 2 weeks or until CSF culture is sterile. Follow CSF yeast cultures for sterilization rather than the cryptococcal antigen titer. This treatment is followed by an 8- to 10-week course of fluconazole [400–800 mg/d (6–12 mg/kg) PO]. If the CSF culture is sterile after 10 weeks of acute therapy, the dose of fluconazole is decreased to 200 mg/d for 6 months to a year. Patients with HIV infection are treated with AmB or a lipid formulation plus flucytosine for at least 2 weeks, followed by fluconazole for a minimum of 8 weeks. HIV-infected patients may require indefinite maintenance therapy with fluconazole (200 mg/d). Meningitis due to *H. capsulatum* is treated with AmB (0.7–1.0 mg/kg per day) for 4–12 weeks. A total dose of 30 mg/kg is recommended. Therapy with AmB is not discontinued until fungal cultures are sterile. After completing a course of AmB, maintenance therapy with itraconazole (200 mg twice daily) is initiated and continued for at least 6 months to a year. *C. immitis* meningitis is treated with either high-dose fluconazole (1000 mg daily) as monotherapy or intravenous AmB (0.5–0.7 mg/kg per day) for >4 weeks. Intrathecal AmB (0.25–0.75 mg/d three times weekly) may be required to eradicate the infection. Lifelong therapy with fluconazole (200–400 mg daily) is recommended to prevent relapse. AmBisome (5 mg/kg per day) or AmB lipid complex (5 mg/kg per day) can be substituted for AmB in patients who have or who develop significant renal dysfunction. The most common complication of fungal meningitis is hydrocephalus. Patients who develop hydrocephalus should receive a CSF diversion device. A ventriculostomy can be used until CSF fungal cultures are sterile, at which time the ventriculostomy is replaced by a ventriculoperitoneal shunt.

Syphilitic meningitis is treated with aqueous penicillin G in a dose of 3–4 million units intravenously every 4 h for 10–14 days. An alternative regimen is 2.4 million units of procaine penicillin G intramuscularly daily with 500 mg of oral probenecid four times daily for 10–14 days. Either regimen is followed with 2.4 million units of benzathine penicillin G intramuscularly once a week for 3 weeks. The standard criterion for treatment success is reexamination of the CSF. The CSF should be reexamined at 6-month intervals for 2 years. The cell count is expected to normalize within 12 months and the VDRL titer to decrease by two dilutions or revert to nonreactive within 2 years of completion of therapy. Failure of the CSF pleocytosis to resolve or an increase in the CSF VDRL titer by two or more dilutions requires retreatment.

CHRONIC ENCEPHALITIS

PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

Clinical features and pathology

Progressive multifocal leukoencephalopathy (PML) is characterized pathologically by multifocal areas of demyelination of varying size distributed throughout the brain but sparing the spinal cord and optic nerves. In addition to demyelination, there are characteristic cytologic alterations in both astrocytes and oligodendrocytes. Astrocytes are enlarged and contain hyperchromatic, deformed, and bizarre nuclei and frequent mitotic figures. Oligodendrocytes have enlarged, densely staining nuclei that contain viral inclusions formed by crystalline arrays of JC virus (JCV) particles. Patients often present with visual deficits (45%), typically a homonymous hemianopia; mental impairment (38%) (dementia, confusion, personality change); weakness, including hemi- or monoparesis; and ataxia. Seizures occur in ~20% of patients, predominantly in those with lesions abutting the cortex.

Almost all patients have an underlying immunosuppressive disorder. In recent series, the most common associated conditions were AIDS (80%), hematologic malignancies (13%), transplant recipients (5%), and chronic inflammatory diseases (2%). It has been estimated that up to 5% of AIDS patients will develop PML. There have been more than 30 reported cases of PML occurring in patients being treated for multiple sclerosis and inflammatory bowel disease with natalizumab, a humanized monoclonal antibody that inhibits lymphocyte trafficking into CNS and bowel mucosa by binding to α_4 integrins. Risk in these patients has been estimated at 1 PML case per 1000 treated patients after a mean of 18 months of therapy. Additional cases have been reported in patients receiving other humanized monoclonal antibodies with immunomodulatory activity, including efalizumab and rituximab. The basic clinical and diagnostic features appear to be similar to those seen in PML related to HIV and other forms of immunosuppression.

Diagnostic studies

The diagnosis of PML is frequently suggested by MRI. MRI reveals multifocal asymmetric, coalescing white matter lesions located periventricularly, in the centrum semiovale, in the parietal-occipital region, and in the cerebellum. These lesions have increased signal on T2 and FLAIR images and decreased signal on T1-weighted images. PML lesions are classically nonenhancing (90%) but may rarely show ring enhancement, especially in

more immunocompetent patients. PML lesions are not typically associated with edema or mass effect. CT scans, which are less sensitive than MRI for the diagnosis of PML, often show hypodense nonenhancing white matter lesions.

The CSF is typically normal, although mild elevation in protein and/or IgG may be found. Pleocytosis occurs in <25% of cases, is predominantly mononuclear, and rarely exceeds 25 cells/μL. PCR amplification of JCV DNA from CSF has become an important diagnostic tool. The presence of a positive CSF PCR for JCV DNA in association with typical MRI lesions in the appropriate clinical setting is diagnostic of PML, reflecting the assay's relatively high specificity (92–100%); however, sensitivity is variable and a negative CSF PCR does not exclude the diagnosis. In HIV-negative patients and HIV-positive patients not receiving highly active antiviral therapy (HAART), sensitivity is likely 70–90%. In HAART-treated patients, sensitivity may be closer to 60%, reflecting the lower JCV CSF viral load in this relatively immunocompetent group. Studies with quantitative JCV CSF PCR indicate that patients with low JCV loads (<100 copies/μL) have a generally better prognosis than those with higher viral loads. Patients with negative CSF PCR studies may require brain biopsy for definitive diagnosis. In biopsy or necropsy specimens of brain, JCV antigen and nucleic acid can be detected by immunocytochemistry, in situ hybridization, or PCR amplification. Detection of JCV antigen or genomic material should be considered diagnostic of PML only if accompanied by characteristic pathologic changes, since both antigen and genomic material have been found in the brains of normal patients.

Serologic studies are of no utility in diagnosis due to high basal seroprevalence level (>80%).

TREATMENT **Progressive Multifocal Leukoencephalopathy**

No effective therapy for PML is available. There are case reports of potential beneficial effects of the 5-HT2a receptor antagonist mirtazapine, which may inhibit binding of JCV to its receptor on oligodendrocytes. Retrospective noncontrolled studies have also suggested a possible beneficial effect of treatment with interferon-alpha. Neither of these agents has been tested in randomized controlled clinical trials. A clinical trial to evaluate the efficacy of the antimalarial drug mefloquine, which inhibits JCV replication in cell culture, is underway (*www.clinicaltrials.gov*, identifier NCT00746941). Intravenous and/or intrathecal cytarabine was not shown to be of benefit in a randomized controlled trial in HIV-associated PML, although some experts suggest that cytarabine may have therapeutic efficacy in situations where breakdown of the blood-brain barrier allows sufficient CSF penetration. A randomized controlled trial of cidofovir in HIV-associated PML also failed to show significant benefit. Since PML almost invariably occurs in immunocompromised individuals, any therapeutic interventions designed to enhance or restore immunocompetence should be considered. Perhaps the most dramatic demonstration of this is disease stabilization and, in rare cases, improvement associated with the improvement in the immune status of HIV-positive patients with AIDS following institution of HAART. In HIV-positive PML patients receiving HAART, 1-year survival is ~50%, although up to 80% of survivors may have significant neurologic sequelae. HIV-positive PML patients with higher CD4 counts (>300/μL) and low or nondetectable HIV viral loads have a better prognosis than those with lower CD4 counts and higher viral loads. Although institution of HAART enhances survival in HIV + PML patients, the associated immune reconstitution in patients with an underlying opportunistic infection such as PML may also result in a severe CNS inflammatory syndrome [immune reconstitution inflammatory syndrome (IRIS)] associated with clinical worsening, CSF pleocytosis, and the appearance of new enhancing MRI lesions. Patients receiving natalizumab or other immunomodulatory antibodies who are suspected of having PML should have therapy halted and circulating antibodies removed by plasma exchange.

SUBACUTE SCLEROSING PANENCEPHALITIS (SSPE)

SSPE is a rare chronic, progressive demyelinating disease of the CNS associated with a chronic nonpermissive infection of brain tissue with measles virus. The frequency has been estimated at 1 in 100,000–500,000 measles cases. An average of five cases per year are reported in the United States. The incidence has declined dramatically since the introduction of a measles vaccine. Most patients give a history of primary measles infection at an early age (2 years), which is followed after a latent interval of 6–8 years by the development of a progressive neurologic disorder. Some 85% of patients are between 5 and 15 years old at diagnosis. Initial manifestations include poor school performance and mood and personality changes. Typical signs of a CNS viral infection, including fever and headache, do not occur. As the disease progresses, patients develop progressive intellectual deterioration, focal and/or generalized seizures, myoclonus, ataxia, and visual disturbances. In the late stage of the illness, patients are unresponsive, quadriparetic, and spastic, with hyperactive tendon reflexes and extensor plantar responses.

Diagnostic studies

MRI is often normal early, although areas of increased T2 signal develop in the white matter of the brain and brainstem as disease progresses. The EEG may initially show only nonspecific slowing, but with disease progression, patients develop a characteristic periodic pattern with bursts of high-voltage, sharp, slow waves every 3–8 s, followed by periods of attenuated ("flat") background. The CSF is acellular with a normal or mildly elevated protein concentration and a markedly elevated

gamma globulin level (>20% of total CSF protein). CSF measles antibody levels are invariably elevated, and oligoclonal measles antibodies are often present. Measles virus can be cultured from brain tissue using special cocultivation techniques. Viral antigen can be identified immunocytochemically, and viral genome can be detected by in situ hybridization or PCR amplification.

TREATMENT **Subacute Sclerosing Panencephalitis**

No definitive therapy for SSPE is available. Treatment with isoprinosine (Inosiplex, 100 mg/kg per day), alone or in combination with intrathecal or intraventricular alpha interferon, has been reported to prolong survival and produce clinical improvement in some patients, but has never been subjected to a controlled clinical trial.

PROGRESSIVE RUBELLA PANENCEPHALITIS

This is an extremely rare disorder that primarily affects males with congenital rubella syndrome, although isolated cases have been reported following childhood rubella. After a latent period of 8–19 years, patients develop progressive neurologic deterioration. The manifestations are similar to those seen in SSPE. CSF shows a mild lymphocytic pleocytosis, slightly elevated protein concentration, markedly increased gamma globulin, and rubella virus–specific oligoclonal bands. No therapy is available. Universal prevention of both congenital and childhood rubella through the use of the available live attenuated rubella vaccine would be expected to eliminate the disease.

BRAIN ABSCESS

DEFINITION

A brain abscess is a focal, suppurative infection within the brain parenchyma, typically surrounded by a vascularized capsule. The term *cerebritis* is often employed to describe a nonencapsulated brain abscess.

EPIDEMIOLOGY

A bacterial brain abscess is a relatively uncommon intracranial infection, with an incidence of ~0.3–1.3:100,000 persons per year. Predisposing conditions include otitis media and mastoiditis, paranasal sinusitis, pyogenic infections in the chest or other body sites, penetrating head trauma or neurosurgical procedures, and dental infections. In immunocompetent individuals the most important pathogens are *Streptococcus* spp. [anaerobic, aerobic, and viridans (40%)], Enterobacteriaceae [*Proteus* spp., *E. coli*, *Klebsiella* spp. (25%)], anaerobes [e.g., *Bacteroides* spp., *Fusobacterium* spp. (30%)], and staphylococci (10%). In immunocompromised hosts with underlying HIV infection, organ transplantation, cancer, or immunosuppressive therapy, most brain abscesses are caused by *Nocardia* spp., *Toxoplasma gondii*, *Aspergillus* spp., *Candida* spp., and *C. neoformans*. In Latin America and in immigrants from Latin America, the most common cause of brain abscess is *Taenia solium* (neurocysticercosis). In India and the Far East, mycobacterial infection (tuberculoma) remains a major cause of focal CNS mass lesions.

ETIOLOGY

A brain abscess may develop (1) by direct spread from a contiguous cranial site of infection, such as paranasal sinusitis, otitis media, mastoiditis, or dental infection; (2) following head trauma or a neurosurgical procedure; or (3) as a result of hematogenous spread from a remote site of infection. In up to 25% of cases, no obvious primary source of infection is apparent (cryptogenic brain abscess).

Approximately one-third of brain abscesses are associated with otitis media and mastoiditis, often with an associated cholesteatoma. Otogenic abscesses occur predominantly in the temporal lobe (55–75%) and cerebellum (20–30%). In some series, up to 90% of cerebellar abscesses are otogenic. Common organisms include streptococci, *Bacteroides* spp., *Pseudomonas* spp., *Haemophilus* spp., and Enterobacteriaceae. Abscesses that develop as a result of direct spread of infection from the frontal, ethmoidal, or sphenoidal sinuses and those that occur due to dental infections are usually located in the frontal lobes. Approximately 10% of brain abscesses are associated with paranasal sinusitis, and this association is particularly strong in young males in their second and third decades of life. The most common pathogens in brain abscesses associated with paranasal sinusitis are streptococci (especially *S. milleri*), *Haemophilus* spp., *Bacteroides* spp., *Pseudomonas* spp., and *S. aureus*. Dental infections are associated with ~2% of brain abscesses, although it is often suggested that many "cryptogenic" abscesses are in fact due to dental infections. The most common pathogens in this setting are streptococci, staphylococci, *Bacteroides* spp., and *Fusobacterium* spp.

Hematogenous abscesses account for ~25% of brain abscesses. Hematogenous abscesses are often multiple, and multiple abscesses often (50%) have a hematogenous origin. These abscesses show a predilection for the territory of the middle cerebral artery (i.e., posterior frontal or parietal lobes). Hematogenous abscesses are often located at the junction of the gray and white matter and are often poorly encapsulated. The microbiology of hematogenous abscesses is dependent on the primary source of infection. For example, brain abscesses that develop as a complication of infective endocarditis are often due to viridans streptococci or *S. aureus*. Abscesses associated with pyogenic lung infections such as lung abscess or bronchiectasis are often due to streptococci, staphylococci, *Bacteroides* spp., *Fusobacterium* spp., or Enterobacteriaceae. Abscesses that follow penetrating head trauma or neurosurgical procedures are frequently due to methicillin-resistant *S. aureus* (MRSA), *S. epidermidis*, Enterobacteriaceae,

Pseudomonas spp., and *Clostridium* spp. Enterobacteriaceae and *P. aeruginosa* are important causes of abscesses associated with urinary sepsis. Congenital cardiac malformations that produce a right-to-left shunt, such as tetralogy of Fallot, patent ductus arteriosus, and atrial and ventricular septal defects, allow bloodborne bacteria to bypass the pulmonary capillary bed and reach the brain. Similar phenomena can occur with pulmonary arteriovenous malformations. The decreased arterial oxygenation and saturation from the right-to-left shunt and polycythemia may cause focal areas of cerebral ischemia, thus providing a nidus for microorganisms that bypassed the pulmonary circulation to multiply and form an abscess. Streptococci are the most common pathogens in this setting.

PATHOGENESIS AND HISTOPATHOLOGY

Results of experimental models of brain abscess formation suggest that for bacterial invasion of brain parenchyma to occur, there must be preexisting or concomitant areas of ischemia, necrosis, or hypoxemia in brain tissue. The intact brain parenchyma is relatively resistant to infection. Once bacteria have established infection, brain abscess frequently evolves through a series of stages, influenced by the nature of the infecting organism and by the immunocompetence of the host. The early cerebritis stage (days 1–3) is characterized by a perivascular infiltration of inflammatory cells, which surround a central core of coagulative necrosis. Marked edema surrounds the lesion at this stage. In the late cerebritis stage (days 4–9), pus formation leads to enlargement of the necrotic center, which is surrounded at its border by an inflammatory infiltrate of macrophages and fibroblasts. A thin capsule of fibroblasts and reticular fibers gradually develops, and the surrounding area of cerebral edema becomes more distinct than in the previous stage. The third stage, early capsule formation (days 10–13), is characterized by the formation of a capsule that is better developed on the cortical than on the ventricular side of the lesion. This stage correlates with the appearance of a ring-enhancing capsule on neuroimaging studies. The final stage, late capsule formation (day 14 and beyond), is defined by a well-formed necrotic center surrounded by a dense collagenous capsule. The surrounding area of cerebral edema has regressed, but marked gliosis with large numbers of reactive astrocytes has developed outside the capsule. This gliotic process may contribute to the development of seizures as a sequelae of brain abscess.

CLINICAL PRESENTATION

A brain abscess typically presents as an expanding intracranial mass lesion rather than as an infectious process. Although the evolution of signs and symptoms is extremely variable, ranging from hours to weeks or even months, most patients present to the hospital 11–12 days following onset of symptoms. The classic clinical triad of headache, fever, and a focal neurologic deficit is present in <50% of cases. The most common symptom in patients with a brain abscess is headache, occurring in >75% of patients. The headache is often characterized as a constant, dull, aching sensation, either hemicranial or generalized, and it becomes progressively more severe and refractory to therapy. Fever is present in only 50% of patients at the time of diagnosis, and its absence should not exclude the diagnosis. The new onset of focal or generalized seizure activity is a presenting sign in 15–35% of patients. Focal neurologic deficits, including hemiparesis, aphasia, or visual field defects, are part of the initial presentation in >60% of patients.

The clinical presentation of a brain abscess depends on its location, the nature of the primary infection if present, and the level of ICP. Hemiparesis is the most common localizing sign of a frontal lobe abscess. A temporal lobe abscess may present with a disturbance of language (dysphasia) or an upper homonymous quadrantanopia. Nystagmus and ataxia are signs of a cerebellar abscess. Signs of raised ICP—papilledema, nausea and vomiting, and drowsiness or confusion—can be the dominant presentation of some abscesses, particularly those in the cerebellum. Meningismus is not present unless the abscess has ruptured into the ventricle or the infection has spread to the subarachnoid space.

DIAGNOSIS

Diagnosis is made by neuroimaging studies. MRI **(Fig. 31-4)** is better than CT for demonstrating abscesses in the early (cerebritis) stages and is superior to CT for identifying abscesses in the posterior fossa. Cerebritis appears on MRI as an area of low signal intensity on T1-weighted images with irregular postgadolinium enhancement and as an area of increased signal intensity on T2-weighted images. Cerebritis is often not visualized by CT scan but, when present, appears as an area of hypodensity. On a contrast-enhanced CT scan, a mature brain abscess appears as a focal area of hypodensity surrounded by ring enhancement with surrounding edema (hypodensity). On contrast-enhanced T1-weighted MRI, a mature brain abscess has a capsule that enhances surrounding a hypodense center and surrounded by a hypodense area of edema. On T2-weighted MRI, there is a hyperintense central area of pus surrounded by a well-defined hypointense capsule and a hyperintense surrounding area of edema. It is important to recognize that the CT and MRI appearance, particularly of the capsule, may be altered by treatment with glucocorticoids. The distinction between a brain abscess and other focal CNS lesions such as primary or metastatic tumors may be facilitated by the use of diffusion-weighted imaging sequences on which brain abscesses typically show increased signal due to restricted diffusion.

Microbiologic diagnosis of the etiologic agent is most accurately determined by Gram's stain and culture of abscess material obtained by CT-guided stereotactic needle aspiration. Aerobic and anaerobic bacterial cultures and mycobacterial and fungal cultures should be obtained.

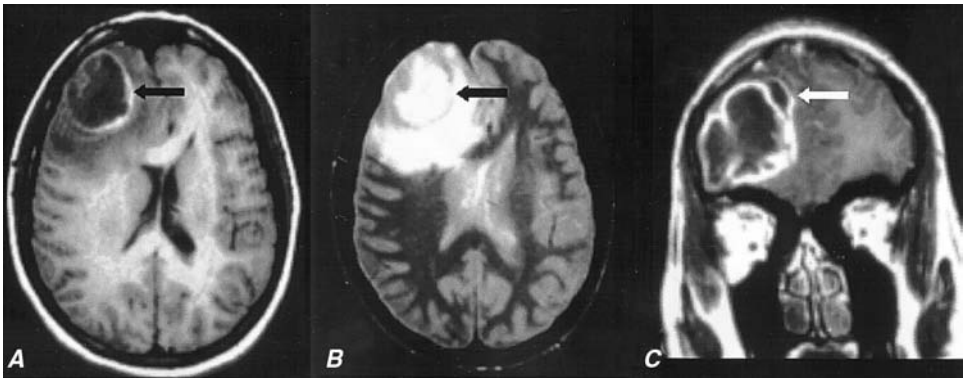


FIGURE 31-4
Pneumococcal brain abscess. Note that the abscess wall has hyperintense signal on the axial T1-weighted MRI (***A***, *black arrow*), has hypointense signal on the axial proton density images (***B***, *black arrow*), and enhances prominently after gadolinium administration on the coronal T1-weighted image (***C***). The abscess is surrounded by a large amount of vasogenic edema and has a small "daughter" abscess (***C***, *white arrow*). (*Courtesy of Joseph Lurito, MD; with permission*.)

Up to 10% of patients will also have positive blood cultures. LP should not be performed in patients with known or suspected focal intracranial infections such as abscess or empyema; CSF analysis contributes nothing to diagnosis or therapy, and LP increases the risk of herniation.

Additional laboratory studies may provide clues to the diagnosis of brain abscess in patients with a CNS mass lesion. About 50% of patients have a peripheral leukocytosis, 60% an elevated ESR, and 80% an elevated C-reactive protein. Blood cultures are positive in ~10% of cases overall but may be positive in >85% of patients with abscesses due to *Listeria*.

DIFFERENTIAL DIAGNOSIS

Conditions that can cause headache, fever, focal neurologic signs, and seizure activity include brain abscess, subdural empyema, bacterial meningitis, viral meningoencephalitis, superior sagittal sinus thrombosis, and acute disseminated encephalomyelitis. When fever is absent, primary and metastatic brain tumors become the major differential diagnosis. Less commonly, cerebral infarction or hematoma can have an MRI or CT appearance resembling brain abscess.

TREATMENT Brain Abscess

Optimal therapy of brain abscesses involves a combination of high-dose parenteral antibiotics and neurosurgical drainage. Empirical therapy of community-acquired brain abscess in an immunocompetent patient typically includes a third- or fourth-generation cephalosporin (e.g., cefotaxime, ceftriaxone, or cefepime) and metronidazole (see Table 31-1 for antibiotic dosages). In patients with penetrating head trauma or recent neurosurgical procedures, treatment should include ceftazidime as the third-generation cephalosporin to enhance coverage of *Pseudomonas* spp. and vancomycin for coverage of staphylococci. Meropenem plus vancomycin also provides good coverage in this setting.

Aspiration and drainage of the abscess under stereotactic guidance are beneficial for both diagnosis and therapy. Empirical antibiotic coverage should be modified based on the results of Gram's stain and culture of the abscess contents. Complete excision of a bacterial abscess via craniotomy or craniectomy is generally reserved for multiloculated abscesses or those in which stereotactic aspiration is unsuccessful.

Medical therapy alone is not optimal for treatment of brain abscess and should be reserved for patients whose abscesses are neurosurgically inaccessible, for patients with small (<2–3 cm) or nonencapsulated abscesses (cerebritis), and patients whose condition is too tenuous to allow performance of a neurosurgical procedure. All patients should receive a minimum of 6–8 weeks of parenteral antibiotic therapy. The role, if any, of supplemental oral antibiotic therapy following completion of a standard course of parenteral therapy has never been adequately studied.

In addition to surgical drainage and antibiotic therapy, patients should receive prophylactic anticonvulsant therapy because of the high risk (~35%) of focal or generalized seizures. Anticonvulsant therapy is continued for at least 3 months after resolution of the abscess, and decisions regarding withdrawal are then based on the EEG. If the EEG is abnormal, anticonvulsant therapy should be continued. If the EEG is normal, anticonvulsant therapy can be slowly withdrawn, with close follow-up and repeat EEG after the medication has been discontinued.

Glucocorticoids should not be given routinely to patients with brain abscesses. Intravenous dexamethasone therapy (10 mg every 6 h) is usually reserved for patients with substantial periabscess edema and associated mass effect and increased ICP. Dexamethasone should be tapered as rapidly as possible to avoid delaying the natural process of encapsulation of the abscess.

Serial MRI or CT scans should be obtained on a monthly or twice-monthly basis to document resolution of the abscess. More frequent studies (e.g., weekly) are probably warranted in the subset of patients who are receiving antibiotic therapy alone. A small amount of enhancement may remain for months after the abscess has been successfully treated.

PROGNOSIS

The mortality rate of brain abscess has declined in parallel with the development of enhanced neuroimaging techniques, improved neurosurgical procedures for stereotactic aspiration, and improved antibiotics. In modern series, the mortality rate is typically <15%. Significant sequelae, including seizures, persisting weakness, aphasia, or mental impairment, occur in ≥20% of survivors.

NONBACTERIAL CAUSES OF INFECTIOUS FOCAL CNS LESIONS

ETIOLOGY

Neurocysticercosis is the most common parasitic disease of the CNS worldwide. Humans acquire cysticercosis by the ingestion of food contaminated with the eggs of the parasite *T. solium*. Toxoplasmosis is a parasitic disease caused by *T. gondii* and acquired from the ingestion of undercooked meat and from handling cat feces.

CLINICAL PRESENTATION

The most common manifestation of neurocysticercosis is new-onset partial seizures with or without secondary generalization. Cysticerci may develop in the brain parenchyma and cause seizures or focal neurologic deficits. When present in the subarachnoid or ventricular spaces, cysticerci can produce increased ICP by interference with CSF flow. Spinal cysticerci can mimic the presentation of intraspinal tumors. When the cysticerci first lodge in the brain, they frequently cause little in the way of an inflammatory response. As the cysticercal cyst degenerates, it elicits an inflammatory response that may present clinically as a seizure. Eventually the cyst dies, a process that may take several years and is typically associated with resolution of the inflammatory response and, often, abatement of seizures.

Primary *Toxoplasma* infection is often asymptomatic. However, during this phase parasites may spread to the CNS, where they become latent. Reactivation of CNS infection is almost exclusively associated with immunocompromised hosts, particularly those with HIV infection. During this phase patients present with headache, fever, seizures, and focal neurologic deficits.

DIAGNOSIS

The lesions of neurocysticercosis are readily visualized by MRI or CT scans. Lesions with viable parasites appear as cystic lesions. The scolex can often be visualized on MRI. Lesions may appear as contrast-enhancing lesions surrounded by edema. A very early sign of cyst death is hypointensity of the vesicular fluid on T2-weighted images when compared with CSF. Parenchymal brain calcifications are the most common finding and evidence that the parasite is no longer viable. MRI findings of toxoplasmosis consist of multiple lesions in the deep white matter, the thalamus, and basal ganglia and at the gray-white junction in the cerebral hemispheres. With contrast administration, the majority of the lesions enhance in a ringed, nodular, or homogeneous pattern and are surrounded by edema. In the presence of the characteristic neuroimaging abnormalities of *T. gondii* infection, serum IgG antibody to *T. gondii* should be obtained and, when positive, the patient should be treated.

TREATMENT Infectious Focal CNS Lesions

Anticonvulsant therapy is initiated when the patient with neurocysticercosis presents with a seizure. There is controversy about whether or not anthelmintic therapy should be given to all patients, and recommendations are based on the stage of the lesion. Cysticerci appearing as cystic lesions in the brain parenchyma with or without pericystic edema or in the subarachnoid space at the convexity of the cerebral hemispheres should prompt cysticidal therapy. Cysticidal drugs accelerate the destruction of the parasites, resulting in a faster resolution of the infection. Albendazole and praziquantel are used in the treatment of neurocysticercosis. Approximately 85% of parenchymal cysts are destroyed by a single course of albendazole, and ~75% are destroyed by a single course of praziquantel. The dose of albendazole is 15 mg/kg per day in two doses for 8 days. The dose of praziquantel is 50 mg/kg per day for 15 days, although a number of other dosage regimens are also frequently cited. Prednisone or dexamethasone is given with cysticidal therapy to reduce the host inflammatory response to degenerating parasites. Many, but not all, experts recommend cysticidal therapy for lesions that are surrounded by a contrast-enhancing ring. There is universal agreement that calcified lesions do not need to be treated with cysticidal agents. Antiepileptic therapy can be stopped once the follow-up CT scan shows resolution of the lesion. Long-term antiepileptic therapy is recommended when seizures occur after resolution of edema and resorption or calcification of the degenerating cyst.

CNS toxoplasmosis is treated with a combination of sulfadiazine (1.5–2.0 g orally qid) plus pyrimethamine (100 mg orally to load, then 75–100 mg orally qd) plus folinic acid (10–15 mg orally qd). Folinic acid is added to the regimen to prevent megaloblastic anemia. Therapy is continued until there is no evidence of active disease on neuroimaging studies, which typically takes at least 6 weeks, and then the dose of sulfadiazine is reduced to 2–4 g/d and pyrimethamine to 50 mg/d. Clindamycin plus pyrimethamine is an alternative therapy for patients

who cannot tolerate sulfadiazine, but the combination of pyrimethamine and sulfadiazine is more effective.

SUBDURAL EMPYEMA

A subdural empyema (SDE) is a collection of pus between the dura and arachnoid membranes **(Fig. 31-5)**.

EPIDEMIOLOGY

SDE is a rare disorder that accounts for 15–25% of focal suppurative CNS infections. Sinusitis is the most common predisposing condition and typically involves the frontal sinuses, either alone or in combination with the ethmoid and maxillary sinuses. Sinusitis-associated empyema has a striking predilection for young males, possibly reflecting sex-related differences in sinus anatomy and development. It has been suggested that SDE may complicate 1–2% of cases of frontal sinusitis severe enough to require hospitalization. As a consequence of this epidemiology, SDE shows an ~3:1 male/female predominance, with 70% of cases occurring in the second and third decades of life. SDE may also develop as a complication of head trauma or neurosurgery. Secondary infection of a subdural effusion may also result in empyema, although secondary infection of hematomas, in the absence of a prior neurosurgical procedure, is rare.

ETIOLOGY

Aerobic and anaerobic streptococci, staphylococci, Enterobacteriaceae, and anaerobic bacteria are the most common causative organisms of sinusitis-associated SDE. Staphylococci and gram-negative bacilli are often the etiologic organisms when SDE follows neurosurgical procedures or head trauma. Up to one-third of cases are culture-negative, possibly reflecting difficulty in obtaining adequate anaerobic cultures.

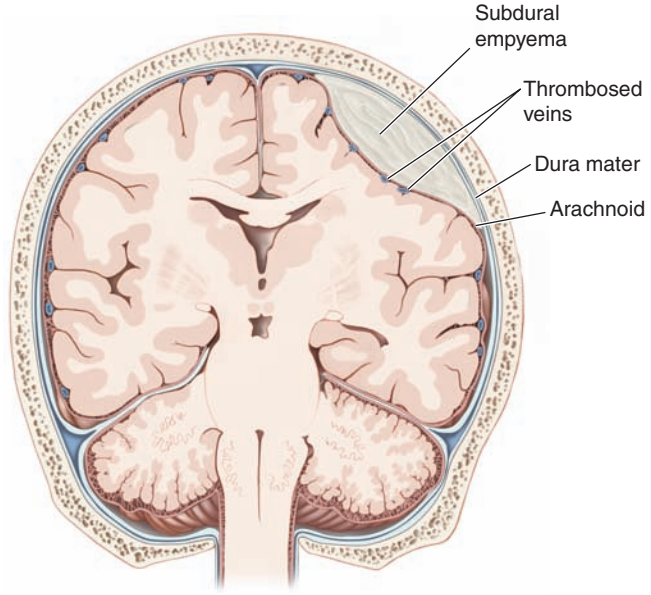


FIGURE 31-5
Subdural empyema.

PATHOPHYSIOLOGY

Sinusitis-associated SDE develops as a result of either retrograde spread of infection from septic thrombophlebitis of the mucosal veins draining the sinuses or contiguous spread of infection to the brain from osteomyelitis in the posterior wall of the frontal or other sinuses. SDE may also develop from direct introduction of bacteria into the subdural space as a complication of a neurosurgical procedure. The evolution of SDE can be extremely rapid because the subdural space is a large compartment that offers few mechanical barriers to the spread of infection. In patients with sinusitis-associated SDE, suppuration typically begins in the upper and anterior portions of one cerebral hemisphere and then extends posteriorly. SDE is often associated with other intracranial infections, including epidural empyema (40%), cortical thrombophlebitis (35%), and intracranial abscess or cerebritis (>25%). Cortical venous infarction produces necrosis of underlying cerebral cortex and subcortical white matter, with focal neurologic deficits and seizures (see next).

CLINICAL PRESENTATION

A patient with SDE typically presents with fever and a progressively worsening headache. The diagnosis of SDE should always be suspected in a patient with known sinusitis who presents with new CNS signs or symptoms. Patients with underlying sinusitis frequently have symptoms related to this infection. As the infection progresses, focal neurologic deficits, seizures, nuchal rigidity, and signs of increased ICP commonly occur. Headache is the most common complaint at the time of presentation; initially it is localized to the side of the subdural infection, but then it becomes more severe and generalized. Contralateral hemiparesis or hemiplegia is the most common focal neurologic deficit and can occur from the direct effects of the SDE on the cortex or as a consequence of venous infarction. Seizures begin as partial motor seizures that then become secondarily generalized. Seizures may be due to the direct irritative effect of the SDE on the underlying cortex or result from cortical venous infarction (see earlier in the chapter). In untreated SDE, the increasing mass effect and increase in ICP cause progressive deterioration in consciousness, leading ultimately to coma.

DIAGNOSIS

MRI **(Fig. 31-6)** is superior to CT in identifying SDE and any associated intracranial infections. The administration of gadolinium greatly improves diagnosis by enhancing the rim of the empyema and allowing the

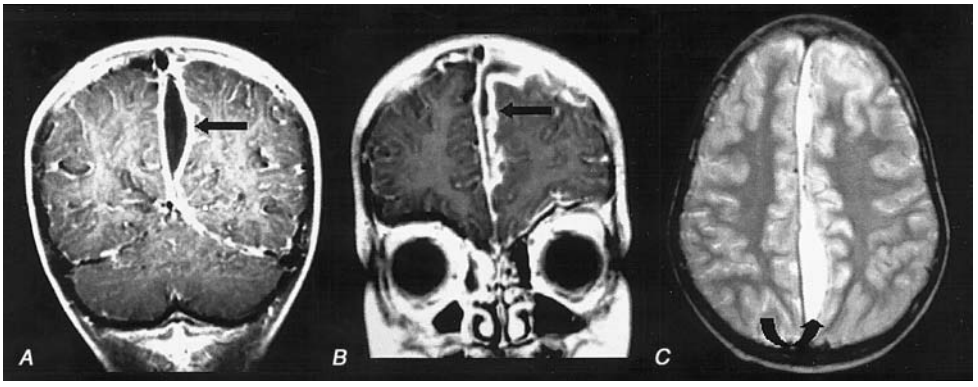


FIGURE 31-6
Subdural empyema. There is marked enhancement of the dura and leptomeninges (***A***, ***B***, *straight arrows*) along the left medial hemisphere. The pus is hypointense on T1-weighted images (***A***, ***B***) but markedly hyperintense on the proton density–weighted image (***C***, *curved arrow*). (*Courtesy of Joseph Lurito, MD; with permission*.)

empyema to be clearly delineated from the underlying brain parenchyma. Cranial MRI is also extremely valuable in identifying sinusitis, other focal CNS infections, cortical venous infarction, cerebral edema, and cerebritis. CT may show a crescent-shaped hypodense lesion over one or both hemispheres or in the interhemispheric fissure. Frequently the degree of mass effect, exemplified by midline shift, ventricular compression, and sulcal effacement, is far out of proportion to the mass of the SDE.

CSF examination should be avoided in patients with known or suspected SDE as it adds no useful information and is associated with the risk of cerebral herniation.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of the combination of headache, fever, focal neurologic signs, and seizure activity that progresses rapidly to an altered level of consciousness includes subdural hematoma, bacterial meningitis, viral encephalitis, brain abscess, superior sagittal sinus thrombosis, and acute disseminated encephalomyelitis. The presence of nuchal rigidity is unusual with brain abscess or epidural empyema and should suggest the possibility of SDE when associated with significant focal neurologic signs and fever. Patients with bacterial meningitis also have nuchal rigidity but do not typically have focal deficits of the severity seen with SDE.

TREATMENT Subdural Empyema

SDE is a medical emergency. Emergent neurosurgical evacuation of the empyema, either through craniotomy, craniectomy, or burr-hole drainage, is the definitive step in the management of this infection. Empirical antimicrobial therapy for community-acquired SDE should include a combination of a third-generation cephalosporin (e.g., cefotaxime or ceftriaxone), vancomycin, and metronidazole (see Table 31-1 for dosages). Patients with hospital-acquired SDE may have infections due to *Pseudomonas* spp. or MRSA and should receive coverage with a carbapenem (e.g., meropenem) and vancomycin. Metronidazole is not necessary for antianaerobic therapy when meropenem is being used. Parenteral antibiotic therapy should be continued for a minimum of 3–4 weeks after SDE drainage. Patients with associated cranial osteomyelitis may require longer therapy. Specific diagnosis of the etiologic organisms is made based on Gram's stain and culture of fluid obtained via either burr holes or craniotomy; the initial empirical antibiotic coverage can be modified accordingly.

PROGNOSIS

Prognosis is influenced by the level of consciousness of the patient at the time of hospital presentation, the size of the empyema, and the speed with which therapy is instituted. Long-term neurologic sequelae, which include seizures and hemiparesis, occur in up to 50% of cases.

CRANIAL EPIDURAL ABSCESS

Cranial epidural abscess is a suppurative infection occurring in the potential space between the inner skull table and dura **(Fig. 31-7)**.

ETIOLOGY AND PATHOPHYSIOLOGY

Cranial epidural abscess is less common than either brain abscess or SDE and accounts for <2% of focal suppurative CNS infections. A cranial epidural abscess develops as a complication of a craniotomy or compound skull fracture or as a result of spread of infection from the frontal sinuses, middle ear, mastoid, or orbit. An epidural abscess may develop contiguous to an area of osteomyelitis, when craniotomy is complicated by infection of the wound or bone flap, or as a result of direct infection of the epidural space. Infection in the frontal sinus, middle ear, mastoid, or orbit can reach the epidural

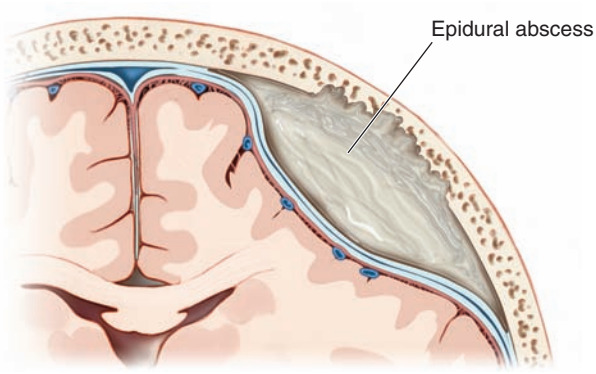


FIGURE 31-7
Cranial epidural abscess is a collection of pus between the dura and the inner table of the skull.

space through retrograde spread of infection from septic thrombophlebitis in the emissary veins that drain these areas or by way of direct spread of infection through areas of osteomyelitis. Unlike the subdural space, the epidural space is really a potential rather than an actual compartment. The dura is normally tightly adherent to the inner skull table, and infection must dissect the dura away from the skull table as it spreads. As a result, epidural abscesses are often smaller than SDEs. Cranial epidural abscesses, unlike brain abscesses, only rarely result from hematogenous spread of infection from extracranial primary sites. The bacteriology of a cranial epidural abscess is similar to that of SDE (see earlier). The etiologic organisms of an epidural abscess that arises from frontal sinusitis, middle-ear infections, or mastoiditis are usually streptococci or anaerobic organisms. Staphylococci or gram-negative organisms are the usual cause of an epidural abscess that develops as a complication of craniotomy or compound skull fracture.

CLINICAL PRESENTATION

Patients present with fever (60%), headache (40%), nuchal rigidity (35%), seizures (10%), and focal deficits (5%). Development of symptoms may be insidious, as the empyema usually enlarges slowly in the confined anatomic space between the dura and the inner table of the skull. Periorbital edema and Potts puffy tumor, reflecting underlying associated frontal bone osteomyelitis, are present in ~40%. In patients with a recent neurosurgical procedure, wound infection is invariably present, but other symptoms may be subtle and can include altered mental status (45%), fever (35%), and headache (20%). The diagnosis should be considered when fever and headache follow recent head trauma or occur in the setting of frontal sinusitis, mastoiditis, or otitis media.

DIAGNOSIS

Cranial MRI with gadolinium enhancement is the procedure of choice to demonstrate a cranial epidural abscess. The sensitivity of CT is limited by the presence of signal artifacts arising from the bone of the inner skull table. The CT appearance of an epidural empyema is that of a lens or crescent-shaped hypodense extraaxial lesion. On MRI, an epidural empyema appears as a lentiform or crescent-shaped fluid collection that is hyperintense compared to CSF on T2-weighted images. On T1-weighted images, the fluid collection may be either isointense or hypointense compared to brain. Following the administration of gadolinium, there is linear enhancement of the dura on T1-weighted images. In distinction to subdural empyema, signs of mass effect or other parenchymal abnormalities are uncommon.

TREATMENT **Epidural Abscess**

Immediate neurosurgical drainage is indicated. Empirical antimicrobial therapy, pending the results of Gram's stain and culture of the purulent material obtained at surgery, should include a combination of a third-generation cephalosporin, vancomycin, and metronidazole (Table 31-1). Ceftazidime or meropenem should be substituted for ceftriaxone or cefotaxime in neurosurgical patients. Metronidazole is not necessary for anti-anaerobic coverage in patients receiving meropenem. When the organism has been identified, antimicrobial therapy can be modified accordingly. Antibiotics should be continued for 3–6 weeks after surgical drainage. Patients with associated osteomyelitis may require additional therapy.

PROGNOSIS

The mortality rate is <5% in modern series, and full recovery is the rule in most survivors.

SUPPURATIVE THROMBOPHLEBITIS

DEFINITION

Suppurative intracranial thrombophlebitis is septic venous thrombosis of cortical veins and sinuses. This may occur as a complication of bacterial meningitis; SDE; epidural abscess; or infection in the skin of the face, paranasal sinuses, middle ear, or mastoid.

ANATOMY AND PATHOPHYSIOLOGY

The cerebral veins and venous sinuses have no valves; therefore, blood within them can flow in either direction. The superior sagittal sinus is the largest of the venous sinuses (Fig. 31-8). It receives blood from the frontal, parietal, and occipital superior cerebral veins and the diploic veins, which communicate with the meningeal veins. Bacterial meningitis is a common predisposing condition for septic thrombosis of the superior sagittal sinus. The diploic veins, which drain into the superior sagittal sinus, provide a route for the spread of infection from the meninges, especially in cases where there is purulent exudate near areas of the

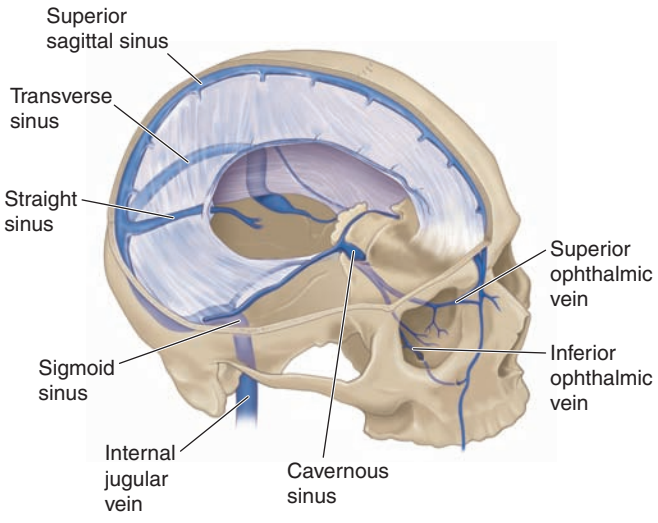


FIGURE 31-8
Anatomy of the cerebral venous sinuses.

superior sagittal sinus. Infection can also spread to the superior sagittal sinus from nearby SDE or epidural abscess. Dehydration from vomiting, hypercoagulable states, and immunologic abnormalities, including the presence of circulating antiphospholipid antibodies, also contribute to cerebral venous sinus thrombosis. Thrombosis may extend from one sinus to another, and at autopsy thrombi of different histologic ages can often be detected in several sinuses. Thrombosis of the superior sagittal sinus is often associated with thrombosis of superior cortical veins and small parenchymal hemorrhages.

The superior sagittal sinus drains into the transverse sinuses (Fig. 31-8). The transverse sinuses also receive venous drainage from small veins from both the middle ear and mastoid cells. The transverse sinus becomes the sigmoid sinus before draining into the internal jugular vein. Septic transverse/sigmoid sinus thrombosis can be a complication of acute and chronic otitis media or mastoiditis. Infection spreads from the mastoid air cells to the transverse sinus via the emissary veins or by direct invasion. The cavernous sinuses are inferior to the superior sagittal sinus at the base of the skull. The cavernous sinuses receive blood from the facial veins via the superior and inferior ophthalmic veins. Bacteria in the facial veins enter the cavernous sinus via these veins. Bacteria in the sphenoid and ethmoid sinuses can spread to the cavernous sinuses via the small emissary veins. The sphenoid and ethmoid sinuses are the most common sites of primary infection resulting in septic cavernous sinus thrombosis.

CLINICAL MANIFESTATIONS

Septic thrombosis of the superior sagittal sinus presents with headache, fever, nausea and vomiting, confusion, and focal or generalized seizures. There may be a rapid development of stupor and coma. Weakness of the lower extremities with bilateral Babinski's signs or hemiparesis is often present. When superior sagittal sinus thrombosis occurs as a complication of bacterial meningitis, nuchal rigidity and Kernig's and Brudzinski's signs may be present.

The oculomotor nerve, the trochlear nerve, the abducens nerve, the ophthalmic and maxillary branches of the trigeminal nerve, and the internal carotid artery all pass through the cavernous sinus. The symptoms of *septic cavernous sinus thrombosis* are fever, headache, frontal and retroorbital pain, and diplopia. The classic signs are ptosis, proptosis, chemosis, and extraocular dysmotility due to deficits of cranial nerves III, IV, and VI; hyperesthesia of the ophthalmic and maxillary divisions of the fifth cranial nerve and a decreased corneal reflex may be detected. There may be evidence of dilated, tortuous retinal veins and papilledema.

Headache and earache are the most frequent symptoms of *transverse sinus thrombosis*. A transverse sinus thrombosis may also present with otitis media, sixth nerve palsy, and retroorbital or facial pain (*Gradenigo's syndrome*). Sigmoid sinus and internal jugular vein thrombosis may present with neck pain.

DIAGNOSIS

The diagnosis of septic venous sinus thrombosis is suggested by an absent flow void within the affected venous sinus on MRI and confirmed by magnetic resonance venography, CT angiogram, or the venous phase of cerebral angiography. The diagnosis of thrombophlebitis of intracerebral and meningeal veins is suggested by the presence of intracerebral hemorrhage, but requires cerebral angiography for definitive diagnosis.

TREATMENT **Suppurative Thrombophlebitis**

Septic venous sinus thrombosis is treated with antibiotics, hydration, and removal of infected tissue and thrombus in septic lateral or cavernous sinus thrombosis. The choice of antimicrobial therapy is based on the bacteria responsible for the predisposing or associated condition. Optimal duration of therapy is unknown, but antibiotics are usually continued for 6 weeks or until there is radiographic evidence of resolution of thrombosis. Anticoagulation with dose-adjusted intravenous heparin is recommended for aseptic venous sinus thrombosis and in the treatment of septic venous sinus thrombosis complicating bacterial meningitis in patients who have progressive neurologic deterioration despite antimicrobial therapy and intravenous fluids. The presence of a small intracerebral hemorrhage from septic thrombophlebitis is not an absolute contraindication to heparin therapy. Successful management of aseptic venous sinus thrombosis has been reported with surgical thrombectomy, catheter-directed urokinase therapy, and a combination of intrathrombus recombinant tissue plasminogen activator (rtPA) and intravenous heparin, but there are not enough data to recommend these therapies in septic venous sinus thrombosis.

CHAPTER 32

CHRONIC AND RECURRENT MENINGITIS

Walter J. Koroshetz ■ Morton N. Swartz

Chronic inflammation of the meninges (pia, arachnoid, and dura) can produce profound neurologic disability and may be fatal if not successfully treated. The condition is most commonly diagnosed when a characteristic neurologic syndrome exists for >4 weeks and is associated with a persistent inflammatory response in the cerebrospinal fluid (CSF) (white blood cell count >5/μL). The causes are varied, and appropriate treatment depends on identification of the etiology. Five categories of disease account for most cases of chronic meningitis: (1) meningeal infections, (2) malignancy, (3) noninfectious inflammatory disorders, (4) chemical meningitis, and (5) parameningeal infections.

CLINICAL PATHOPHYSIOLOGY

Neurologic manifestations of chronic meningitis (Table 32-1) are determined by the anatomic location of the inflammation and its consequences. Persistent headache with or without stiff neck, hydrocephalus, cranial neuropathies, radiculopathies, and cognitive or personality changes are the cardinal features. These can occur alone or in combination. When they appear in combination, widespread dissemination of the inflammatory process along CSF pathways has occurred. In some cases, the presence of an underlying systemic illness points to a specific agent or class of agents as the probable cause. The diagnosis of chronic meningitis is usually made when the clinical presentation prompts the astute physician to examine the CSF for signs of inflammation. CSF is produced by the choroid plexus of the cerebral ventricles, exits through narrow foramina into the subarachnoid space surrounding the brain and spinal cord, circulates around the base of the brain and over the cerebral hemispheres, and is resorbed by arachnoid villi projecting into the superior sagittal sinus. CSF flow provides a pathway for rapid spread of infectious and other infiltrative processes over the brain, spinal cord, and cranial and spinal nerve roots. Spread from the subarachnoid space into brain parenchyma may occur via the arachnoid cuffs that surround blood vessels that penetrate brain tissue (Virchow-Robin spaces).

Intracranial meningitis

Nociceptive fibers of the meninges are stimulated by the inflammatory process, resulting in headache or neck or back pain. Obstruction of CSF pathways at the foramina or arachnoid villi may produce *hydrocephalus* and symptoms of raised intracranial pressure (ICP), including headache, vomiting, apathy or drowsiness, gait instability, papilledema, visual loss, impaired upgaze, or palsy of the sixth cranial nerve (CN). Cognitive and behavioral changes during the course of chronic meningitis may also result from vascular damage, which may similarly produce seizures, stroke,

TABLE 32-1

SYMPTOMS AND SIGNS OF CHRONIC MENINGITIS

SYMPTOM	SIGN
Chronic headache	+/– Papilledema
Neck or back pain	Brudzinski's or Kernig's sign of meningeal irritation
Change in personality	Altered mental status—drowsiness, inattention, disorientation, memory loss, frontal release signs (grasp, suck, snout), perseveration
Facial weakness	Peripheral seventh CN palsy
Double vision	Palsy of CNs III, IV, VI
Visual loss	Papilledema, optic atrophy
Hearing loss	Eighth CN palsy
Arm or leg weakness	Myelopathy or radiculopathy
Numbness in arms or legs	Myelopathy or radiculopathy
Sphincter dysfunction	Myelopathy or radiculopathy Frontal lobe dysfunction (hydrocephalus)
Clumsiness	Ataxia

Abbreviation: CN, cranial nerve.

or myelopathy. Inflammatory deposits seeded via the CSF circulation are often prominent around the brainstem and cranial nerves and along the undersurface of the frontal and temporal lobes. Such cases, termed *basal meningitis*, often present as multiple cranial neuropathies, with visual loss (CN II), facial weakness (CN VII), hearing loss (CN VIII), diplopia (CNs III, IV, and VI), sensory or motor abnormalities of the oropharynx (CNs IX, X, and XII), decreased olfaction (CN I), or facial sensory loss and masseter weakness (CN V).

Spinal meningitis

Injury may occur to motor and sensory roots as they traverse the subarachnoid space and penetrate the meninges. These cases present as multiple radiculopathies with combinations of radicular pain, sensory loss, motor weakness, and sphincter dysfunction. Meningeal inflammation can encircle the cord, resulting in myelopathy. Patients with slowly progressive involvement of multiple cranial nerves and/or spinal nerve roots are likely to have chronic meningitis. Electrophysiologic testing (electromyography, nerve conduction studies, and evoked response testing) may be helpful in determining whether there is involvement of cranial and spinal nerve roots.

Systemic manifestations

In some patients, evidence of systemic disease provides clues to the underlying cause of chronic meningitis. A careful history and physical examination are essential before embarking on a diagnostic workup, which may be costly, prolonged, and associated with risk from invasive procedures. A complete history of travel, sexual practice, and exposure to infectious agents should be sought. Infectious causes are often associated with fever, malaise, anorexia, and signs of localized or disseminated infection outside the nervous system. Infectious causes are of major concern in the immunosuppressed patient, especially in patients with AIDS, in whom chronic meningitis may present without headache or fever. Noninfectious inflammatory disorders often produce systemic manifestations, but meningitis may be the initial manifestation. Carcinomatous meningitis may or may not be accompanied by clinical evidence of the primary neoplasm.

APPROACH TO THE PATIENT Chronic Meningitis

The occurrence of chronic headache, hydrocephalus, cranial neuropathy, radiculopathy, and/or cognitive decline in a patient should prompt consideration of a lumbar puncture for evidence of meningeal inflammation. On occasion, the diagnosis is made when an imaging study (CT or MRI) shows contrast enhancement of the meninges, which is always abnormal with the exception of dural enhancement after lumbar puncture, neurosurgical procedures, or spontaneous CSF leakage. Once chronic meningitis is confirmed by CSF examination, effort is focused on identifying the cause (Tables 32-2 and 32-3) by (1) further analysis of the CSF, (2) diagnosis of an underlying systemic infection or noninfectious inflammatory condition, or (3) pathologic examination of meningeal biopsy specimens.

Two clinical forms of chronic meningitis exist. In the first, the symptoms are chronic and persistent, whereas in the second there are recurrent, discrete episodes of illness. In the latter group, all symptoms, signs, and CSF parameters of meningeal inflammation resolve completely between episodes without specific therapy. In such patients, the likely etiologies include herpes simplex virus (HSV) type 2; chemical meningitis due to leakage into CSF of contents from an epidermoid tumor, craniopharyngioma, or cholesteatoma; primary inflammatory conditions, including Vogt-Koyanagi-Harada syndrome, Behçet's syndrome, systemic lupus erythematosus; and drug hypersensitivity with repeated administration of the offending agent.

The epidemiologic history is of considerable importance and may provide direction for selection of laboratory studies. Pertinent features include a history of tuberculosis or exposure to a likely case; past travel to areas endemic for fungal infections (the San Joaquin Valley in California and southwestern states for coccidioidomycosis, midwestern states for histoplasmosis, southeastern states for blastomycosis); travel to the Mediterranean region or ingestion of imported unpasteurized dairy products (*Brucella*); time spent in wooded areas endemic for Lyme disease; exposure to sexually transmitted disease (syphilis); exposure of an immunocompromised host to pigeons and their droppings (*Cryptococcus*); gardening (*Sporothrix schenkii*); ingestion of poorly cooked meat or contact with a household cat (*Toxoplasma gondii*); residence in Thailand or Japan (*Gnathostoma spinigerum*), Latin America (*Paracoccidioides brasiliensis*), or the South Pacific (*Angiostrongylus cantonensis*); rural residence and raccoon exposure (*Baylisascaris procyonis*); and residence in Latin America, the Philippines, or Southeast Asia when eosinophilic meningitis is present (*Taenia solium*).

The presence of focal cerebral signs in a patient with chronic meningitis suggests the possibility of a brain abscess or other parameningeal infection; identification of a potential source of infection (chronic draining ear, sinusitis, right-to-left cardiac or pulmonary shunt, chronic pleuropulmonary infection) supports this diagnosis. In some cases, diagnosis may be established by recognition and biopsy of unusual skin lesions (Behçet's syndrome, cryptococcosis, blastomycosis, SLE, Lyme disease, IV drug use, sporotrichosis, trypanosomiasis) or enlarged lymph nodes (lymphoma, tuberculosis, sarcoid, infection with HIV, secondary syphilis, or Whipple's disease). A careful ophthalmologic examination may reveal uveitis [Vogt-Koyanagi-Harada syndrome, sarcoid, or central nervous system (CNS) lymphoma], keratoconjunctivitis sicca (Sjögren's syndrome), or iridocyclitis (Behçet's syndrome) and is essential to assess visual loss from papilledema.

TABLE 32-2

INFECTIOUS CAUSES OF CHRONIC MENINGITIS

CAUSATIVE AGENT	CSF FORMULA	HELPFUL DIAGNOSTIC TESTS	RISK FACTORS AND SYSTEMIC MANIFESTATIONS
Common Bacterial Causes			
Partially treated suppurative meningitis	Mononuclear or mixed mononuclear-polymorphonuclear cells	CSF culture and Gram's stain	History consistent with acute bacterial meningitis and incomplete treatment
Parameningeal infection	Mononuclear or mixed polymorphonuclear-mononuclear cells	Contrast-enhanced CT or MRI to detect parenchymal, subdural, epidural, or sinus infection	Otitis media, pleuropulmonary infection, right-to-left cardiopulmonary shunt for brain abscess; focal neurologic signs; neck, back, ear, or sinus tenderness
Mycobacterium tuberculosis	Mononuclear cells except polymorphonuclear cells in early infection (commonly <500 WBCs/μL); low CSF glucose, high protein	Tuberculin skin test may be negative; AFB culture of CSF (sputum, urine, gastric contents if indicated); tuberculostearic acid detection in CSF; identify tubercle bacillus on acid-fast stain of CSF or protein pellicle; PCR	Exposure history; previous tuberculous illness; immunosuppressed or AIDS; young children; fever, meningismus, night sweats, miliary TB on x-ray or liver biopsy; stroke due to arteritis
Lyme disease (Bannwarth's syndrome) (*Borrelia burgdorferi*)	Mononuclear cells; elevated protein	Serum Lyme antibody titer; western blot confirmation (patients with syphilis may have false-positive Lyme titer)	History of tick bite or appropriate exposure history; erythema chronicum migrans skin rash; arthritis, radiculopathy, Bell's palsy, meningoencephalitis–multiple sclerosis-like syndrome
Syphilis (secondary, tertiary) (*Treponema pallidum*)	Mononuclear cells; elevated protein	CSF VDRL; serum VDRL (or RPR); fluorescent treponemal antibody-absorbed (FTA) or MHA-TP; serum VDRL may be negative in tertiary syphilis	Appropriate exposure history; HIV-seropositive individuals at increased risk of aggressive infection; "dementia"; cerebral infarction due to endarteritis
Uncommon Bacterial Causes			
Actinomyces	Polymorphonuclear cells	Anaerobic culture	Parameningeal abscess or sinus tract (oral or dental focus); pneumonitis
Nocardia	Polymorphonuclear; occasionally mononuclear cells; often low glucose	Isolation may require weeks; weakly acid fast	Associated brain abscess may be present
Brucella	Mononuclear cells (rarely polymorphonuclear); elevated protein; often low glucose	CSF antibody detection; serum antibody detection	Intake of unpasteurized dairy products; exposure to goats, sheep, cows; fever, arthralgia, myalgia, vertebral osteomyelitis
Whipple's disease (*Tropheryma whipplei*)	Mononuclear cells	Biopsy of small bowel or lymph node; CSF PCR for *T. whipplei*) brain and meningeal biopsy (with PAS stain and EM examination)	Diarrhea, weight loss, arthralgias, fever; dementia, ataxia, paresis, ophthalmoplegia, oculomasticatory myoclonus
Rare Bacterial Causes			
Leptospirosis (occasionally if left untreated may last 3–4 weeks)			
Fungal Causes			
Cryptococcus neoformans	Mononuclear cells; count not elevated in some patients with AIDS	India ink or fungal wet mount of CSF (budding yeast); blood and urine cultures; antigen detection in CSF	AIDS and immune suppression; pigeon exposure; skin and other organ involvement due to disseminated infection
Coccidioides immitis	Mononuclear cells (sometimes 10–20% eosinophils); often low glucose	Antibody detection in CSF and serum	Exposure history—southwestern US; increased virulence in dark-skinned individuals

(*continued*)

TABLE 32-2

INFECTIOUS CAUSES OF CHRONIC MENINGITIS (*CONTINUED*)

CAUSATIVE AGENT	CSF FORMULA	HELPFUL DIAGNOSTIC TESTS	RISK FACTORS AND SYSTEMIC MANIFESTATIONS
Fungal Causes (*continued*)			
Candida spp.	Polymorphonuclear or mononuclear	Fungal stain and culture of CSF	IV drug abuse; post-surgery; prolonged intravenous therapy; disseminated candidiasis
Histoplasma capsulatum	Mononuclear cells; low glucose	Fungal stain and culture of large volumes of CSF; antigen detection in CSF, serum, and urine; antibody detection in serum, CSF	Exposure history—Ohio and central Mississippi River Valley; AIDS; mucosal lesions
Blastomyces dermatitidis	Mononuclear cells	Fungal stain and culture of CSF; biopsy and culture of skin, lung lesions; antibody detection in serum	Midwestern and southeastern US; usually systemic infection; abscesses, draining sinus, ulcers
Aspergillus spp.	Mononuclear or polymorphonuclear	CSF culture	Sinusitis; granulocytopenia or immunosuppression
Sporothrix schenckii	Mononuclear cells	Antibody detection in CSF and serum; CSF culture	Traumatic inoculation; IV drug use; ulcerated skin lesion
Rare Fungal Causes			
Xylohypha (formerly *Cladosporium*) *trichoides* and other dark-walled (dematiaceous) fungi such as *Curvularia, Drechslera; Mucor*, and, after water aspiration, *Pseudallescheria boydii*			
Protozoal Causes			
Toxoplasma gondii	Mononuclear cells	Biopsy or response to empirical therapy in clinically appropriate context (including presence of antibody in serum)	Usually with intracerebral abscesses; common in HIV-seropositive patients
Trypanosomiasis (*Trypanosoma gambiense, T. rhodesiense*)	Mononuclear cells, elevated protein	Elevated CSF IgM; identification of trypanosomes in CSF and blood smear	Endemic in Africa; chancre, lymphadenopathy; prominent sleep disorder
Rare Protozoal Causes			
Acanthamoeba spp. causing granulomatous amebic encephalitis and meningoencephalitis in immunocompromised and debilitated individuals: *Balamuthia mandrillaris* causing chronic meningoencephalitis in immunocompetent hosts			
Helminthic Causes			
Cysticercosis (infection with cysts of *Taenia solium*)	Mononuclear cells; may have eosinophils; glucose level may be low	Indirect hemagglutination assay in CSF; ELISA immunoblotting in serum	Usually with multiple cysts in basal meninges and hydrocephalus; cerebral cysts, muscle calcification
Gnathostoma spinigerum	Eosinophils, mononuclear cells	Peripheral eosinophilia	History of eating raw fish; common in Thailand and Japan; subarachnoid hemorrhage; painful radiculopathy
Angiostrongylus cantonensis	Eosinophils, mononuclear cells	Recovery of worms from CSF	History of eating raw shellfish; common in tropical Pacific regions; often benign
Baylisascaris procyonis (raccoon ascarid)	Eosinophils, mononuclear cells		Infection follows accidental ingestion of *B. procyonis* eggs from raccoon feces; fatal meningoencephalitis
Rare Helminthic Causes			
Trichinella spiralis (trichinosis); *Fasciola hepatica* (liver fluke), *Echinococcus cysts; Schistosoma* spp. The former may produce a lymphocytic pleocytosis, whereas the latter two may produce an eosinophilic response in CSF associated with cerebral cysts (*Echinococcus*) or granulomatous lesions of brain or spinal cord			

(*continued*)

TABLE 32-2

INFECTIOUS CAUSES OF CHRONIC MENINGITIS (*CONTINUED*)

CAUSATIVE AGENT	CSF FORMULA	HELPFUL DIAGNOSTIC TESTS	RISK FACTORS AND SYSTEMIC MANIFESTATIONS
Viral causes			
Mumps virus	Mononuclear cells	Antibody in serum	No prior mumps or immunization; may produce meningoencephalitis; may persist for 3–4 weeks
Lymphocytic choriomeningitis virus	Mononuclear cells	Antibody in serum	Contact with rodents or their excreta; may persist for 3–4 weeks
Echovirus	Mononuclear cells; may have low glucose	Virus isolation from CSF	Congenital hypogammaglobulinemia; history of recurrent meningitis
HIV (acute retroviral syndrome)	Mononuclear cells	p24 antigen in serum and CSF; high level of HIV viremia	HIV risk factors; rash, fever, lymphadenopathy; lymphopenia in peripheral blood; syndrome may persist long enough to be considered as "chronic meningitis"; or chronic meningitis may develop in later stages (AIDS) due to HIV
Herpes simplex virus (HSV)	Mononuclear cells	PCR for HSV, CMV DNA; CSF antibody for HSV, EBV	Recurrent meningitis due to HSV-2 (rarely HSV-1) often associated with genital recurrences; EBV associated with myeloradiculopathy, CMV with polyradiculopathy

Abbreviations: AFB, acid-fast bacillus; CMV, cytomegalovirus; CSF, cerebrospinal fluid; CT, computed tomography; EBV, Epstein-Barr virus; ELISA, enzyme-linked immunosorbent assay; EM, electron microscopy; FTA, fluorescent treponemal antibody absorption test; HSV, herpes simplex virus; MHA-TP, microhemagglutination assay–*T. pallidum*; MRI, magnetic resonance imaging; PAS, periodic acid–Schiff; PCR, polymerase chain reaction; RPR, rapid plasma reagin test; TB, tuberculosis; VDRL, Venereal Disease Research Laboratory test.

Aphthous oral lesions, genital ulcers, and hypopyon suggest Behçet's syndrome. Hepatosplenomegaly suggests lymphoma, sarcoid, tuberculosis, or brucellosis. Herpetic lesions in the genital area or on the thighs suggest HSV-2 infection. A breast nodule, a suspicious pigmented skin lesion, focal bone pain, or an abdominal mass directs attention to possible carcinomatous meningitis.

IMAGING Once the clinical syndrome is recognized as a potential manifestation of chronic meningitis, proper analysis of the CSF is essential. However, if the possibility of raised ICP exists, a brain imaging study should be performed before lumbar puncture. If ICP is elevated because of a mass lesion, brain swelling, or a block in ventricular CSF outflow (obstructive hydrocephalus), then lumbar puncture carries the potential risk of brain herniation. Obstructive hydrocephalus usually requires direct ventricular drainage of CSF. In patients with open CSF flow pathways, elevated ICP can still occur due to impaired resorption of CSF by arachnoid villi. In such patients, lumbar puncture is usually safe, but repetitive or continuous lumbar drainage may be necessary to prevent abrupt deterioration and death from raised ICP. In some patients, especially with cryptococcal meningitis, fatal levels of raised ICP can occur without enlarged ventricles.

Contrast-enhanced MRI or CT studies of the brain and spinal cord can identify meningeal enhancement, parameningeal infections (including brain abscess), encasement of the spinal cord (malignancy or inflammation and infection), or nodular deposits on the meninges or nerve roots (malignancy or sarcoidosis) (Fig. 32-1). Imaging studies are also useful to localize areas of meningeal disease prior to meningeal biopsy.

Cerebral angiography may be indicated in patients with chronic meningitis and stroke to identify cerebral arteritis (granulomatous angiitis, other inflammatory arteritides, or infectious arteritis).

CEREBROSPINAL FLUID ANALYSIS The CSF pressure should be measured and samples sent for bacterial, fungal, and tuberculous culture; Venereal Disease Research Laboratory (VDRL) test; cell count and differential; Gram's stain; and measurement of glucose and protein. Wet mount for fungus and parasites, India ink preparation and culture, culture for fastidious bacteria and fungi, assays for cryptococcal antigen and oligoclonal immunoglobulin bands, and cytology should be performed. Other specific CSF tests (Tables 32-2 and 32-3) or blood tests and cultures should be ordered as indicated on the basis of the history, physical examination, or preliminary CSF results (i.e., eosinophilic, mononuclear, or polymorphonuclear meningitis). Rapid diagnosis may be facilitated by serologic tests and polymerase chain reaction (PCR) testing to identify DNA sequences in the CSF that are specific for the suspected pathogen.

TABLE 32-3

NONINFECTIOUS CAUSES OF CHRONIC MENINGITIS

CAUSATIVE AGENTS	CSF FORMULA	HELPFUL DIAGNOSTIC TESTS	RISK FACTORS AND SYSTEMIC MANIFESTATIONS
Malignancy	Mononuclear cells, elevated protein, low glucose	Repeated cytologic examination of large volumes of CSF; CSF exam by polarizing microscopy; clonal lymphocyte markers; deposits on nerve roots or meninges seen on myelogram or contrast-enhanced MRI; meningeal biopsy	Metastatic cancer of breast, lung, stomach, or pancreas; melanoma, lymphoma, leukemia; meningeal gliomatosis; meningeal sarcoma; cerebral dysgerminoma; meningeal melanoma or B cell lymphoma
Chemical compounds (may cause recurrent meningitis)	Mononuclear or PMNs, low glucose, elevated protein; xanthochromia from subarachnoid hemorrhage in week prior to presentation with "meningitis"	Contrast-enhanced CT scan or MRI Cerebral angiogram to detect aneurysm	History of recent injection into the subarachnoid space; history of sudden onset of headache; recent resection of acoustic neuroma or craniopharyngioma; epidermoid tumor of brain or spine, sometimes with dermoid sinus tract; pituitary apoplexy
Primary Inflammation			
CNS sarcoidosis	Mononuclear cells; elevated protein; often low glucose	Serum and CSF angiotensin-converting enzyme levels; biopsy of extraneural affected tissues or brain lesion/meningeal biopsy	CN palsy, especially of CN VII; hypothalamic dysfunction, especially diabetes insipidus; abnormal chest radiograph; peripheral neuropathy or myopathy
Vogt-Koyanagi-Harada syndrome (recurrent meningitis)	Mononuclear cells		Recurrent meningoencephalitis with uveitis, retinal detachment, alopecia, lightening of eyebrows and lashes, dysacousia, cataracts, glaucoma
Isolated granulomatous angiitis of the nervous system	Mononuclear cells, elevated protein	Angiography or meningeal biopsy	Subacute dementia; multiple cerebral infarctions; recent zoster ophthalmicus
Systemic lupus erythematosus	Mononuclear or PMNs	Anti-DNA antibody, antinuclear antibodies	Encephalopathy; seizures; stroke; transverse myelopathy; rash; arthritis
Behçet's syndrome (recurrent meningitis)	Mononuclear or PMNs, elevated protein		Oral and genital aphthous ulcers; iridocyclitis; retinal hemorrhages; pathergic lesions at site of skin puncture
Chronic benign lymphocytic meningitis	Mononuclear cells		Recovery in 2–6 months, diagnosis by exclusion
Mollaret's meningitis (recurrent meningitis)	Large endothelial cells and PMNs in first hours, followed by mononuclear cells	PCR for herpes; MRI/CT to rule out epidermoid tumor or dural cyst	Recurrent meningitis; exclude HSV-2; rare cases due to HSV-1; occasional case associated with dural cyst
Drug hypersensitivity	PMNs; occasionally mononuclear cells or eosinophils	Complete blood count (eosinophilia)	Exposure to non steroidal anti-inflammatory agents, sulfonamides, isoniazid, tolmetin, ciprofloxacin, penicillin, carbamazepine, lamotrigine, IV immunoglobulin, OKT3 antibodies, phenazopyridine; improvement after discontinuation of drug; recurrence with repeat exposure

(*continued*)

TABLE 32-3

NONINFECTIOUS CAUSES OF CHRONIC MENINGITIS (*CONTINUED*)

CAUSATIVE AGENTS	CSF FORMULA	HELPFUL DIAGNOSTIC TESTS	RISK FACTORS AND SYSTEMIC MANIFESTATIONS
Primary Inflammation (*continued*)			
Granulomatosis with polyangiitis	Mononuclear cells	Chest and sinus radiographs; urinalysis; ANCA antibodies in serum	Associated sinus, pulmonary, or renal lesions; CN palsies; skin lesions; peripheral neuropathy
Other: multiple sclerosis, Sjögren's syndrome, neonatal-onset multisystemic inflammatory disease (NOMID), and rarer forms of vasculitis (e.g., Cogan's syndrome)			

Abbreviations: ANCA, anti-neutrophil cytoplasmic antibodies; CN, cranial nerve; CSF, cerebrospinal fluid; CT, computed tomography; HSV, herpes simplex virus; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; PMNs, polymorphonuclear cells.

In most categories of chronic (not recurrent) meningitis, mononuclear cells predominate in the CSF. When neutrophils predominate after 3 weeks of illness, the principal etiologic considerations are *Nocardia asteroides*, *Actinomyces israelii*, *Brucella*, *Mycobacterium tuberculosis* (5–10% of early cases only), various fungi (*Blastomyces dermatitidis*, *Candida albicans*, *Histoplasma capsulatum*, *Aspergillus* spp., *Pseudallescheria boydii*, *Cladophialophora bantiana*), and noninfectious causes (SLE, exogenous chemical meningitis). When eosinophils predominate or are present in limited numbers in a primarily mononuclear cell response in the CSF, the differential diagnosis includes parasitic diseases (*A. cantonensis*, *G. spinigerum*, *B. procyonis*, or *Toxocara canis* infection; cysticercosis; schistosomiasis; echinococcal disease; *T. gondii* infection), fungal infections (6–20% eosinophils along with a predominantly lymphocyte pleocytosis, particularly with coccidioidal meningitis), neoplastic disease (lymphoma, leukemia, metastatic carcinoma), or other inflammatory processes (sarcoidosis, hypereosinophilic syndrome).

It is often necessary to broaden the number of diagnostic tests if the initial workup does not reveal the cause. In addition, repeated samples of large volumes of CSF may be required to diagnose certain infectious and malignant causes of chronic meningitis. For instance, lymphomatous or carcinomatous meningitis may be diagnosed by examination of sections cut from a cell block formed by spinning down the sediment from a large volume of CSF. The diagnosis of fungal meningitis may require large volumes of CSF for culture of sediment. If standard lumbar puncture is unrewarding, a cervical cisternal tap to sample CSF near to the basal meninges may be fruitful.

LABORATORY INVESTIGATION In addition to the CSF examination, an attempt should be made to uncover pertinent underlying illnesses. Tuberculin skin test, chest radiograph, urine analysis and culture, blood count and differential, renal and liver function tests, alkaline phosphatase, sedimentation rate, antinuclear antibody, anti-Ro, anti-La antibody, and serum angiotensin-converting enzyme level are often indicated. Liver or bone marrow biopsy may be diagnostic in some cases of miliary tuberculosis, disseminated fungal infection, sarcoidosis, or metastatic malignancy. Abnormalities discovered on chest radiograph or chest CT can be pursued by bronchoscopy or transthoracic needle biopsy.

MENINGEAL BIOPSY A meningeal biopsy should be strongly considered in patients who are severely disabled, who need chronic ventricular decompression, or whose illness is progressing rapidly. The activities of the surgeon, pathologist, microbiologist, and cytologist should be coordinated so that a large enough sample is obtained and the appropriate cultures and histologic and molecular studies, including electron-microscopic and PCR studies, are performed. The diagnostic yield of meningeal biopsy can be increased by targeting regions that enhance with contrast on MRI or CT. With current microsurgical techniques, most areas of the basal meninges can be accessed for biopsy via

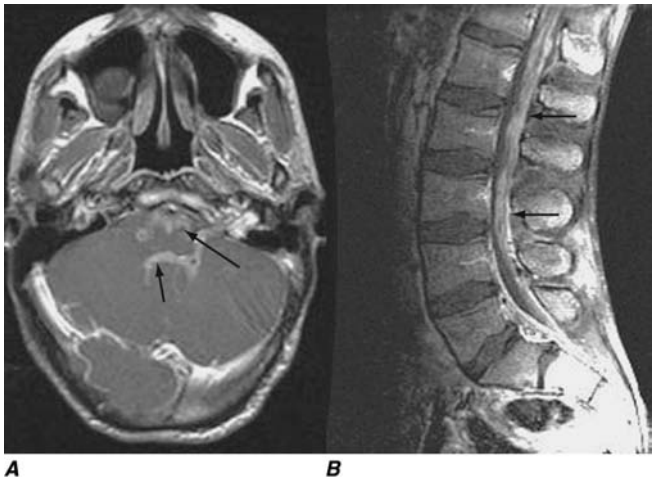


FIGURE 32-1

Primary central nervous system lymphoma. A 24-year-old man, immunosuppressed due to intestinal lymphangiectasia, developed multiple cranial neuropathies. CSF findings consisted of 100 lymphocytes/μL and a protein of 2.5 g/L (250 mg/dL); cytology and cultures were negative. Gadolinium-enhanced T1 MRI revealed diffuse, multifocal meningeal enhancement surrounding the brainstem (***A***), spinal cord, and cauda equina (***B***).

a limited craniotomy. In a series from the Mayo Clinic reported by Cheng et al., MRI demonstrated meningeal enhancement in 47% of patients undergoing meningeal biopsy. Biopsy of an enhancing region was diagnostic in 80% of cases; biopsy of nonenhancing regions was diagnostic in only 9%; sarcoid (31%) and metastatic adenocarcinoma (25%) were the most common conditions identified. Tuberculosis is the most common condition identified in many reports from outside the United States.

APPROACH TO THE ENIGMATIC CASE In approximately one-third of cases, the diagnosis is not known despite careful evaluation of CSF and potential extraneural sites of disease. A number of the organisms that cause chronic meningitis may take weeks to be identified by cultures. In enigmatic cases, several options are available, determined by the extent of the clinical deficits and rate of progression. It is prudent to wait until cultures are finalized if the patient is asymptomatic or symptoms are mild and not progressive. Unfortunately, in many cases progressive neurologic deterioration occurs, and rapid treatment is required. Ventricular-peritoneal shunts may be placed to relieve hydrocephalus, but the risk of disseminating the undiagnosed inflammatory process into the abdomen must be considered.

EMPIRICAL TREATMENT Diagnosis of the causative agent is essential because effective therapies exist for many etiologies of chronic meningitis, but if the condition is left untreated, progressive damage to the CNS and cranial nerves and roots is likely to occur. Occasionally, empirical therapy must be initiated when all attempts at diagnosis fail. In general, empirical therapy in the United States consists of antimycobacterial agents, amphotericin for fungal infection, or glucocorticoids for noninfectious inflammatory causes. It is important to direct empirical therapy of lymphocytic meningitis at tuberculosis, particularly if the condition is associated with hypoglycorrhachia and sixth and other CN palsies, since untreated disease is fatal in 4–8 weeks. In the Mayo Clinic series, the most useful empirical therapy was administration of glucocorticoids rather than antituberculous therapy. Carcinomatous or lymphomatous meningitis may be difficult to diagnose initially, but the diagnosis becomes evident with time.

THE IMMUNOSUPPRESSED PATIENT

Chronic meningitis is not uncommon in the course of HIV infection. Pleocytosis and mild meningeal signs often occur at the onset of HIV infection, and occasionally low-grade meningitis persists. Toxoplasmosis commonly presents as intracranial abscesses and may also be associated with meningitis. Other important causes of chronic meningitis in AIDS include infection with *Cryptococcus*, *Nocardia*, *Candida*, or other fungi; syphilis; and lymphoma (Fig. 32-1). Toxoplasmosis, cryptococcosis, nocardiosis, and other fungal infections are important etiologic considerations in individuals with immunodeficiency states other than AIDS, including those due to immunosuppressive medications. Because of the increased risk of chronic meningitis and the attenuation of clinical signs of meningeal irritation in immunosuppressed individuals, CSF examination should be performed for any persistent headache or unexplained change in mental state.

CHAPTER 33

CHRONIC FATIGUE SYNDROME

Gijs Bleijenberg ■ Jos W.M. van der Meer

DEFINITION

Chronic fatigue syndrome (CFS) is a disorder characterized by persistent and unexplained fatigue resulting in severe impairment in daily functioning. Besides intense fatigue, most patients with CFS report concomitant symptoms such as pain, cognitive dysfunction, and unrefreshing sleep. Additional symptoms can include headache, sore throat, tender lymph nodes, muscle aches, joint aches, feverishness, difficulty sleeping, psychiatric problems, allergies, and

abdominal cramps. Criteria for the diagnosis of CFS have been developed by the U.S. Centers for Disease Control and Prevention (Table 33-1).

EPIDEMIOLOGY

CFS is seen worldwide, with adult prevalence rates varying between 0.2 and 0.4%. In the United States, the prevalence is higher in women, members of minority groups (African and Native Americans), and individuals with lower levels of education and occupational status. Approximately 75% of all CFS patients are women. The mean age of onset is between 29 and 35 years. It is probable that many patients go undiagnosed and/or do not seek help.

ETIOLOGY

There are numerous hypotheses about the etiology of CFS; there is no definitively indentified cause. Distinguishing between predisposing, precipitating, and perpetuating factors in CFS helps to provide a framework for understanding this complex condition (Table 33-2).

Predisposing factors

Physical inactivity and trauma in childhood tend to increase the risk of CFS in adults. Neuroendocrine dysfunction may be associated with childhood trauma, reflecting a biological correlate of vulnerability. Psychiatric illness and physical hyperactivity in adulthood raise the risk of CFS in later life. Twin studies suggest a familial predisposition to CFS, but no causative genes have been identified.

TABLE 33-1

DIAGNOSTIC CRITERIA FOR CHRONIC FATIGUE SYNDROME

Characterized by Persistent or Relapsing Unexplained Chronic Fatigue
Fatigue lasts for at least 6 months
Fatigue is of new or definite onset
Fatigue is not the result of an organic disease or of continuing exertion
Fatigue is not alleviated by rest
Fatigue results in a substantial reduction in previous occupational, educational, social, and personal activities
Four or more of the following symptoms, concurrently present for 6 months: impaired memory or concentration, sore throat, tender cervical or axillary lymph nodes, muscle pain, pain in several joints, new headaches, unrefreshing sleep, or malaise after exertion
Exclusion Criteria
Medical condition explaining fatigue
Major depressive disorder (psychotic features) or bipolar disorder
Schizophrenia, dementia, or delusional disorder
Anorexia nervosa, bulimia nervosa
Alcohol or substance abuse
Severe obesity (BMI >40)

TABLE 33-2

PREDISPOSING, PRECIPITATING, AND PERPETUATING FACTORS IN CHRONIC FATIGUE SYNDROME

TIME
Predisposing Factors
Childhood trauma (sexual, physical, emotional abuse; emotional and physical neglect)
Physical inactivity during childhood
Premorbid psychiatric illness or psychopathology
Premorbid hyperactivity
↓
Precipitating Factors
Somatic events: infection (mononucleosis, Q fever, Lyme disease), surgery, pregnancy
Psychosocial stress, life events
↓
Perpetuating Factors
(Non)acknowledgement by physician
Negative self-efficacy
Strong physical attributions
Strong focus on bodily symptoms
Fear of fatigue
(Lack of) social support
Low physical activity pattern

Precipitating factors

Physical or psychological stress may elicit the onset of CFS. Most patients report an infection (usually a flu-like illness or infectious mononucleosis) as the trigger of their fatigue. Relatively high percentages of CFS follow Q fever and Lyme disease. However, no differences were found in Epstein-Barr virus load and immunologic reactivity in individuals who developed CFS and those who did not. While antecedent infections are associated with CFS, a direct microbial causality is unproven and unlikely. A recent study identified a murine leukemia virus-related retrovirus (XMRV); however, several subsequent studies have failed to confirm this result. Patients also often report other precipitating somatic events such as serious injury, surgery, pregnancy, or childbirth. Serious life events such as the loss of a loved one or a job, military combat, and other stressful situations may also precipitate CFS. A third of all patients cannot recall a trigger.

Perpetuating factors

Once CFS has developed, numerous factors may impede recovery. Physicians may contribute to chronicity by ordering unnecessary diagnostic procedures, by persistently suggesting psychological causes, and by not acknowledging CFS as a diagnosis.

A patient's focus on illness and avoidance of activities may perpetuate symptoms. A firm belief in a physical cause, a strong focus on bodily sensations, and a poor sense of control over symptoms may also prolong or exacerbate the fatigue and functional impairment. In most patients, inactivity is caused by negative illness perceptions rather than by poor physical fitness. Solicitous behavior of others may reinforce a patient's illness-related perceptions and behavior. A lack of social support is another known perpetuating factor.

PATHOPHYSIOLOGY

The pathophysiology of CFS is unclear. Neuroimaging studies have reported that CFS is associated with reduced gray matter volume, which in turn is associated with a decline in physical activity; these changes were partially reversed following cognitive behavioral therapy (CBT). In addition, functional MRI data have suggested that abnormal patterns of activation correlate with self-reported problems with information processing. Neurophysiologic studies have shown altered CNS activation patterns during muscle contraction.

Evidence for immunologic dysfunction is inconsistent. Modest elevations in titers of antinuclear antibodies, reductions in immunoglobulin subclasses, deficiencies in mitogen-driven lymphocyte proliferation, reductions in natural killer cell activity, disturbances in cytokine production, and shifts in lymphocyte subsets have been described. None of these immune findings appears in most patients, nor does any correlate with the severity of CFS. In theory, symptoms of CFS could result from excessive production of a cytokine, such as interleukin 1, that induces asthenia and other flulike symptoms; however, compelling data in support of this hypothesis are lacking.

There is some evidence that CFS patients have mild hypocortisolism, the degree of which is associated with a poorer response to CBT.

Discrepancies in perceived and actual cognitive performance are a consistent finding in patients with CFS.

DIAGNOSIS

In addition to a thorough history, a systematic physical examination is warranted to exclude disorders causing fatigue (e.g. endocrine disorders, neoplasms, heart failure, etc.). The heart rate of CFS patients is often slightly above normal. Laboratory tests primarily serve to exclude other diagnoses; there is no test that can diagnose CFS. The following laboratory screen usually suffices: complete blood count; ESR, CRP; serum creatinine, electrolytes, calcium and iron; blood glucose; creatine kinase; liver function tests; TSH; anti-gliadin antibodies; urinalysis. Serology for viral or bacterial infections is usually not helpful. No specific abnormalities have been identified on MRI or CT scans. CFS is a constellation of symptoms with no pathognomonic features and remains a diagnosis of exclusion.

Bipolar disorders, schizophrenia, and substance abuse exclude a diagnosis of CFS, as do eating disorders, unless these have been resolved 5 years or longer before symptom onset. Also, CFS is excluded if the chronic fatigue developed immediately after a depressive episode. Depression developing in the course of the fatigue, however, does not preclude CFS. Co-occurring psychiatric disorders, especially anxiety and mood disorders, are seen in 30–60% of all cases.

INITIAL MANAGEMENT

In cases of suspected CFS, the clinician should acknowledge the impact of the patient's symptoms on daily functioning. Disbelief or denial can provoke an exacerbation of genuine symptoms, which in turn strengthens the clinician's disbelief, leading to an unfortunate cycle of miscommunication. The possibility of CFS should be considered if a patient fulfils all criteria (Table 33-1) and if other diagnoses have been excluded.

The patient should be asked to describe the symptoms (fatigue and accompanying symptoms) and their duration as well as the consequences (reduction in daily activities). To assess symptom severity and the extent of daily-life impairment, the patient should describe a typical day, from waking to retiring, and contrast this with an average day prior to symptom onset. Next, potential fatigue-precipitating factors are sought. The severity of fatigue is difficult to assess quantitatively; a brief questionnaire is often helpful **(Fig. 33-1)**.

The patient should be informed of the current understanding of precipitating and perpetuating factors and effective treatments and should be offered general advice about disease management. If CBT for CFS is not available as an initial treatment option (see Treatment box later) and depression and anxiety are present, these symptoms should be treated. For patients with headache, diffuse pain, and feverishness, nonsteroidal anti-inflammatory drugs may be helpful. Even modest improvements in symptoms can make an important difference in the patient's degree of self-sufficiency and ability to appreciate life's pleasures.

Controlled therapeutic trials have established that acyclovir, fludrocortisone, galantamine, modafinil, and IV immunoglobulin, among other agents, offer no significant benefit in CFS. Countless anecdotes circulate regarding other traditional and nontraditional therapies. It is important to guide patients away from those therapeutic modalities that are toxic, expensive, or unreasonable.

The patient should be encouraged to maintain regular sleep patterns, to remain as active as possible, and to gradually return to previous exercise and activity (work) levels.

TREATMENT **Chronic Fatigue Syndrome**

CBT and graded exercise therapy (GET) have been found to be the only beneficial interventions in CFS. Some patient groups argue against these approaches because of the implication that CFS is a purely mental disorder. CBT is a psychotherapeutic approach directed at changing condition-related cognitions and behaviors. CBT for CFS aims at changing a patient's perpetuating

How have you felt during the last two weeks?

Please rate all four statements and per statement check the box that reflects your situation best.

1.	I feel tired	Yes, that is true	☐☐☐☐☐☐☐	No, that is not true
2.	I tire easily	Yes, that is true	☐☐☐☐☐☐☐	No, that is not true
3.	I feel fit	Yes, that is true	☐☐☐☐☐☐☐	No, that is not true
4.	Physically I feel exhausted	Yes, that is true	☐☐☐☐☐☐☐	No, that is not true

Scoring:
1, 2 and 4: Yes, that is true | 7 | 6 | 5 | 4 | 3 | 2 | 1 | No, that is not true — 3: Reversed

Sum scores >18 indicate severe fatigue

FIGURE 33-1
Shortened fatigue questionnaire (SFQ).

factors by exploiting various techniques and components. It includes educating the patient about the etiologic model, setting goals, restoring fixed bedtime and wake-up time, challenging and changing fatigue- and activity-related cognitions, reducing symptom focusing, spreading activities evenly throughout the day, gradually increasing physical activity, planning a return to work, and resuming other activities. The intervention, which typically consists of 12–14 sessions spread over 6 months, helps CFS patients gain control over their symptoms.

GET is based on the model of deconditioning and exercise intolerance and usually involves a home exercise program that continues for 3–5 months. Walking or cycling is systematically increased, with set target heart rates. Evidence that deconditioning is the basis for symptoms in CFS is lacking, however. The primary component of CBT and GET that results in a reduction in fatigue is the change in the patient's perception of fatigue and focus on symptoms.

CBT is generally the more complex treatment, which might explain why CBT studies tend to yield better improvement rates than GET trials.

Not all patients benefit from CBT or GET. Predictors of poor outcome are somatic comorbidity, current disability claims, and severe pain. CBT offered in an early stage of the illness reduces the burden of CFS for the patient as well as society in terms of decreased medical and disability-related costs.

PROGNOSIS

Full recovery from untreated CFS is rare: the median annual recovery rate is 5% (range 0–31%) and the improvement rate 39% (range 8–63%). Patients with an underlying psychiatric disorder and those who continue to attribute their symptoms to an undiagnosed medical condition have poorer outcomes.

CHAPTER 34

INFECTIOUS COMPLICATIONS OF BURNS

Lawrence C. Madoff ■ Florencia Pereyra

The skin is an essential component of the nonspecific immune system, protecting the host from potential pathogens in the environment. Breaches in this protective barrier thus represent a form of immunocompromise that predisposes a patient to infection. Thermal burns may cause massive destruction of the integument as well as derangements in humoral and cellular immunity, permitting the development of infection caused by environmental opportunists and components of the host's skin flora.

EPIDEMIOLOGY

Over the last decade, the estimated incidence of burn injuries in the United States has declined steadily; however, >1 million burn injuries are brought to medical attention each year. Although many burn injuries are minor and require little or no intervention, 50,000 persons are hospitalized for these injuries, 60% of whom require intensive care in a specialized burn center and 20,000 of whom have major burns involving at least 25% of the total body surface area. The majority of burn patients are men. Infants account for ~10% of all reported cases. Scalds, structural fires, and flammable liquids and gases are the major causes of burns, but electrical, chemical, and smoking-related sources are also important. Burns predispose to infection by damaging the protective barrier function of the skin, thus facilitating the entry of pathogenic microorganisms, and by inducing systemic immunosuppression. It is therefore unsurprising that multiorgan failure and infectious complications are the major causes of morbidity and death in serious burn injuries. As many as 10,000 patients in the United States die of burn-related infections each year, and 6 of the top 10 complications recently identified by the American Burn Association's 10-year review are infectious. These 10 most common complications are pneumonia (4.6%), septicemia (2.7%), cellulitis/traumatic injury (2.6%), respiratory failure (2.5%), wound infection (2.2%), other infection (2.0%), renal failure (1.5%), line infection (1.4%), acute respiratory distress syndrome (1.2%), and arrhythmia (1.0%) (*www.ameriburn.org/2007NBRAnnualReport.pdf*).

PATHOPHYSIOLOGY

Loss of the cutaneous barrier facilitates entry of the patient's own flora and of organisms from the hospital environment into a burn wound. Initially, the wound is colonized with gram-positive bacteria from the surrounding tissue, but the number of bacteria grows rapidly beneath the burn eschar, reaching ~8.4×10^3 cfu/g on day 4 after the burn. The avascularity of the eschar, along with the impairment of local immune responses, favors further bacterial colonization and proliferation. By day 7, the wound is colonized with other microbes, including gram-positive bacteria, gram-negative bacteria, and yeasts derived from the gastrointestinal and upper respiratory flora. Invasive infection—localized and/or systemic—occurs when these bacteria penetrate viable tissue. In addition, a role for biofilms has been recognized in experimental animal models of burn-wound infection. (Biofilms are surface-associated communities of bacteria, often embedded in a matrix, that allow the microbes to persist and to resist the effects of host immunity and antimicrobial agents.)

Streptococci and staphylococci were the predominant causes of burn-wound infection in the preantibiotic era and are still important pathogens. With the advent of antimicrobial agents, *Pseudomonas aeruginosa* became a major problem in burn-wound management. Less common anaerobic bacteria typically are found in infections from electrical burns or when open wound dressings are used. The widespread use of topical and more effective antimicrobial drugs has resulted in a decline in bacterial wound infections and the emergence of fungi (particularly *Candida albicans*, *Aspergillus* species, and the agents of mucormycosis) as increasingly important pathogens in burn-wound patients. Herpes simplex virus has been found in burn wounds, especially those on the neck and face and those associated with inhalation injury. Autopsy reports on patients with severe thermal burns over the last decade have identified an association of *P. aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Staphylococcus aureus* with death; this association is independent of the percentage of the total body surface area covered by burns, the percentage of burns that are full-thickness (as opposed to

partial-thickness), inhalation injury, and day of death after a burn. In addition, members of the *Acinetobacter calcoaceticus-baumannii* complex are among the most common pathogens at some burn centers.

The cascade of events that follows a severe burn injury and that leads to multiorgan system failure and death is thought to represent a two-step process; i.e., the burn injury itself, with ensuing hypo-volemia and tissue hypoxia, is followed by invasive infection arising from large amounts of devitalized tissue. The frequency of infection parallels the extent and severity of the burn injury. Severe burn injuries cause a state of immunosuppression that affects innate and adaptive immune responses. The substantial impact of immunocompromise on infection is due to effects on both the cellular and the humoral arms of the immune system. For example, decreases in the number and activity of circulating helper T cells, increases in the number and activity of suppressor T cells, decreases in production and release of monocytes and macrophages, and diminution in levels of immunoglobulin follow major burns. Neutrophil and complement functions also have been shown to be impaired after burns. The increased levels of multiple cytokines detected in burn patients are compatible with the widely held belief that the inflammatory response becomes dysregulated in these individuals; bacterial cell products play a potent role in inducing proinflammatory mediators that contribute to this uncontrolled systemic inflammatory response. Increased permeability of the gut wall to bacteria and their components (e.g., endotoxin) also contributes to immune dysregulation and sepsis. Thus, a burn patient is predisposed to infection at remote sites (see later) as well as at the sites of burn injury. Another contributor to secondary immunosuppression after burn injuries is the endocrine system; increasing levels of vasopressin, aldosterone, cortisol, glucagon, growth hormone, catecholamines, and other hormones that directly affect lymphocyte proliferation, secretion of proinflammatory cytokines, natural killer cell activity, and suppressor T cells are seen.

CLINICAL MANIFESTATIONS

Since clinical indications of wound infection are difficult to interpret, wounds must be monitored carefully for changes that may reflect infection. A margin of erythema frequently surrounds the sites of burns and by itself is not usually indicative of infection. Signs of infection include the conversion of a partial-thickness to a full-thickness burn, color changes (e.g., the appearance of a dark brown or black discoloration of the wound), the new appearance of erythema or violaceous edema in normal tissue at the wound margins, the sudden separation of the eschar from subcutaneous tissues, and the degeneration of the wound with the appearance of a new eschar.

Early surgical excision of devitalized tissue is now widely performed, and burn-wound infections can be classified in relation to the excision site as (1) burn-wound impetigo (infection characterized by loss of epithelium from a previously reepithelialized surface, as seen in a partial-thickness burn that is allowed to close by secondary intention, a grafted burn, or a healed skin donor site), (2) burn-related surgical wound infection (purulent infection of excised burn and donor sites that have not yet epithelialized, accompanied by positive cultures), (3) burn-wound cellulitis (extension of infection to surrounding healthy tissue; **Fig. 34-1**), and (4) invasive infection in unexcised burn wounds (infection that is secondary to a partial- or full-thickness burn wound and is manifested by separation of the eschar or by violaceous, dark brown, or black discoloration of the eschar; **Fig. 34-2**). The appearance of a green discoloration of the wound or subcutaneous fat **(Fig. 34-3)** or the development of ecthyma gangrenosum (see Fig. 11-35) at a remote site points to a diagnosis of invasive *P. aeruginosa* infection.

Changes in body temperature, hypotension, tachycardia, altered mentation, neutropenia or neutrophilia, thrombocytopenia, and renal failure may result from invasive burn wounds and sepsis. However, because profound alterations in homeostasis occur as a consequence of burns per se and because inflammation without infection is a normal component of these injuries, the assessment of these changes is complicated. Alterations in body temperature, for example, are attributable to thermoregulatory dysfunction; tachycardia and hyperventilation accompany the metabolic changes induced by extensive burn injury and are not necessarily indicative of bacterial sepsis.

In light of the difficulty of evaluating burn wounds solely on the basis of clinical observation and laboratory data, wound biopsies are necessary for definitive diagnosis of infection. The timing of these biopsies can be guided by clinical changes, but in some centers burn wounds are biopsied routinely at regular intervals. The biopsy specimen is examined for histologic evidence of bacterial invasion, and quantitative microbiologic cultures are performed. The presence of $>10^5$

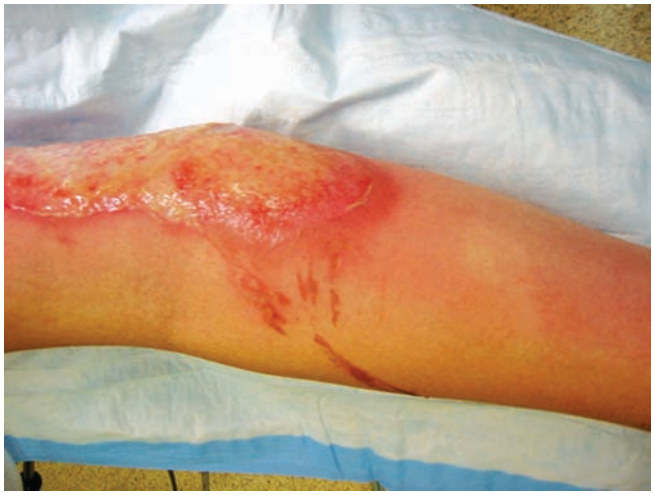


FIGURE 34-1
Cellulitis complicating a burn wound of the arm and demonstrating extension of the infection to adjacent healthy tissue. (*Courtesy of Dr. Robert L. Sheridan, Massachusetts General Hospital, Boston; with permission.*)

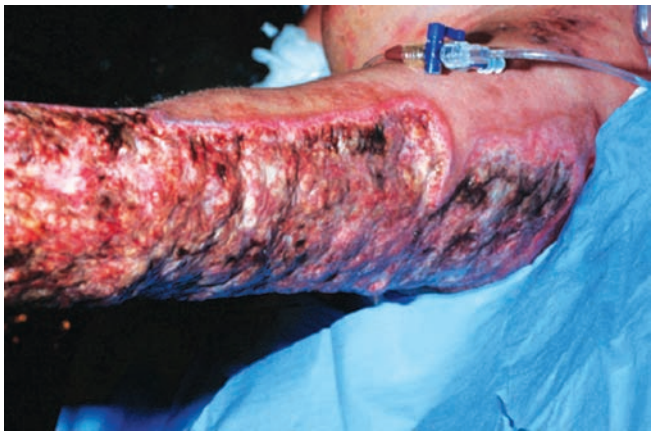


FIGURE 34-2
A severe upper-extremity burn infected with *Pseudomonas aeruginosa*. The wound requires additional debridement. Note the dark brown to black discoloration of the eschar. *(Courtesy of Dr. Robert L. Sheridan, Massachusetts General Hospital, Boston; with permission.)*

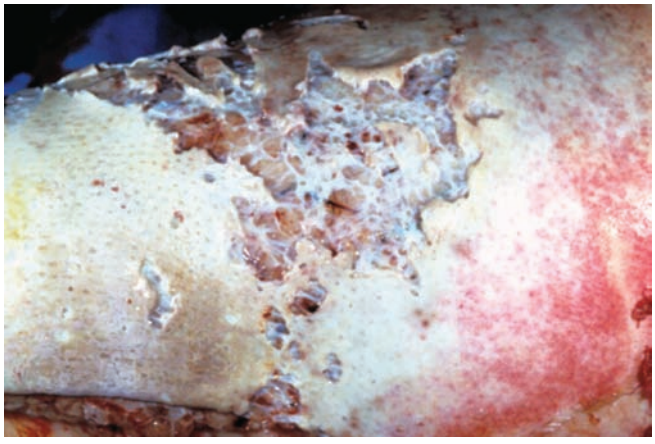


FIGURE 34-3
A burn wound infected with *Pseudomonas aeruginosa*, with liquefaction of tissue. Note the green discoloration at the wound margins, which is suggestive of *Pseudomonas* infection. (*Courtesy of Dr. Robert L. Sheridan, Massachusetts General Hospital, Boston; with permission.*)

viable bacteria per gram of tissue is highly suggestive of invasive infection and of a dramatically increased risk of sepsis. Histopathologic evidence of invasion of viable tissue and the presence of microorganisms in unburned blood vessels and lymphatics are more definitive indicators of infection. A blood culture positive for the same organism seen in large quantities in biopsied tissue is a reliable indicator of burn sepsis. Surface cultures may provide some indication of the microorganisms present in the hospital environment but are not indicative of the etiology of infection. This noninvasive technique might be of use in determining the flora present in excised burn areas or in areas where the skin is too thin for biopsy (e.g., over the ears, eyes, or digits).

In addition to infection of the burn wound itself, a number of other infections due to the immunosuppression caused by extensive burns and the manipulations necessary for clinical care put burn patients at risk. Pneumonia, now the most common infectious complication among hospitalized burn patients, is most often nosocomially acquired via the respiratory route; among the risk factors associated with secondary pneumonia are inhalation injury, intubation, full-thickness chest wall burns, immobility, and uncontrolled wound sepsis with hematogenous spread. Septic pulmonary emboli also may occur. Suppurative thrombophlebitis may complicate the vascular catheterization necessary for fluid and nutritional support in burns. Endocarditis, urinary tract infection, bacterial chondritis (particularly in patients with burned ears), and intraabdominal infection also complicate serious burn injury.

TREATMENT Burn-Wound Infections

The ultimate goal of burn-wound management is closure and healing of the wound. Early surgical excision of burned tissue, with extensive debridement of necrotic tissue and grafting of skin or skin substitutes, greatly decreases mortality rates associated with severe burns. In addition, the four widely used topical antimicrobial agents—silver sulfadiazine cream, mafenide acetate cream, silver nitrate cream, and nanocrystalline silver dressings—dramatically decrease the bacterial burden of burn wounds and reduce the incidence of burn-wound infection; these agents are applied routinely to partial- and full-thickness burns. The bactericidal properties of silver are related to its effect on respiratory enzymes on bacterial cell walls; its interaction with structural proteins causes keratinocyte and fibroblast toxicity that can delay wound healing if silver-based compounds are used indiscriminately. All four agents are broadly active against many bacteria and some fungi and are useful before bacterial colonization is established. Silver sulfadiazine often is used initially, but its value can be limited by bacterial resistance, poor wound penetration, or toxicity (leukopenia). Mafenide acetate has broader activity against gram-negative bacteria. The cream penetrates eschars and thus can prevent or treat infection beneath them; its use without dressings allows regular examination of the wound area. The foremost disadvantages of mafenide acetate are that it can inhibit carbonic anhydrase, resulting in metabolic acidosis, and that it elicits hypersensitivity reactions in up to 7% of patients. This agent is used most often when gram-negative bacteria invade the burn wound and when treatment with silver sulfadiazine fails. The activity of mafenide acetate against gram-positive bacteria is limited. Nanocrystalline silver dressings provide broader antimicrobial coverage than does any other available topical preparation, exhibiting activity against methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant enterococci, moderate ability to penetrate eschars, and limited toxicity. In addition, this approach provides controlled and prolonged release of nanocrystalline silver into the wound, limiting the

number of dressing changes and, therefore, reducing the risk of nosocomial infections as well as the cost of treatment. Mupirocin, a topical antimicrobial agent used to eradicate nasal colonization with MRSA, is being used increasingly in burn units where MRSA is prevalent. The efficacy of mupirocin in reducing burn-wound bacterial counts and preventing systemic infections is comparable to that of silver sulfadiazine.

In recent years, rates of fungal infection have increased in burn patients. When superficial fungal infection occurs, nystatin may be mixed with silver sulfadiazine or mafenide acetate as topical therapy. A small study found that nystatin powder (6 million units/g) was effective for treatment of superficial and deep burn-wound infections caused by *Aspergillus* or *Fusarium* species. In addition to these products, moisture-retention ointments with antimicrobial properties can promote rapid autolysis, debridement, and moist healing of partial-thickness wounds.

When invasive wound infection is diagnosed, topical therapy should be changed to mafenide acetate. Subeschar clysis (the direct instillation of an antibiotic, often piperacillin, into wound tissues under the eschar) is a useful adjunct to surgical and systemic antimicrobial therapy. Systemic treatment with antibiotics active against the pathogens present in the wound should be instituted. In the absence of culture data, treatment should be broad in spectrum, covering organisms commonly encountered in that particular burn unit. Such coverage usually is achieved with an antibiotic active against gram-positive pathogens (e.g., vancomycin, 1 g IV every 12 h) and with a drug active against *P. aeruginosa* and other gram-negative rods (e.g., ceftazidime, 2 g IV every 8 h). In penicillin-allergic patients, ciprofloxacin (400 mg IV every 12 h) may be substituted for ceftazidime. In settings where MRSA is not prevalent, oxacillin (2 g IV every 4 h) may be substituted for vancomycin. Patients with burn wounds frequently have alterations in metabolism and renal clearance mechanisms that mandate the monitoring of serum antibiotic levels; the levels achieved with standard doses are often subtherapeutic.

Treatment of infections caused by emerging resistant pathogens remains a challenge in the care of burn patients. MRSA, resistant enterococci, multidrug-resistant gram-negative rods, and Enterobacteriaceae producing extended-spectrum β-lactamases have been associated with burn-wound infections and identified in burn-unit outbreaks. Strict infection-control practices (including microbiologic surveillance in burn units) and appropriate antimicrobial therapy remain important measures in reducing rates of infection due to resistant organisms.

In general, prophylactic systemic antibiotics have no role in the management of burn wounds and can, in fact, lead to colonization with resistant microorganisms. In some studies, antibiotic prophylaxis has been associated with increased secondary infections of the upper and lower respiratory tract and the urinary tract as well as with prolonged hospitalization. An exception involves cases requiring burn-wound manipulation. Since procedures such as debridement, excision, and grafting frequently result in bacteremia, prophylactic systemic antibiotics are administered at the time of wound manipulation; the specific agents used should be chosen on the basis of data obtained by wound culture or data on the hospital's resident flora.

The use of oral antibiotics for selective digestive decontamination (SDD) to decrease bacterial colonization and the risk of burn-wound infection is controversial and has not been widely adopted. In a randomized, double-blind, placebo-controlled trial in patients with burns involving >20% of the total body surface area, SDD was associated with reduced mortality rates in the burn intensive care unit and in the hospital and also with a reduced incidence of pneumonia. The effects of SDD on the normal anaerobic bowel flora must be taken into consideration before this approach is used.

All burn-injury patients should undergo tetanus booster immunization if they have completed primary immunization but have not received a booster dose in the last 5 years. Patients without prior immunization should receive tetanus immune globulin and undergo primary immunization.

CHAPTER 35

INFECTIOUS COMPLICATIONS OF BITES

Lawrence C. Madoff ■ Florencia Pereyra

The skin is an essential component of the nonspecific immune system, protecting the host from potential pathogens in the environment. Breaches in this protective barrier thus represent a form of immunocompromise that predisposes the patient to infection. Bites and scratches from animals and humans allow the inoculation of microorganisms past the skin's protective barrier into deeper, susceptible host tissues.

Each year in the United States, millions of animal-bite wounds are sustained. The vast majority are inflicted by pet dogs and cats, which number >100 million; the annual incidence of dog and cat bites has been reported as 300 bites per 100,000 population. Other bite wounds are a consequence of encounters with animals in the wild or in occupational settings. While many of these wounds require minimal or no therapy, a significant number result in infection, which may be life-threatening. The microbiology of bite-wound infections in general reflects the oropharyngeal flora of the biting animal, although organisms from the soil, the skin of the animal and victim, and the animal's feces may also be involved.

DOG BITES

In the United States, dogs bite >4.7 million people each year and are responsible for 80% of all animal-bite wounds, an estimated 15–20% of which become infected. Each year, 800,000 Americans seek medical attention for dog bites; of those injured, 386,000 require treatment in an emergency department, with >1000 emergency department visits each day and about a dozen deaths per year. Most dog bites are provoked and are inflicted by the victim's pet or by a dog known to the victim. These bites frequently occur during efforts to break up a dogfight. Children are more likely than adults to sustain canine bites, with the highest incidence of 6 bites per 1000 population among boys 5–9 years old. Victims are more often male than female, and bites most often involve an upper extremity. Among children <4 years old, two-thirds of all these injuries involve the head or neck. Infection typically manifests 8–24 h after the bite as pain at the site of injury with cellulitis accompanied by purulent, sometimes foul-smelling discharge. Septic arthritis and osteomyelitis may develop if a canine tooth penetrates synovium or bone. Systemic manifestations (e.g., fever, lymphadenopathy, and lymphangitis) may also occur. The microbiology of dog-bite wound infections is usually mixed and includes β-hemolytic streptococci, *Pasteurella* species, *Staphylococcus* species [including methicillin-resistant *Staphylococcus aureus* (MRSA)], *Eikenella corrodens*, and *Capnocytophaga canimorsus*. Many wounds also include anaerobic bacteria such as *Actinomyces, Fusobacterium, Prevotella*, and *Porphyromonas* species.

While most infections resulting from dog-bite injuries are localized to the area of injury, many of the microorganisms involved are capable of causing systemic infection, including bacteremia, meningitis, brain abscess, endocarditis, and chorioamnionitis. These infections are particularly likely in hosts with edema or compromised lymphatic drainage in the involved extremity (e.g., after a bite on the arm in a woman who has undergone mastectomy) and in patients who are immunocompromised by medication or disease (e.g., glucocorticoid use, systemic lupus erythematosus, acute leukemia, or hepatic cirrhosis). In addition, dog bites and scratches may result in systemic illnesses such as rabies (Chap. 101) and tetanus (Chap. 44).

Infection with *C. canimorsus* following dog-bite wounds may result in fulminant sepsis, disseminated intravascular coagulation, and renal failure, particularly in hosts who have impaired hepatic function, who have undergone splenectomy, or who are immunosuppressed. This organism is a thin gram-negative rod that is difficult to culture on most solid media but grows in a variety of liquid media. The bacteria are occasionally seen within polymorphonuclear leukocytes on Wright-stained smears of peripheral blood from septic patients. Tularemia (Chap. 63) has also been reported to follow dog bites.

CAT BITES

Although less common than dog bites, cat bites and scratches result in infection in more than half of all cases. Because the cat's narrow, sharp canine teeth penetrate

deeply into tissue, cat bites are more likely than dog bites to cause septic arthritis and osteomyelitis; the development of these conditions is particularly likely when punctures are located over or near a joint, especially in the hand. Women sustain cat bites more frequently than do men. These bites most often involve the hands and arms. Both bites and scratches from cats are prone to infection from organisms in the cat's oropharynx. *Pasteurella multocida*, a normal component of the feline oral flora, is a small gram-negative coccobacillus implicated in the majority of cat-bite wound infections. Like that of dog-bite wound infections, however, the microflora of cat-bite wound infections is usually mixed. Other microorganisms causing infection after cat bites are similar to those causing dog-bite wound infections.

The same risk factors for systemic infection following dog-bite wounds apply to cat-bite wounds. *Pasteurella* infections tend to advance rapidly, often within hours, causing severe inflammation accompanied by purulent drainage; *Pasteurella* may also be spread by respiratory droplets from animals, resulting in pneumonia or bacteremia. Like dog-bite wounds, cat-bite wounds may result in the transmission of rabies or in the development of tetanus. Infection with *Bartonella henselae* causes cat-scratch disease (Chap. 65) and is an important late consequence of cat bites and scratches. Tularemia (Chap. 63) has also been reported to follow cat bites.

OTHER ANIMAL BITES

Infections have been attributed to bites from many animal species. Often these bites are sustained as a consequence of occupational exposure (farmers, laboratory workers, veterinarians) or recreational exposure (hunters and trappers, wilderness campers, owners of exotic pets). Generally, the microflora of bite wounds reflects the oral flora of the biting animal. Most members of the cat family, including feral cats, harbor *P. multocida*. Bite wounds from aquatic animals such as alligators or piranhas may contain *Aeromonas hydrophila*. Venomous snakebites (Chap. 131) result in severe inflammatory responses and tissue necrosis—conditions that render these injuries prone to infection. The snake's oral flora includes many species of aerobes and anaerobes, such as *Pseudomonas aeruginosa*, *Proteus* species, *Staphylococcus epidermidis*, *Bacteroides fragilis*, and *Clostridium* species. Bites from nonhuman primates are highly susceptible to infection with pathogens similar to those isolated from human bites (see below). Bites from Old World monkeys (*Macaca*) may also result in the transmission of B virus (*Herpesvirus simiae*, cercopithecine herpesvirus), a cause of serious infection of the human central nervous system. Bites of seals, walruses, and polar bears may cause a chronic suppurative infection known as *seal finger*, which is probably due to one or more species of *Mycoplasma* colonizing these animals.

Small rodents, including rats, mice, and gerbils, as well as animals that prey on rodents may transmit *Streptobacillus moniliformis* (a microaerophilic, pleomorphic gram-negative rod) or *Spirillum minor* (a spirochete), which cause a clinical illness known as *rat-bite fever*. The vast majority of cases in the United States are streptobacillary, whereas *Spirillum* infection occurs mainly in Asia.

In the United States, the risk of rodent bites is usually greatest among laboratory workers or inhabitants of rodent-infested dwellings (particularly children). Rat-bite fever is distinguished from acute bite-wound infection by its typical manifestation after the initial wound has healed. Streptobacillary disease follows an incubation period of 3–10 days. Fever, chills, myalgias, headache, and severe migratory arthralgias are usually followed by a maculopapular rash, which characteristically involves the palms and soles and may become confluent or purpuric. Complications include endocarditis, myocarditis, meningitis, pneumonia, and abscesses in many organs. *Haverhill fever* is an *S. moniliformis* infection acquired from contaminated milk or drinking water and has similar manifestations. Streptobacillary rat-bite fever was frequently fatal in the preantibiotic era. The differential diagnosis includes Rocky Mountain spotted fever, Lyme disease, leptospirosis, and secondary syphilis. The diagnosis is made by direct observation of the causative organisms in tissue or blood, by culture of the organisms on enriched media, or by serologic testing with specific agglutinins.

Spirillum infection (referred to in Japan as *sodoku*) causes pain and purple swelling at the site of the initial bite, with associated lymphangitis and regional lymphadenopathy, after an incubation period of 1–4 weeks. The systemic illness includes fever, chills, and headache. The original lesion may eventually progress to an eschar. The infection is diagnosed by direct visualization of the spirochetes in blood or tissue or by animal inoculation.

Finally, NO-1 (CDC nonoxidizer group 1) is a bacterium associated with dog- and cat-bite wounds. Infections in which NO-1 has been isolated have tended to manifest locally (i.e., as abscess and cellulitis). These infections have occurred in healthy persons with no underlying illness and in some instances have progressed from localized to systemic illnesses. The phenotypic characteristics of NO-1 are similar to those of asaccharolytic *Acinetobacter* species; i.e., NO-1 is oxidase-, indole-, and urease-negative. To date, all strains identified have been shown to be susceptible to aminoglycosides, β-lactam antibiotics, tetracyclines, quinolones, and sulfonamides.

HUMAN BITES

Human bites may be self-inflicted; may be sustained by medical personnel caring for patients; or may take place during fights, domestic abuse, or sexual activity. Human-bite wounds become infected more frequently (~10–15% of the time) than do bites inflicted by other animals. These infections reflect the diverse oral microflora of humans, which includes multiple species of aerobic and anaerobic bacteria. Common aerobic isolates include viridans streptococci, *S. aureus*, *E. corrodens* (which is particularly common in clenched-fist injury; see below), and *Haemophilus influenzae*. Anaerobic species, including *Fusobacterium nucleatum* and *Prevotella*, *Porphyromonas*, and *Peptostreptococcus* species, are isolated

from 50% of human-bite wound infections; many of these isolates produce β-lactamases. The oral flora of hospitalized and debilitated patients often includes Enterobacteriaceae in addition to the usual organisms. Hepatitis B, hepatitis C, herpes simplex virus infection, syphilis, tuberculosis, actinomycosis, and tetanus have been reported to be transmitted by human bites; it is biologically possible to transmit HIV through human bites, although this event is quite unlikely.

Human bites are categorized as either "occlusional" injuries, which are inflicted by actual biting, or "clenched-fist" injuries, which are sustained when the fist of one individual strikes the teeth of another, causing traumatic laceration of the hand. For several reasons, clenched-fist injuries, which are more common than occlusional injuries, result in particularly serious infections. The deep spaces of the hand, including the bones, joints, and tendons, are frequently inoculated with organisms in the course of such injuries. The clenched position of the fist during injury, followed by extension of the hand, may further promote the introduction of bacteria as contaminated tendons retract beneath the skin's surface. Moreover, medical attention is often sought only after frank infection develops.

APPROACH TO THE PATIENT Animal or Human Bites

A careful history should be elicited, including the type of biting animal, the type of attack (provoked or unprovoked), and the amount of time elapsed since injury. Local and regional public-health authorities should be contacted to determine whether an individual species could be rabid and/or to locate and observe the biting animal when rabies prophylaxis may be indicated (Chap. 101). Suspicious human-bite wounds should provoke careful questioning regarding domestic or child abuse. Details on antibiotic allergies, immunosuppression, splenectomy, liver disease, mastectomy, and immunization history should be obtained. The wound should be inspected carefully for evidence of infection, including redness, exudate, and foul odor. The type of wound (puncture, laceration, or scratch); the depth of penetration; and the possible involvement of joints, tendons, nerves, and bones should be assessed. It is often useful to include a diagram or photograph of the wound in the medical record. In addition, a general physical examination should be conducted and should include an assessment of vital signs as well as an evaluation for evidence of lymphangitis, lymphadenopathy, dermatologic lesions, and functional limitations. Injuries to the hand warrant consultation with a hand surgeon for the assessment of tendon, nerve, and muscular damage. Radiographs should be obtained when bone may have been penetrated or a tooth fragment may be present. Culture and Gram's staining of all infected wounds are essential; anaerobic cultures should be undertaken if abscesses, devitalized tissue, or foul-smelling exudate is present. A small-tipped swab may be used to culture deep punctures or small lacerations. It is also reasonable to culture samples from uninfected wounds due to bites inflicted by animals other than dogs and cats, since the microorganisms causing disease are less predictable in these cases. The white blood cell count should be determined and blood cultured if systemic infection is suspected.

TREATMENT Bite-Wound Infections

WOUND MANAGEMENT Wound closure is controversial in bite injuries. Many authorities prefer not to attempt primary closure of wounds that are or may become infected, preferring to irrigate these wounds copiously, debride devitalized tissue, remove foreign bodies, and approximate the wound edges. Delayed primary closure may be undertaken after the risk of infection is over. Small uninfected wounds may be allowed to close by secondary intention. Puncture wounds due to cat bites should be left unsutured because of the high rate at which they become infected. Facial wounds are usually sutured after thorough cleaning and irrigation because of the importance of a good cosmetic result in this area and because anatomic factors such as an excellent blood supply and the absence of dependent edema lessen the risk of infection.

ANTIBIOTIC THERAPY

Established Infection Antibiotics should be administered in all established bite-wound infections and should be chosen in light of the most likely potential pathogens, as indicated by the biting species and by Gram's stain and culture results (Table 35-1). For dog and cat bites, antibiotics should be effective against *S. aureus, Pasteurella* species, *C. canimorsus*, streptococci, and oral anaerobes. For human bites, agents with activity against *S. aureus, H. influenzae*, and β-lactamase-positive oral anaerobes should be used. The combination of an extended-spectrum penicillin with a β-lactamase inhibitor (amoxicillin/clavulanic acid, ticarcillin/clavulanic acid, ampicillin/sulbactam) appears to offer the most reliable coverage for these pathogens. Second-generation cephalosporins (cefuroxime, cefoxitin) also offer substantial coverage. The choice of antibiotics for penicillin-allergic patients (particularly those in whom immediate-type hypersensitivity makes the use of cephalosporins hazardous) is more difficult and is based primarily on in vitro sensitivity since data on clinical efficacy are inadequate. The combination of an antibiotic active against gram-positive cocci and anaerobes (such as clindamycin) with trimethoprim-sulfamethoxazole or a fluoroquinolone, which is active against many of the other potential pathogens, would appear reasonable. In vitro data suggest that azithromycin alone provides coverage against most commonly isolated bite-wound pathogens. As MRSA becomes more common in the community and evidence of its transmission between humans and their animal contacts increases, empirical

use of agents active against MRSA should be considered in high-risk situations while culture results are awaited.

Antibiotics are generally given for 10–14 days, but the response to therapy must be carefully monitored. Failure to respond should prompt a consideration of diagnostic alternatives and surgical evaluation for possible drainage or debridement. Complications such as osteomyelitis or septic arthritis mandate a longer duration of therapy.

Management of *C. canimorsus* sepsis requires a 2-week course of IV penicillin G (2 million units IV every 4 h) and supportive measures. Alternative agents for the treatment of *C. canimorsus* infection include cephalosporins and fluoroquinolones. Serious infection with *P. multocida* (e.g., pneumonia, sepsis, or meningitis) should also be treated with IV penicillin G. Alternative agents include second- or third-generation cephalosporins or ciprofloxacin.

Bites by venomous snakes (Chap. 131) may not require antibiotic treatment. Because it is often difficult to distinguish signs of infection from tissue damage caused by the envenomation, many authorities continue

TABLE 35-1

MANAGEMENT OF WOUND INFECTIONS FOLLOWING ANIMAL AND HUMAN BITES

BITING SPECIES	COMMONLY ISOLATED PATHOGENS	PREFERRED ANTIBIOTIC(S)[a]	ALTERNATIVE IN PENICILLIN-ALLERGIC PATIENT	PROPHYLAXIS ADVISED FOR EARLY UNINFECTED WOUNDS	OTHER CONSIDERATIONS
Dog	*Staphylococcus aureus, Pasteurella multocida*, anaerobes, *Capnocytophaga canimorsus*	Amoxicillin/clavulanate (250–500 mg PO tid) or ampicillin/sulbactam (1.5–3.0 g IV q6h)	Clindamycin (150–300 mg PO qid) plus either TMP-SMX (1 DS tablet PO bid) or ciprofloxacin (500 mg PO bid)	Sometimes[b]	Consider rabies prophylaxis.
Cat	*P. multocida, S. aureus*, anaerobes	Amoxicillin/clavulanate or ampicillin/sulbactam, as above	Clindamycin plus TMP-SMX as above or a fluoroquinolone	Usually	Consider rabies prophylaxis. Carefully evaluate for joint/bone penetration.
Human, occlusional	Viridans streptococci, *S. aureus, Haemophilus influenzae*, anaerobes	Amoxicillin/clavulanate or ampicillin/sulbactam, as above	Erythromycin (500 mg PO qid) or a fluoroquinolone	Always	Examine for tendon, nerve, or joint involvement.
Human, clenched-fist	As for occlusional plus *Eikenella corrodens*	Ampicillin/sulbactam as above or imipenem (500 mg q6h)	Cefoxitin[c]	Always	Examine for tendon, nerve, or joint involvement.
Monkey	As for human bite	As for human bite	As for human bite	Always	For macaque monkeys, consider B virus prophylaxis with acyclovir.
Snake	*Pseudomonas aeruginosa, Proteus* spp., *Bacteroides fragilis, Clostridium* spp.	Ampicillin/sulbactam as above	Clindamycin plus TMP-SMX as above or a fluoroquinolone	Sometimes, especially with venomous snakes	Antivenin for venomous snake bite
Rodent	*Streptobacillus moniliformis, Leptospira* spp., *P. multocida*	Penicillin VK (500 mg PO qid)	Doxycycline (100 mg PO bid)	Sometimes	—

[a]Antibiotic choices should be based on culture data when available. These suggestions for empirical therapy need to be tailored to individual circumstances and local conditions. IV regimens should be used for hospitalized patients. A single IV dose of antibiotic may be given to patients who will be discharged after initial management.

[b]Prophylactic antibiotics are suggested for severe or extensive wounds, facial wounds, and crush injuries; when bone or joint may be involved; and when comorbidity is present (see text).

[c]May be hazardous in patients with immediate-type hypersensitivity reaction to penicillin.

Abbreviations: DS, double-strength; TMP-SMX, trimethoprim-sulfamethoxazole.

to recommend treatment directed against the snake's oral flora—i.e., the administration of broadly active agents such as ceftriaxone (1–2 g IV every 12–24 h) or ampicillin/sulbactam (1.5–3.0 g IV every 6 h).

Seal finger appears to respond to doxycycline (100 mg twice daily for a duration guided by the response to therapy).

Presumptive or Prophylactic Therapy The use of antibiotics for patients presenting early (within 8 h) after bite injury is controversial. Although symptomatic infection frequently will not yet have manifested at this point, many early wounds will harbor pathogens, and many will become infected. Studies of antibiotic prophylaxis for wound infections are limited and have often included only small numbers of cases in which various types of wounds have been managed according to various protocols. A meta-analysis of eight randomized trials of prophylactic antibiotics in patients with dog-bite wounds demonstrated a reduction in the rate of infection by 50% with prophylaxis. However, in the absence of sound clinical trials, many clinicians base the decision to treat bite wounds with empirical antibiotics on the species of the biting animal; the location, severity, and extent of the bite wound; and the existence of comorbid conditions in the host. All human- and monkey-bite wounds should be treated presumptively because of the high rate of infection. Most cat-bite wounds, particularly those involving the hand, should be treated. Other factors favoring treatment for bite wounds include severe injury, as in crush wounds; potential bone or joint involvement; involvement of the hands or genital region; host immunocompromise, including that due to liver disease or splenectomy; and prior mastectomy on the side of an involved upper extremity. When prophylactic antibiotics are administered, they are usually given for 3–5 days.

Rabies and Tetanus Prophylaxis Rabies prophylaxis, consisting of both passive administration of rabies immune globulin (with as much of the dose as possible infiltrated into and around the wound) and active immunization with rabies vaccine, should be given in consultation with local and regional public health authorities for many wild-animal (and some domestic-animal) bites and scratches as well as for certain nonbite exposures (Chap. 101). Rabies is endemic in a variety of animals, including dogs and cats in many areas of the world. Many local health authorities require the reporting of all animal bites. A tetanus booster immunization should be given if the patient has undergone primary immunization, but has not received a booster dose in the past 5 years. Patients who have not previously completed primary immunization should be immunized and should also receive tetanus immune globulin. Elevation of the site of injury is an important adjunct to antimicrobial therapy. Immobilization of the infected area, especially the hand, is also beneficial.

This page intentionally left blank

SECTION IV

BACTERIAL INFECTIONS

CHAPTER 36

TREATMENT AND PROPHYLAXIS OF BACTERIAL INFECTIONS

Gordon L. Archer ■ Ronald E. Polk

The development of vaccines and drugs that prevent and cure bacterial infections was one of the twentieth century's major contributions to human longevity and quality of life. Antibacterial agents are among the most commonly prescribed drugs of any kind worldwide. Used appropriately, these drugs are lifesaving. However, their indiscriminate use drives up the cost of health care, leads to a plethora of side effects and drug interactions, and fosters the emergence of bacterial resistance, rendering previously valuable drugs useless. The rational use of antibacterial agents depends on an understanding of (1) the drugs' mechanisms of action, spectra of activity, pharmacokinetics, pharmacodynamics, toxicities, and interactions; (2) mechanisms underlying bacterial resistance; and (3) strategies that can be used by clinicians to limit resistance. In addition, patient-associated parameters, such as infection site, other drugs being taken, allergies, and immune and excretory status, are critically important to appropriate therapeutic decisions. This chapter provides specific data required for making an informed choice of antibacterial agent.

MECHANISMS OF ACTION

Antibacterial agents, like all antimicrobial drugs, are directed against unique targets not present in mammalian cells. The goal is to limit toxicity to the host and maximize chemotherapeutic activity affecting invading microbes only. *Bactericidal drugs* kill the bacteria that are within their spectrum of activity; *bacteriostatic drugs* only inhibit bacterial growth. While bacteriostatic activity is adequate for the treatment of most infections, bactericidal activity may be necessary for cure in patients with altered immune systems (e.g., neutropenia), protected infectious foci (e.g., endocarditis or meningitis), or specific infections (e.g., complicated *Staphylococcus aureus* bacteremia). The mechanisms of action of the antibacterial agents to be discussed in this section are summarized in **Table 36-1** and are depicted in **Fig. 36-1**.

INHIBITION OF CELL-WALL SYNTHESIS

One major difference between bacterial and mammalian cells is the presence in bacteria of a rigid wall external to the cell membrane. The wall protects bacterial cells from osmotic rupture, which would result from the cell's usual marked hyperosmolarity (by up to 20 atm) relative to the host environment. The structure conferring cell-wall rigidity and resistance to osmotic lysis in both gram-positive and gram-negative bacteria is peptidoglycan, a large, covalently linked sacculus that surrounds the bacterium. In gram-positive bacteria, peptidoglycan is the only layered structure external to the cell membrane and is thick (20–80 nm); in gram-negative bacteria, there is an outer membrane external to a very thin (1-nm) peptidoglycan layer.

Chemotherapeutic agents directed at any stage of the synthesis, export, assembly, or cross-linking of peptidoglycan lead to inhibition of bacterial cell growth and, in most cases, to cell death. Peptidoglycan is composed of (1) a backbone of two alternating sugars, *N*-acetylglucosamine and *N*-acetylmuramic acid; (2) a chain of four amino acids that extends down from the backbone (stem peptides); and (3) a peptide bridge that cross-links the peptide chains. Peptidoglycan is formed by the addition of subunits (a sugar with its five attached amino acids) that are assembled in the cytoplasm and transported through the cytoplasmic membrane to the cell surface. Subsequent cross-linking is driven by cleavage of the terminal stem-peptide amino acid.

Virtually all the antibiotics that inhibit bacterial cell-wall synthesis are bactericidal. That is, they eventually result in the cell's death due to osmotic lysis. However, much of the loss of cell-wall integrity following treatment with cell wall–active agents is due to the bacteria's own cell-wall remodeling enzymes (autolysins) that cleave peptidoglycan bonds in the normal course of cell growth. In the presence of antibacterial agents that inhibit cell-wall growth, autolysis proceeds without normal cell-wall repair; weakness and eventual cellular

TABLE 36-1

MECHANISMS OF ACTION OF AND RESISTANCE TO MAJOR CLASSES OF ANTIBACTERIAL AGENTS

LETTER FOR FIG. 36-1	ANTIBACTERIAL AGENT[a]	MAJOR CELLULAR TARGET	MECHANISM OF ACTION	MAJOR MECHANISMS OF RESISTANCE
A	β-Lactams (penicillins, cephalosporins)	Cell wall	Inhibit cell-wall cross-linking	1. Drug inactivation (β-lactamase) 2. Insensitivity of target (altered penicillin-binding proteins) 3. Decreased permeability (altered gram-negative outer-membrane porins) 4. Active efflux
B	Vancomycin	Cell wall	Interferes with addition of new cell-wall subunits (muramyl pentapeptides)	Alteration of target (substitution of terminal amino acid of peptidoglycan subunit)
	Bacitracin	Cell wall	Prevents addition of cell-wall subunits by inhibiting recycling of membrane lipid carrier	Not defined
C	Macrolides (erythromycin)	Protein synthesis	Bind to 50S ribosomal subunit	1. Alteration of target (ribosomal methylation and mutation of 23S rRNA) 2. Active efflux
	Lincosamides (clindamycin)	Protein synthesis	Bind to 50S ribosomal subunit Block peptide chain elongation	1. Alteration of target (ribosomal methylation) 2. Active efflux
D	Chloramphenicol	Protein synthesis	Binds to 50S ribosomal subunit Blocks aminoacyl tRNA attachment	1. Drug inactivation (chloramphenicol acetyltransferase) 2. Active efflux
E	Tetracycline	Protein synthesis	Binds to 30S ribosomal subunit Blocks binding of aminoacyl tRNA	1. Decreased intracellular drug accumulation (active efflux) 2. Insensitivity of target
F	Aminoglycosides (gentamicin)	Protein synthesis	Bind to 30S ribosomal subunit Inhibit translocation of peptidyl-tRNA	1. Drug inactivation (aminoglycoside-modifying enzyme) 2. Decreased permeability through gram-negative outer membrane 3. Active efflux 4. Ribosomal methylation
G	Mupirocin	Protein synthesis	Inhibits isoleucine tRNA synthetase	Mutation of gene for target protein or acquisition of new gene for drug-insensitive target
H	Streptogramins [quinupristin/dalfopristin (Synercid)]	Protein synthesis	Bind to 50S ribosomal subunit Block peptide chain elongation	1. Alteration of target (ribosomal methylation: dalfopristin) 2. Active efflux (quinupristin) 3. Drug inactivation (quinupristin and dalfopristin)
I	Linezolid	Protein synthesis	Binds to 50S ribosomal subunit Inhibits initiation of protein synthesis	Alteration of target (mutation of 23S rRNA)
J	Sulfonamides and trimethoprim	Cell metabolism	Competitively inhibit enzymes involved in two steps of folic acid biosynthesis	Production of insensitive targets [dihydropteroate synthetase (sulfonamides) and dihydrofolate reductase (trimethoprim)] that bypass metabolic block

(*continued*)

TABLE 36-1

MECHANISMS OF ACTION OF AND RESISTANCE TO MAJOR CLASSES OF ANTIBACTERIAL AGENTS (*CONTINUED*)

LETTER FOR FIG. 36-1	ANTIBACTERIAL AGENTA	MAJOR CELLULAR TARGET	MECHANISM OF ACTION	MAJOR MECHANISMS OF RESISTANCE
K	Rifampin	Nucleic acid synthesis	Inhibits DNA-dependent RNA polymerase	Insensitivity of target (mutation of polymerase gene)
L	Metronidazole	Nucleic acid synthesis	Intracellularly generates short-lived reactive intermediates that damage DNA by electron transfer system	Not defined
M	Quinolones (ciprofloxacin)	DNA synthesis	Inhibit activity of DNA gyrase (A subunit) and topoisomerase IV	1. Insensitivity of target (mutation of gyrase genes) 2. Decreased intracellular drug accumulation (active efflux)
	Novobiocin	DNA synthesis	Inhibits activity of DNA gyrase (B subunit)	Not defined
N	Polymyxins (polymyxin B)	Cell membrane	Disrupt membrane permeability by charge alteration	Not defined
	Gramicidin	Cell membrane	Forms pores	Not defined
O	Daptomycin	Cell membrane	Forms channels that disrupt membrane potential	Alteration of membrane charge

[a]Compounds in parentheses are major representatives for the class.

lysis occur. Antibacterial agents act to inhibit cell-wall synthesis in several ways, as described next.

Bacitracin

Bacitracin, a cyclic peptide antibiotic, inhibits the conversion to its active form of the lipid carrier that moves the water-soluble cytoplasmic peptidoglycan subunits through the cell membrane to the cell exterior.

Glycopeptides

Glycopeptides [vancomycin, teicoplanin, and telavancin (lipoglycopeptide)] are high-molecular-weight antibiotics that bind to the terminal D-alanine–D-alanine component of the stem peptide while the subunits are external to the cell membrane but still linked to the lipid carrier. This binding sterically inhibits the addition of subunits to the peptidoglycan backbone.

β-Lactam antibiotics

β-Lactam antibiotics (penicillins, cephalosporins, carbapenems, and monobactams; **Table 36-2**) are characterized by a four-membered β-lactam ring and prevent the cross-linking reaction called *transpeptidation*. The energy for attaching a peptide cross-bridge from the stem peptide of one peptidoglycan subunit to another is derived from the cleavage of a terminal D-alanine residue from the subunit stem peptide. The cross-bridge amino acid is then attached to the penultimate D-alanine by transpeptidase enzymes. The β-lactam ring of the antibiotic forms an irreversible covalent acyl bond with the transpeptidase enzyme (probably because of the antibiotic's steric similarity to the enzyme's D-alanine–D-alanine target), preventing the cross-linking reaction. Transpeptidases and similar enzymes involved in cross-linking are called *penicillin-binding proteins* (PBPs) because they all have active sites that bind β-lactam antibiotics.

INHIBITION OF PROTEIN SYNTHESIS

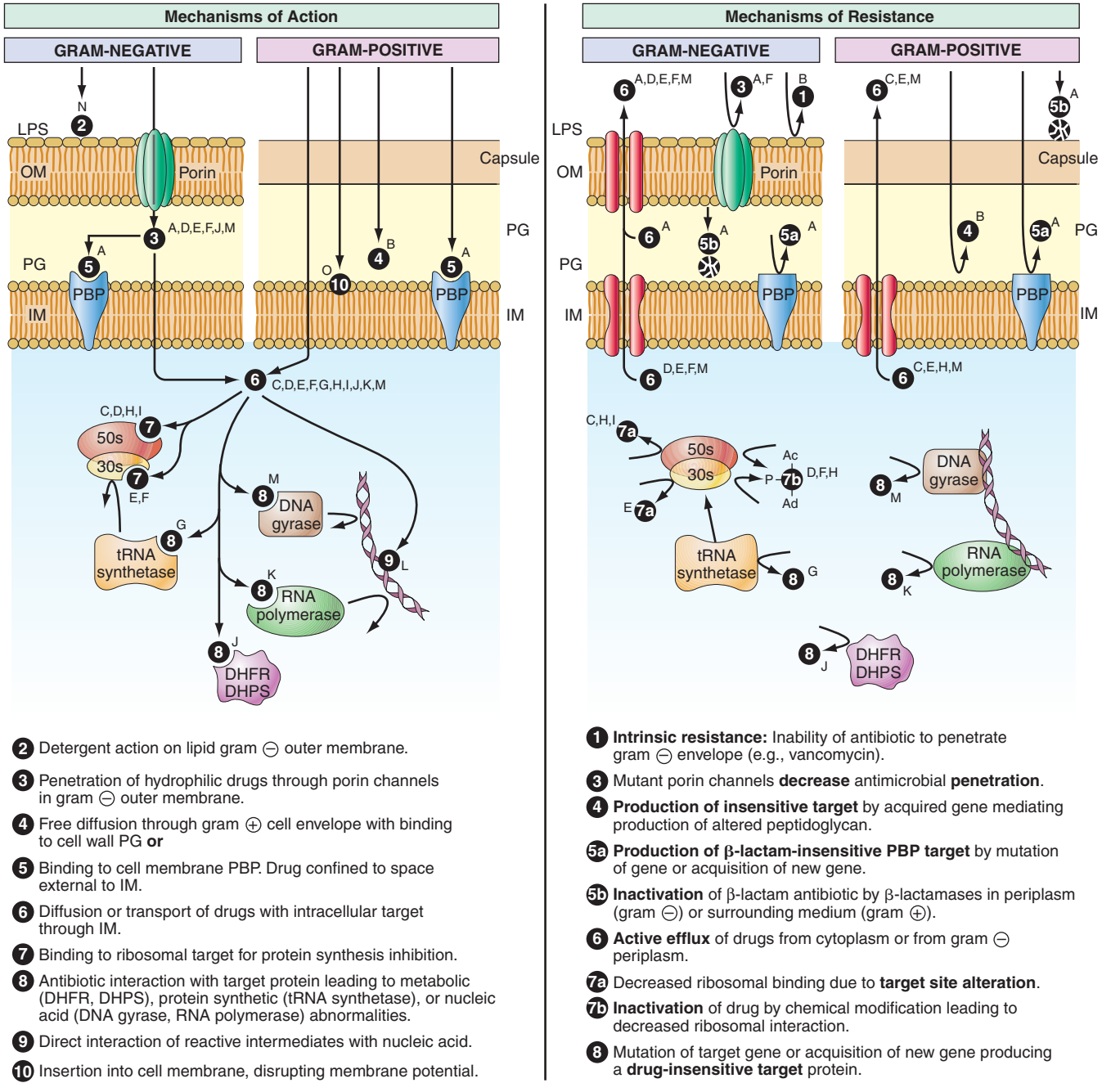
Most of the antibacterial agents that inhibit protein synthesis interact with the bacterial ribosome. The difference between the composition of bacterial and mammalian ribosomes gives these compounds their selectivity.

Aminoglycosides

Aminoglycosides (gentamicin, kanamycin, tobramycin, streptomycin, neomycin, and amikacin) are a group of structurally related compounds containing three linked hexose sugars. They exert a bactericidal effect by binding irreversibly to the 30S subunit of the bacterial ribosome and inhibiting translocation of peptidyl-tRNA from the A to the P site. Uptake of aminoglycosides and their penetration through the cell membrane constitute an aerobic, energy-dependent process. Thus, aminoglycoside activity is markedly reduced in an anaerobic environment. *Spectinomycin*, an aminocyclitol antibiotic, also acts on the 30S ribosomal subunit but has a different mechanism of action from the aminoglycosides and is bacteriostatic rather than bactericidal.

Macrolides, ketolides, and lincosamides

Macrolide antibiotics (erythromycin, clarithromycin, and azithromycin) consist of a large lactone ring to which sugars are attached. *Ketolide antibiotics*, including telithromycin, replace the cladinose sugar on the macrolactone ring with a ketone group. These drugs bind specifically to the 50S portion of the bacterial ribosome and inhibit



2 Detergent action on lipid gram ⊖ outer membrane.

3 Penetration of hydrophilic drugs through porin channels in gram ⊖ outer membrane.

4 Free diffusion through gram ⊕ cell envelope with binding to cell wall PG **or**

5 Binding to cell membrane PBP. Drug confined to space external to IM.

6 Diffusion or transport of drugs with intracellular target through IM.

7 Binding to ribosomal target for protein synthesis inhibition.

8 Antibiotic interaction with target protein leading to metabolic (DHFR, DHPS), protein synthetic (tRNA synthetase), or nucleic acid (DNA gyrase, RNA polymerase) abnormalities.

9 Direct interaction of reactive intermediates with nucleic acid.

10 Insertion into cell membrane, disrupting membrane potential.

1 **Intrinsic resistance:** Inability of antibiotic to penetrate gram ⊖ envelope (e.g., vancomycin).

3 Mutant porin channels **decrease** antimicrobial **penetration**.

4 **Production of insensitive target** by acquired gene mediating production of altered peptidoglycan.

5a **Production of β-lactam-insensitive PBP target** by mutation of gene or acquisition of new gene.

5b **Inactivation** of β-lactam antibiotic by β-lactamases in periplasm (gram ⊖) or surrounding medium (gram ⊕).

6 **Active efflux** of drugs from cytoplasm or from gram ⊖ periplasm.

7a Decreased ribosomal binding due to **target site alteration**.

7b **Inactivation** of drug by chemical modification leading to decreased ribosomal interaction.

8 Mutation of target gene or acquisition of new gene producing a **drug-insensitive target** protein.

FIGURE 36-1

Mechanisms of action of and resistance to antibacterial agents. Black lines trace the routes of drug interaction with bacterial cells, from entry to target site. The letters in each figure indicate specific antibacterial agents or classes of agents, as shown in Table 36-1. The numbers correspond to mechanisms listed beneath each panel. Abbreviations: 50s and 30s, large and small ribosome subunits; Ac, acetylation; Ad, adenylation; DHFR, dihydrofolate reductase; DHPS, dihydropteroate synthetase; IM, inner (cytoplasmic) membrane; LPS, lipopolysaccharide; OM, outer membrane; P, phosphorylation; PBP, penicillin-binding protein; PG, peptidoglycan.

protein chain elongation. Although structurally unrelated to the macrolides, *lincosamides* (clindamycin and lincomycin) bind to a site on the 50S ribosome nearly identical to the binding site for macrolides.

Streptogramins

Streptogramins (quinupristin [streptogramin B] and dalfopristin [streptogramin A]), which are supplied as a combination in Synercid, are peptide macrolactones that also bind to the 50S ribosomal subunit and block protein synthesis. Streptogramin B binds to a ribosomal site similar to the binding site for macrolides and lincosamides, whereas streptogramin A binds to a different ribosomal site, blocking the late phase of protein synthesis. The two streptogramins act synergistically to kill bacteria if the strain is susceptible to both components.

TABLE 36-2

CLASSIFICATION OF β-LACTAM ANTIBIOTICS

CLASS	ROUTE OF ADMINISTRATION: PARENTERAL	ROUTE OF ADMINISTRATION: ORAL
Penicillins		
β-Lactamase-susceptible		
Narrow-spectrum	Penicillin G	Penicillin V
Enteric-active	Ampicillin	Amoxicillin, ampicillin
Enteric-active and antipseudomonal	Ticarcillin, piperacillin	None
β-Lactamase-resistant		
Antistaphylococcal	Oxacillin, nafcillin	Cloxacillin, dicloxacillin
Combined with β-lactamase inhibitors	Ticarcillin plus clavulanic acid, ampicillin plus sulbactam, piperacillin plus tazobactam	Amoxicillin plus clavulanic acid
Cephalosporins		
First-generation	Cefazolin, cephapirin	Cephalexin, cefadroxil
Second-generation		
Haemophilus-active	Cefuroxime, cefonicid, ceforanide	Cefaclor, cefuroxime axetil, ceftibuten, cefdinir, cefprozil, cefditoren, cefpodoxime[a]
Bacteroides-active	Cefoxitin, cefotetan	None
Third-generation		
Extended-spectrum	Ceftriaxone, cefotaxime, ceftizoxime	None
Extended-spectrum and antipseudomonal	Ceftazidime, cefepime	None
Extended-spectrum and anti-MRSA[b]	Ceftobiprole	None
Carbapenems	Imipenem/cilastatin, meropenem, ertapenem, doripenem	None
Monobactams	Aztreonam	None

[a]Some sources classify cefpodoxime as a third-generation oral agent because of a marginally broader spectrum.
[b]Methicillin-resistant *Staphylococcus aureus*.

Chloramphenicol

Chloramphenicol consists of a single aromatic ring and a short side chain. This antibiotic binds reversibly to the 50S portion of the bacterial ribosome at a site close to but not identical with the binding sites for the macrolides and lincosamides, inhibiting peptide bond formation by blocking attachment of the amino acid end of aminoacyl-tRNA to the ribosome.

Linezolid

Linezolid is the only commercially available drug in the oxazolidinone class. Linezolid binds to the 50S ribosomal subunit and blocks the initiation of protein synthesis.

Tetracyclines and glycylcyclines

Tetracyclines (tetracycline, doxycycline, and minocycline) and glycylcyclines (tigecycline) consist of four aromatic rings with various substituent groups. They interact reversibly with the bacterial 30S ribosomal subunit, blocking the binding of aminoacyl tRNA to the mRNA-ribosome complex. This mechanism is markedly different from that of the aminoglycosides, which also bind to the 30S subunit.

Mupirocin

Mupirocin (pseudomonic acid) inhibits isoleucine tRNA synthetase by competing with bacterial isoleucine for its binding site on the enzyme and depleting cellular stores of isoleucine-charged tRNA.

INHIBITION OF BACTERIAL METABOLISM

The *antimetabolites* are all synthetic compounds that interfere with bacterial synthesis of folic acid. Products of the folic acid synthesis pathway function as coenzymes for the one-carbon transfer reactions that are essential for the synthesis of thymidine, all purines, and several amino acids. Inhibition of folate synthesis leads to cessation of bacterial cell growth and, in some cases, to bacterial cell death. The principal antibacterial antimetabolites are sulfonamides (sulfisoxazole, sulfadiazine, and sulfamethoxazole) and trimethoprim.

Sulfonamides

Sulfonamides are structural analogues of *p*-aminobenzoic acid (PABA), one of the three structural components of folic acid (the other two being pteridine and glutamate). The first step in the synthesis of folic acid is the addition of PABA to pteridine by the enzyme dihydropteroic acid synthetase. Sulfonamides compete with PABA as substrates for the enzyme. The selective effect of sulfonamides is due to the fact that bacteria synthesize folic acid, while mammalian cells cannot synthesize the cofactor and

must use exogenous supplies. However, the activity of sulfonamides can be greatly reduced by the presence of excess PABA or by the exogenous addition of end products of one-carbon transfer reactions (e.g., thymidine and purines). High concentrations of the latter substances may be present in some infections as a result of tissue and white cell breakdown, compromising sulfonamide activity.

Trimethoprim

Trimethoprim is a diaminopyrimidine, a structural analogue of the pteridine moiety of folic acid. Trimethoprim is a competitive inhibitor of dihydrofolate reductase; this enzyme is responsible for reduction of dihydrofolic acid to tetrahydrofolic acid—the essential final component in the folic acid synthesis pathway. Like that of the sulfonamides, the activity of trimethoprim is compromised in the presence of exogenous thymine or thymidine.

INHIBITION OF NUCLEIC ACID SYNTHESIS OR ACTIVITY

Numerous antibacterial compounds have disparate effects on nucleic acids.

Quinolones

The quinolones, including nalidixic acid and its fluorinated derivatives (ciprofloxacin, levofloxacin, and moxifloxacin), are synthetic compounds that inhibit the activity of the A subunit of the bacterial enzyme DNA gyrase as well as topoisomerase IV. DNA gyrase and topoisomerases are responsible for negative supercoiling of DNA—an essential conformation for DNA replication in the intact cell. Inhibition of the activity of DNA gyrase and topoisomerase IV is lethal to bacterial cells. The antibiotic *novobiocin* also interferes with the activity of DNA gyrase, but it interferes with the B subunit.

Rifampin

Rifampin, used primarily against *Mycobacterium tuberculosis*, is also active against a variety of other bacteria. Rifampin binds tightly to the B subunit of bacterial DNA-dependent RNA polymerase, thus inhibiting transcription of DNA into RNA. Mammalian-cell RNA polymerase is not sensitive to this compound.

Nitrofurantoin

Nitrofurantoin, a synthetic compound, causes DNA damage. The nitrofurans, compounds containing a single five-membered ring, are reduced by a bacterial enzyme to highly reactive, short-lived intermediates that are thought to cause DNA strand breakage, either directly or indirectly.

Metronidazole

Metronidazole, a synthetic imidazole, is active only against anaerobic bacteria and protozoa. The reduction of metronidazole's nitro group by the bacterial anaerobic electron-transport system produces a transient series of reactive intermediates that are thought to cause DNA damage.

ALTERATION OF CELL-MEMBRANE PERMEABILITY

Polymyxins

The polymyxins [polymyxin B and colistin (polymyxin E)] are cyclic, basic polypeptides. They behave as cationic, surface-active compounds that disrupt the permeability of both the outer and the cytoplasmic membranes of gram-negative bacteria.

Gramicidin A

Gramicidin A is a polypeptide of 15 amino acids that acts as an ionophore, forming pores or channels in lipid bilayers.

Daptomycin

Insertion of daptomycin, a bactericidal lipopeptide antibiotic, into the cell membrane of gram-positive bacteria forms a channel that causes depolarization of the membrane by efflux of intracellular ions, resulting in cell death.

MECHANISMS OF RESISTANCE

Some bacteria exhibit *intrinsic resistance* to certain classes of antibacterial agents (e.g., obligate anaerobic bacteria to aminoglycosides and gram-negative bacteria to vancomycin). In addition, bacteria that are ordinarily susceptible to antibacterial agents can acquire resistance. *Acquired resistance* is a major limitation to effective antibacterial chemotherapy. Resistance can develop by mutation of resident genes or by acquisition of new genes. New genes mediating resistance are usually spread from cell to cell by way of mobile genetic elements such as plasmids, transposons, and bacteriophages. The resistant bacterial populations flourish in areas of high antimicrobial use, where they enjoy a selective advantage over susceptible populations.

The major mechanisms used by bacteria to resist the action of antimicrobial agents are inactivation of the compound, alteration or overproduction of the antibacterial target through mutation of the target protein's gene, acquisition of a new gene that encodes a drug-insensitive target, decreased permeability of the cell envelope to the agent, failure to convert an inactive prodrug to its active derivative, and active efflux of the compound from the periplasm or interior of the cell. Specific mechanisms of bacterial resistance to the major antibacterial agents are outlined next, summarized in Table 36-1, and depicted in Fig. 36-1.

β-LACTAM ANTIBIOTICS

Bacteria develop resistance to β-lactam antibiotics by a variety of mechanisms. Most common is the destruction of the drug by β-lactamases. The β-lactamases of gram-negative bacteria are confined to the periplasm, between the inner and outer membranes, while gram-positive bacteria secrete their β-lactamases into the surrounding medium. These enzymes have a higher

affinity for the antibiotic than the antibiotic has for its target. Binding results in hydrolysis of the β-lactam ring. Genes encoding β-lactamases have been found in both chromosomal and extrachromosomal locations and in both gram-positive and gram-negative bacteria; these genes are often on mobile genetic elements. Many "advanced-generation" β-lactam antibiotics, such as ceftriaxone and cefepime, are stable in the presence of plasmid-mediated β-lactamases and are active against bacteria resistant to earlier-generation β-lactam antibiotics. However, extended-spectrum β-lactamases (ESBLs), either acquired on mobile genetic elements by gram-negative bacteria (e.g., *Klebsiella pneumoniae* and *Escherichia coli*) or present as stable chromosomal genes in other gram-negative species (e.g., *Enterobacter* spp.), have broad substrate specificity, hydrolyzing virtually all penicillins and cephalosporins. Carbapenems are generally resistant to ESBL hydrolysis and are the drugs of choice for the treatment of infections caused by ESBL-producing Enterobacteriaceae. However, Enterobacteriaceae (particularly *K. pneumoniae*) that produce arbapenemases and are resistant to virtually all β-lactam antibiotics have now emerged. One strategy that has been devised for circumventing resistance mediated by β-lactamases is to combine the β-lactam agent with an inhibitor that avidly binds the inactivating enzyme, preventing its attack on the antibiotic. Unfortunately, the inhibitors (e.g., clavulanic acid, sulbactam, and tazobactam) do not bind all chromosomal β-lactamases (e.g., that of *Enterobacter*) or carbapenemases and thus cannot be depended on to prevent the inactivation of β-lactam antibiotics by such enzymes. No β-lactam antibiotic or inhibitor has been produced that can resist all of the many β-lactamases that have been identified.

A second mechanism of bacterial resistance to β-lactam antibiotics is an alteration in PBP targets so that the PBPs have a markedly reduced affinity for the drug. While this alteration may occur by mutation of existing genes, the acquisition of new PBP genes (as in staphylococcal resistance to methicillin) or of new pieces of PBP genes (as in streptococcal, gonococcal, and meningococcal resistance to penicillin) is more important.

A final resistance mechanism is the coupling, in gram-negative bacteria, of a decrease in outer-membrane permeability with rapid efflux of the antibiotic from the periplasm to the cell exterior. Mutations of genes encoding outer-membrane protein channels called *porins* decrease the entry of β-lactam antibiotics into the cell, while additional proteins form channels that actively pump β-lactams out of the cell. Resistance of Enterobacteriaceae to some cephalosporins and resistance of *Pseudomonas* spp. to cephalosporins and piperacillin are the best examples of this mechanism.

VANCOMYCIN

Clinically important resistance to vancomycin was first described among enterococci in France in 1988. ancomycin-resistant enterococci (VRE) have subsequently become disseminated worldwide. The genes encoding resistance are carried on plasmids that can transfer themselves from cell to cell and on transposons that can jump from plasmids to chromosomes. Resistance is mediated by enzymes that substitute D-lactate for D-alanine on the peptidoglycan stem peptide so that there is no longer an appropriate target for vancomycin binding. This alteration does not appear to affect cell-wall integrity, however. This type of acquired vancomycin resistance was confined for 14 years to enterococci—more specifically, to *Enterococcus faecium* rather than the more common pathogen *E. faecalis*. However, since 2002, *S. aureus* isolates that are highly resistant to vancomycin have been recovered from 11 patients in the United States. All of the isolates contain *vanA*, the gene that mediates vancomycin resistance in enterococci. In addition, since 1996, a few isolates of both *S. aureus* and *Staphylococcus epidermidis* that display a four- to eightfold reduction in susceptibility to vancomycin have been found worldwide; such *S. aureus* strains are termed vancomycin-intermediate-susceptibility *S. aureus*, or VISA. Many more isolates may contain subpopulations with reduced vancomycin susceptibility (hetero-VISA, or hVISA). These isolates have not acquired the genes that mediate vancomycin resistance in enterococci but are mutant bacteria with markedly thickened cell walls. These mutants were apparently selected in patients who were undergoing prolonged vancomycin therapy. The failure of vancomycin therapy in some patients infected with *S. aureus* or *S. epidermidis* strains exhibiting only intermediate susceptibility to this drug is thought to have resulted from this resistance.

DAPTOMYCIN

In some *S. aureus* isolates with reduced susceptibility to daptomycin, a mutation in the *mprF* gene leads to an increase in the net positive charge of the bacterial membrane, repelling the antibiotic.

AMINOGLYCOSIDES

The most common aminoglycoside resistance mechanism is inactivation of the antibiotic. Aminoglycoside-modifying enzymes, usually encoded on plasmids, transfer phosphate, adenyl, or acetyl residues from intracellular molecules to hydroxyl or amino side groups on the antibiotic. The modified antibiotic is less active because of diminished binding to its ribosomal target. Modifying enzymes that can inactivate any of the available aminoglycosides have been found in both gram-positive and gram-negative bacteria. A second aminoglycoside resistance mechanism, which has been identified predominantly in clinical isolates of *Pseudomonas aeruginosa*, is decreased antibiotic uptake, presumably due to alterations in the bacterial outer membrane. A third, emerging form of resistance in gram-negative bacteria is methylation of the target 16S ribosomal RNA, which is mediated by plasmid-encoded methylases.

MACROLIDES, KETOLIDES, LINCOSAMIDES, AND STREPTOGRAMINS

Resistance in gram-positive bacteria, which are the usual target organisms for macrolides, ketolides, lincosamides, and streptogramins, can be due to the production of an enzyme—most commonly plasmid-encoded—that methylates ribosomal RNA, interfering with binding of the antibiotics to their target. Methylation mediates resistance to erythromycin, clarithromycin, azithromycin, clindamycin, and streptogramin B. Resistance to streptogramin B converts quinupristin/dalfopristin from a bactericidal to a bacteriostatic antibiotic. Streptococci can also actively cause the efflux of macrolides, and staphylococci can cause the efflux of macrolides, clindamycin, and streptogramin A. Ketolides such as telithromycin retain activity against most isolates of *Streptococcus pneumoniae* that are resistant to macrolides. In addition, staphylococci can inactivate streptogramin A by acetylation and streptogramin B by either acetylation or hydrolysis. Finally, mutations in 23S ribosomal RNA that alter the binding of macrolides to their targets have been found in both staphylococci and streptococci.

CHLORAMPHENICOL

Most bacteria resistant to chloramphenicol produce a plasmid-encoded enzyme, chloramphenicol acetyltransferase, that inactivates the compound by acetylation.

TETRACYCLINES AND TIGECYCLINE

The most common mechanism of tetracycline resistance in gram-negative bacteria is a plasmid-encoded active-efflux pump that is inserted into the cytoplasmic membrane and extrudes antibiotic from the cell. Resistance in gram-positive bacteria is due either to active efflux or to ribosomal alterations that diminish binding of the antibiotic to its target. Genes involved in ribosomal protection are found on mobile genetic elements. The parenteral tetracycline derivative tigecycline (a glycylcycline) is active against tetracycline-resistant bacteria because it is not removed by efflux and can bind to altered ribosomes.

MUPIROCIN

Although the topical compound mupirocin was introduced into clinical use relatively recently, resistance is already becoming widespread in some areas. The mechanism appears to be either mutation of the target isoleucine tRNA synthetase so that it is no longer inhibited by the antibiotic or plasmid-encoded production of a form of the target enzyme that binds mupirocin poorly.

TRIMETHOPRIM AND SULFONAMIDES

The most prevalent mechanism of resistance to trimethoprim and the sulfonamides in both gram-positive and gram-negative bacteria is the acquisition of plasmid-encoded genes that produce a new, drug-insensitive target—specifically, an insensitive dihydrofolate reductase for trimethoprim and an altered dihydropteroate synthetase for sulfonamides.

QUINOLONES

The most common mechanism of resistance to quinolones is the development of one or more mutations in target DNA gyrases and topoisomerase IV that prevent the antibacterial agent from interfering with the enzymes' activity. Some gram-negative bacteria develop mutations that both decrease outer-membrane porin permeability and cause active drug efflux from the cytoplasm. Mutations that result in active quinolone efflux are also found in gram-positive bacteria.

RIFAMPIN

Bacteria rapidly become resistant to rifampin by developing mutations in the B subunit of RNA polymerase that render the enzyme unable to bind the antibiotic. The rapid selection of resistant mutants is the major limitation to the use of this antibiotic against otherwise-susceptible staphylococci and requires that the drug be used in combination with another antistaphylococcal agent.

LINEZOLID

Enterococci, streptococci, and staphylococci can become resistant to linezolid in vitro by mutation of the 23S rRNA binding site. Clinical isolates of *E. faecium* and *E. faecalis* acquire resistance to linezolid readily by this mechanism, often during therapy. A new plasmid-encoded resistance gene has been found in staphylococci that methylates the linezolid ribosomal binding site. At least one outbreak of linezolid-resistant *S. aureus* infections caused by isolates carrying this gene has been described.

MULTIPLE ANTIBIOTIC RESISTANCE

The acquisition by one bacterium of resistance to multiple antibacterial agents is becoming increasingly common. The two major mechanisms are the acquisition of multiple unrelated resistance genes and the development of mutations in a single gene or gene complex that mediate resistance to a series of unrelated compounds. The construction of multiresistant strains by acquisition of multiple genes occurs by sequential steps of gene transfer and environmental selection in areas of high-level antimicrobial use. In contrast, mutations in a single gene can conceivably be selected in a single step. Bacteria that are multiresistant by virtue of the acquisition of new genes include hospital-associated strains of gram-negative bacteria, enterococci, and staphylococci and community-acquired strains of salmonellae, gonococci, and pneumococci. Mutations that confer resistance to multiple unrelated antimicrobial agents occur in the genes encoding outer-membrane porins and efflux proteins of gram-negative bacteria. These mutations decrease bacterial intracellular

and periplasmic accumulation of β-lactams, quinolones, tetracyclines, chloramphenicol, and aminoglycosides. Multiresistant bacterial isolates pose increasing problems in U.S. hospitals; strains resistant to all available antibacterial chemotherapy have already been identified.

PHARMACOKINETICS OF ANTIBIOTICS

The *pharmacokinetic profile* of an antibacterial agent refers to its concentrations in serum and tissue versus time and reflects the processes of absorption, distribution, metabolism, and excretion. Important characteristics include peak and trough serum concentrations and mathematically derived parameters such as half-life, clearance, and distribution volume. Pharmacokinetic information is useful for estimating the appropriate antibacterial dose and frequency of administration, for adjusting dosages in patients with impaired excretory capacity, and for comparing one drug with another. In contrast, the *pharmacodynamic profile* of an antibiotic refers to the relationship between the pharmacokinetics of the antibiotic and its minimal inhibitory concentrations (MICs) for bacteria (see "Principles of Antibacterial Chemotherapy," later in chapter).

ABSORPTION

Antibiotic *absorption* refers to the rate and extent of a drug's systemic bioavailability after oral, IM, or IV administration.

Oral administration

Most patients with infection are treated with oral antibacterial agents in the outpatient setting. Advantages of oral therapy over parenteral therapy include lower cost, generally fewer adverse effects (including complications of indwelling lines), and greater acceptance by patients. The percentage of an orally administered antibacterial agent that is absorbed (i.e., its *bioavailability*) ranges from as little as 10–20% (erythromycin and penicillin G) to nearly 100% [amoxicillin, clindamycin, metronidazole, doxycycline, trimethoprim-sulfamethoxazole (TMP-SMX), linezolid, and most fluoroquinolones]. These differences in bioavailability are not clinically important as long as drug concentrations at the site of infection are sufficient to inhibit or kill the pathogen. However, therapeutic efficacy may be compromised when absorption is reduced as a result of physiologic or pathologic conditions (such as the presence of food for some drugs or the shunting of blood away from the gastrointestinal tract in patients with hypotension), drug interactions (e.g., of quinolones and metal cations), or noncompliance. The oral route is usually used for patients with relatively mild infections in whom absorption is not thought to be compromised by the preceding conditions. In addition, the oral route can often be used in more severely ill patients after they have responded to parenteral therapy and can take oral medications.

Intramuscular administration

Although the IM route of administration usually results in 100% bioavailability, it is not as widely used in the United States as the oral and IV routes, in part because of the pain often associated with IM injections and the relative ease of IV access in the hospitalized patient. IM injection may be suitable for specific indications requiring an "immediate" and reliable effect (e.g., with long-acting forms of penicillin, including benzathine and procaine, and with single doses of ceftriaxone for acute otitis media or uncomplicated gonococcal infection).

Intravenous administration

The IV route is appropriate when oral antibacterial agents are not effective against a particular pathogen, when bioavailability is uncertain, or when larger doses are required than are feasible with the oral route. After IV administration, bioavailability is 100%; serum concentrations are maximal at the end of the infusion. For many patients in whom long-term antimicrobial therapy is required and oral therapy is not feasible, outpatient parenteral antibiotic therapy (OPAT), including the use of convenient portable pumps, may be cost-effective and safe. Alternatively, some oral antibacterial drugs (e.g., fluoroquinolones) are sufficiently active against many Enterobacteriaceae to provide potency equal to that of parenteral therapy; oral use of such drugs may allow the patient to return home from the hospital earlier or to avoid hospitalization entirely.

DISTRIBUTION

To be effective, concentrations of an antibacterial agent must exceed the pathogen's MIC. Serum antibiotic concentrations usually exceed the MIC for susceptible bacteria, but since most infections are extravascular, the antibiotic must also distribute to the site of the infection. Concentrations of most antibacterial agents in interstitial fluid are similar to free-drug concentrations in serum. However, when the infection is located in a "protected" site where penetration is poor, such as cerebrospinal fluid (CSF), the eye, the prostate, or infected cardiac vegetations, high parenteral doses or local administration for prolonged periods may be required for cure. In addition, even though an antibacterial agent may penetrate to the site of infection, its activity may be antagonized by factors in the local environment, such as an unfavorable pH or inactivation by cellular degradation products. For example, daptomycin's binding to pulmonary surfactant is believed to account for its poor efficacy in the treatment of pneumonia. In addition, the abscess milieu reduces the penetration and local activity of many antibacterial compounds, so that surgical drainage may be required for cure.

Most bacteria that cause human infections are located extracellularly. Intracellular pathogens such as *Legionella*, *Chlamydia*, *Brucella*, and *Salmonella* may persist or cause relapse if the antibacterial agent does not enter the cell. In general, β-lactams, vancomycin, and aminoglycosides

penetrate cells poorly, whereas macrolides, ketolides, tetracyclines, metronidazole, chloramphenicol, rifampin, TMP-SMX, and quinolones penetrate cells well.

METABOLISM AND ELIMINATION

Like other drugs, antibacterial agents are disposed of by hepatic elimination (metabolism or biliary elimination), by renal excretion of the unchanged or metabolized form, or by a combination of the two processes. For most of the antibacterial drugs, metabolism leads to loss of in vitro activity, although some agents, such as cefotaxime, rifampin, and clarithromycin, have bioactive metabolites that may contribute to their overall efficacy.

The most practical application of information on the mode of excretion of an antibacterial agent is in adjusting dosage when elimination capability is impaired **(Table 36-3)**. Direct, nonidiosyncratic toxicity from antibacterial drugs may result from failure to reduce the dosage given to patients with impaired elimination. For agents that are primarily cleared intact by glomerular filtration, drug clearance is correlated with creatinine clearance, and estimates of the latter can be used to guide dosage. For drugs, the elimination of which is primarily hepatic, no simple marker is useful for dosage adjustment in patients with liver disease. However, in patients with severe hepatic disease, residual metabolic capability is usually sufficient to preclude accumulation and toxic effects.

TABLE 36-3

ANTIBACTERIAL DRUG DOSE ADJUSTMENTS IN PATIENTS WITH RENAL IMPAIRMENT

ANTIBIOTIC	MAJOR ROUTE OF EXCRETION	DOSAGE ADJUSTMENT WITH RENAL IMPAIRMENT
Aminoglycosides	Renal	Yes
Azithromycin	Biliary	No
Cefazolin	Renal	Yes
Cefepime	Renal	Yes
Ceftazidime	Renal	Yes
Ceftriaxone	Renal/biliary	Modest reduction in severe renal impairment
Ciprofloxacin	Renal/biliary	Only in severe renal insufficiency
Clarithromycin	Renal/biliary	Only in severe renal insufficiency
Daptomycin	Renal	Yes
Erythromycin	Biliary	Only when given in high IV doses
Levofloxacin	Renal	Yes
Linezolid	Metabolism	No
Metronidazole	Biliary	No
Nafcillin	Biliary	No
Penicillin G	Renal	Yes (when given in high IV doses)
Piperacillin	Renal	Only with Cl_{cr} of <40 mL/min
Quinupristin/dalfopristin	Metabolism	No
Tigecycline	Biliary	No
TMP-SMX	Renal/biliary	Only in severe renal insufficiency
Vancomycin	Renal	Yes

Note: Cl_{cr}, creatinine clearance rate; TMP-SMX, trimethoprim-sulfamethoxazole.

PRINCIPLES OF ANTIBACTERIAL CHEMOTHERAPY

The choice of an antibacterial compound for a particular patient and a specific infection involves more than just a knowledge of the agent's pharmacokinetic profile and in vitro activity. The basic tenets of chemotherapy, to be elaborated later, include the following: When appropriate, material containing the infecting organism(s) should be obtained before the start of treatment so that presumptive identification can be made by microscopic examination of stained specimens and the organism can be grown for definitive identification and susceptibility testing. Awareness of local susceptibility patterns is useful when the patient is treated empirically. Once the organism is identified and its susceptibility to antibacterial agents is determined, the regimen with the narrowest effective spectrum should be chosen. The choice of antibacterial agent is guided by the pharmacokinetic and adverse-reaction profile of active compounds, the site of infection, the immune status of the host, and evidence of efficacy from well-performed clinical trials. If all other factors are equal, the least expensive antibacterial regimen should be chosen.

SUSCEPTIBILITY OF BACTERIA TO ANTIBACTERIAL DRUGS IN VITRO

Determination of the susceptibility of the patient's infecting organism to a panel of appropriate antibacterial agents is an essential first step in devising a chemotherapeutic regimen. Susceptibility testing is designed to estimate the susceptibility of a bacterial isolate to an antibacterial drug under standardized conditions. These conditions favor rapidly growing aerobic or facultative organisms and assess bacteriostasis only. Specialized testing is required for the assessment of bactericidal antimicrobial activity; for the detection of resistance among such fastidious organisms as obligate anaerobes, *Haemophilus* spp., and pneumococci; and for the determination of resistance phenotypes with variable expression, such as resistance to methicillin or oxacillin among staphylococci. Antimicrobial susceptibility testing is important when susceptibility is unpredictable, most often as a result of increasing acquired resistance among bacteria infecting hospitalized patients.

PHARMACODYNAMICS: RELATIONSHIP OF PHARMACOKINETICS AND IN VITRO SUSCEPTIBILITY TO CLINICAL RESPONSE

Bacteria have historically been considered *susceptible* to an antibacterial drug if the achievable peak serum concentration exceeds the MIC by approximately fourfold. Each antibiotic has a *breakpoint* concentration that separates susceptible from resistant bacteria (Fig. 36-2). When a majority of isolates of a given bacterial species are inhibited at concentrations below the breakpoint, the species is considered to be within the spectrum of the antibiotic.

The *pharmacokinetic-pharmacodynamic (PK-PD) profile* of an antibiotic refers to the quantitative relationships between the time course of antibiotic concentrations in serum and tissue, in vitro susceptibility (MIC), and microbial response (inhibition of growth or rate of killing). Three PK-PD parameters quantify these relationships: the ratio of the area under the plasma concentration vs. time curve to the MIC (AUC/MIC), the ratio of the maximal serum concentration to the MIC (C_{max}/MIC), and the time during a dosing interval that plasma concentrations exceed the MIC ($T >$ MIC). The PK-PD profile of an antibiotic class is characterized as either *concentration dependent* (fluoroquinolones, aminoglycosides), such that an increase in antibiotic concentration leads to a more rapid rate of bacterial death, or *time dependent* (β-lactams), such that the reduction in bacterial density is proportional to the time that concentrations exceed the MIC. For concentration-dependent antibiotics, the C_{max}/MIC or AUC/MIC ratio correlates best with the reduction in microbial density in vitro and in animal investigations. Dosing strategies attempt to maximize these ratios by the administration of a large dose relative to the MIC for anticipated pathogens, often at long intervals (relative to the serum half-life). Once-daily dosing of aminoglycoside antibiotics is one practical consequence of these relationships. Another is the administration of larger doses of vancomycin than have been used in the past (e.g., >2 g/d for an adult with normal renal function) to increase the AUC/MIC ratio in an effort to improve the response rates of patients infected with methicillin-resistant *S. aureus* (MRSA). In contrast, dosage strategies for time-dependent antibiotics emphasize the maintenance of serum concentrations above the MIC for 30–50% of the dose interval. For example, some clinicians advocate prolonged—or even constant—infusions of some β-lactam antibiotics, such as the carbapenems and the β-lactam/β-lactamase inhibitors, to increase the $T >$ MIC between doses. The clinical implications of these pharmacodynamic relationships continue to be elucidated; their consideration has led to more rational antibacterial dosage regimens. Table 36-4 summarizes the pharmacodynamic properties of the major antibiotic classes.

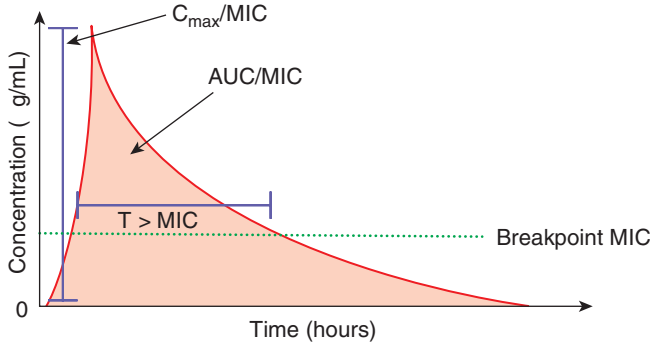


FIGURE 36-2
Relationship between the pharmacokinetic-pharmacodynamic (PK-PD) properties of an antibiotic and susceptibility. An organism is considered "susceptible" to an antibiotic if the drug's minimal inhibitory concentration (MIC) is below its "breakpoint" concentration (see text). PK-PD investigations explore various pharmacodynamic indices and clinical responses, including the ratio of the maximal serum concentration to the MIC (C_{max}/MIC), the ratio of the area under the serum concentration vs. time curve to the MIC (AUC/MIC), and the time during which serum concentrations exceed the MIC ($T >$ MIC). See Table 36-4.

STATUS OF THE HOST

Various host factors must be considered in the devising of antibacterial chemotherapy. The host's antibacterial *immune function* is of importance, particularly as it relates to opsonophagocytic function. Since the major host defense against acute, overwhelming bacterial infection is the polymorphonuclear leukocyte, patients with neutropenia must be treated aggressively and empirically with bactericidal drugs for suspected infection (Chap. 12). Likewise, patients who have deficient humoral immunity (e.g., those with chronic lymphocytic leukemia and multiple myeloma) and individuals with surgical or functional asplenia (e.g., those with sickle cell disease) should be treated empirically for infections with encapsulated organisms, especially the pneumococcus.

Pregnancy increases the risk of toxicity of certain antibacterial drugs for the mother (e.g., hepatic toxicity of

TABLE 36-4
PHARMACODYNAMIC INDICES OF MAJOR ANTIMICROBIAL CLASSES

PARAMETER PREDICTING RESPONSE	DRUG OR DRUG CLASS
Time above the MIC	Penicillins, cephalosporins, carbapenems, aztreonam
24-h AUC/MIC	Aminoglycosides, fluoroquinolones, tetracyclines, vancomycin, macrolides, clindamycin, quinupristin/dalfopristin, tigecycline, daptomycin
Peak to MIC	Aminoglycosides, fluoroquinolones

Note: MIC, minimal inhibitory concentration; AUC, area under the concentration curve.

tetracycline), affects drug disposition and pharmacokinetics, and—because of the risk of fetal toxicity—severely limits the choice of agents for treating infections. Certain antibacterial agents are contraindicated in pregnancy either because their safety has not been established (categories B and C) or because they are known to be toxic (categories D and X). Table 36-5 summarizes antibacterial drug safety in pregnancy.

In patients with *concomitant viral infections*, the incidence of adverse reactions to antibacterial drugs may be unusually high. For example, persons with infectious mononucleosis and those infected with HIV experience skin reactions more often to penicillins and folic acid synthesis inhibitors such as TMP-SMX, respectively.

In addition, the patient's age, sex, racial heritage, genetic background, concomitant drugs, and excretory status all determine the incidence and type of side effects that can be expected with certain antibacterial agents.

SITE OF INFECTION

The location of the infected site may play a major role in the choice and dose of antimicrobial drug. Patients with suspected *meningitis* should receive drugs that can cross the blood-CSF barrier; in addition, because of the relative paucity of phagocytes and opsonins at the site of infection, the agents should be bactericidal. β-Lactam drugs are the mainstay of therapy for most of these infections, even though they do not normally reach high concentrations in CSF. Their efficacy is based on the increased permeability of the blood-brain and blood-CSF barriers to hydrophilic molecules during inflammation and the low minimal bactericidal concentrations (MBCs) for most infectious organisms.

The vegetation, which is the major site of infection in *bacterial endocarditis*, is also a focus that is protected from normal host-defense mechanisms. Antibacterial therapy needs to be bactericidal, with the selected agent administered parenterally over a long period and at a dose that can eradicate the infecting organism. Likewise, *osteomyelitis* involves a site that is resistant to opsonophagocytic removal of infecting bacteria; furthermore, avascular bone (sequestrum) represents a foreign body that thwarts normal host-defense mechanisms. *Chronic prostatitis* is exceedingly difficult to cure because most antibiotics do not penetrate through the capillaries serving the prostate, especially when acute inflammation is absent. *Intraocular infections*, especially endophthalmitis,

TABLE 36-5

ANTIBACTERIAL DRUGS IN PREGNANCY

ANTIBACTERIAL DRUG (PREGNANCY CLASS[a])	TOXICITY IN PREGNANCY	RECOMMENDATION
Aminoglycosides (C/D)	Possible 8th-nerve toxicity	Caution[b]
Chloramphenicol (C)	Gray syndrome in newborn	Caution at term
Fluoroquinolones (C)	Arthropathy in immature animals	Caution
Clarithromycin (C)	Teratogenicity in animals	Contraindicated
Ertapenem (B)	Decreased weight in animals	Caution
Erythromycin estolate (B)	Cholestatic hepatitis	Contraindicated
Imipenem/cilastatin (C)	Toxicity in some pregnant animals	Caution
Linezolid (C)	Embryonic and fetal toxicity in rats	Caution
Meropenem (B)	Unknown	Caution
Metronidazole (B)	None known, but carcinogenic in rats	Caution
Nitrofurantoin (B)	Hemolytic anemia in newborns	Caution; contraindicated at term[c]
Quinupristin/dalfopristin (B)	Unknown	Caution
Sulfonamides (C/D)	Hemolysis in newborn with G6PD[d] deficiency; kernicterus in newborn	Caution; contraindicated at term[c]
Telavancin (C)	Unknown (adverse development in animals)	Pregnancy test before use
Tetracyclines/tigecycline (D)	Tooth discoloration, inhibition of bone growth in fetus; hepatotoxicity	Contraindicated
Vancomycin (C)	Unknown	Caution

[a]***Category A:*** Controlled studies in women fail to demonstrate a risk to the fetus; the possibility of fetal harm appears remote.
Category B: Either (1) animal reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women or (2) animal reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies of women in the first trimester (and there is no evidence of risk in later trimesters).
Category C: Studies in animals have revealed adverse effects on the fetus (teratogenic, embryocidal, or other), but no controlled studies of women have been conducted. Drug should be given only if the potential benefit justifies the potential risk to the fetus.
Category D: There is positive evidence of human fetal risk, but the benefits from use in pregnant women may nevertheless be acceptable (e.g., if the drug is needed in a life-threatening situation or for a serious disease against which safer drugs cannot be used or are ineffective).
[b]Use only for strong clinical indication in the absence of a suitable alternative.
[c]See KS Crider et al: Arch Pediatr Adolesc Med 163:978, 2009.
[d]G6PD, glucose-6-phosphate dehydrogenase.

are difficult to treat because retinal capillaries lacking fenestration hinder drug penetration into the vitreous from blood. Inflammation does little to disrupt this barrier. Thus, direct injection into the vitreous is necessary in many cases. Antibiotic penetration into *abscesses* is usually poor, and local conditions (e.g., low pH or the presence of enzymes that hydrolyze the drug) may further antagonize antibacterial activity.

In contrast, *urinary tract infections* (UTIs), when confined to the bladder, are relatively easy to cure, in part because of the higher concentration of most antibiotics in urine than in blood. Since blood is the usual reference fluid in defining susceptibility (Fig. 36-2), even organisms found to be resistant to achievable serum concentrations may be susceptible to achievable urine concentrations. For drugs that are used only for the treatment of UTIs, such as the urinary tract antiseptics nitrofurantoin and methenamine salts, achievable urine concentrations are used to determine susceptibility.

COMBINATION CHEMOTHERAPY

One of the tenets of antibacterial chemotherapy is that if the infecting bacterium has been identified, the most specific chemotherapy possible should be used. The use of a single agent with a narrow spectrum of activity against the pathogen diminishes the alteration of normal flora and thus limits the overgrowth of resistant nosocomial organisms (e.g., *Candida albicans*, enterococci, *Clostridium difficile*, or MRSA), avoids the potential toxicity of multiple-drug regimens, and reduces cost. However, certain circumstances call for the use of more than one antibacterial agent. These are summarized below.

1. *Prevention of the emergence of resistant mutants.* Spontaneous mutations occur at a detectable frequency in certain genes encoding the target proteins for some antibacterial agents. The use of these agents can eliminate the susceptible population, select out resistant mutants at the site of infection, and result in the failure of chemotherapy. Resistant mutants are usually selected when the MIC of the antibacterial agent for the infecting bacterium is close to achievable levels in serum or tissues and/or when the site of infection limits the access or activity of the agent. Among the most common examples are rifampin for staphylococci, imipenem for *Pseudomonas*, and fluoroquinolones for staphylococci and *Pseudomonas*. Small-colony variants of staphylococci resistant to aminoglycosides also emerge during monotherapy with these antibiotics. A second antibacterial agent with a mechanism of action different from that of the first is added in an attempt to prevent the emergence of resistant mutants (e.g., imipenem plus an aminoglycoside or a fluoroquinolone for systemic *Pseudomonas* infections). However, since resistant mutants have emerged following combination chemotherapy, this approach clearly is not uniformly successful.
2. *Synergistic or additive activity.* Synergistic or additive activity involves a lowering of the MIC or MBC of each or all of the drugs tested in combination against a specific bacterium. In *synergy*, each agent is more active when combined with a second drug than it would be alone, and the drugs' combined activity is therefore greater than the sum of the individual activities of each drug. In an *additive relationship*, the combined activity of the drugs is equal to the sum of their individual activities. Among the best examples of a synergistic or additive effect, confirmed both in vitro and by animal studies, are the enhanced bactericidal activities of certain β-lactam/aminoglycoside combinations against enterococci, viridans streptococci, and *P. aeruginosa*. The synergistic or additive activity of these combinations has also been demonstrated against selected isolates of enteric gram-negative bacteria and staphylococci. The combination of trimethoprim and sulfamethoxazole has synergistic or additive activity against many enteric gram-negative bacteria. Most other antimicrobial combinations display indifferent activity (i.e., the combination is *no better* than the more active of the two agents alone), and some combinations (e.g., penicillin plus tetracycline against pneumococci) may be antagonistic (i.e., the combination is *worse* than either drug alone).
3. *Therapy directed against multiple potential pathogens.* For certain infections, either a mixture of pathogens is suspected or the patient is desperately ill with an as-yet-unidentified infection (see "Empirical Therapy," next). In these situations, the most important of the likely infecting bacteria must be covered by therapy until culture and susceptibility results become available. Examples of the former infections are intraabdominal or brain abscesses and infections of limbs in diabetic patients with microvascular disease. The latter situations include fevers in neutropenic patients, acute pneumonia from aspiration of oral flora by hospitalized patients, and septic shock or sepsis syndrome.

EMPIRICAL THERAPY

In most situations, antibacterial therapy is begun before a specific bacterial pathogen has been identified. The choice of agent is guided by the results of studies identifying the usual pathogens at that site or in that clinical setting, by pharmacodynamic considerations, and by the resistance profile of the expected pathogens in a particular hospital or geographic area. Situations in which empirical therapy is appropriate include the following:

1. *Life-threatening infection.* Any suspected bacterial infection in a patient with a life-threatening illness should be treated presumptively. Therapy is usually begun with more than one agent and is later tailored to a specific pathogen if one is eventually identified. Early therapy with an effective antimicrobial regimen has consistently been demonstrated to improve survival rates.
2. *Treatment of community-acquired infections.* In most situations, it is appropriate to treat non-life-threatening infections without obtaining cultures. These situations

include outpatient infections such as community-acquired upper and lower respiratory tract infections, cystitis, cellulitis or local wound infection, urethritis, and prostatitis. However, if any of these infections recurs or fails to respond to initial therapy, every effort should be made to obtain cultures to guide re-treatment.

CHOICE OF ANTIBACTERIAL THERAPY

Infections for which specific antibacterial agents are among the drugs of choice are detailed in **Table 36-6**. No attempt has been made to include all of the potential situations in which antibacterial agents may be used. A more detailed discussion of specific bacteria and infections that they cause can be found elsewhere in this volume.

The choice of antibacterial therapy increasingly involves an assessment of the acquired resistance of major microbial pathogens to the antimicrobial agents available to treat them. Resistance rates are dynamic (Table 36-6), both increasing and decreasing in response to the environmental pressure applied by antimicrobial use. For example, increased fluoroquinolone use in the community is associated with increasing rates of quinolone resistance in community-acquired strains of *S. pneumoniae*, *E. coli*, *Neisseria gonorrhoeae*, and *K. pneumoniae*. Fluoroquinolone resistance has also emerged rapidly among nosocomial isolates of *S. aureus* and *Pseudomonas* spp. as hospital use of this drug class has increased. It is important to note that, in many cases, wide variations in worldwide antimicrobial-resistance trends may not be reflected in the values recorded at U.S. hospitals. Therefore, the most important factor in choosing initial therapy for an infection in which the susceptibility of the specific pathogen(s) is not known is information on local resistance rates. This information can be obtained from local clinical microbiology laboratories in the annual hospital "antibiogram," from state health departments, or from publications of the Centers for Disease Control and Prevention (e.g., *Antimicrobial Resistance in Healthcare Settings*; *www.cdc.gov/ncidod/dhqp/ar.html*).

ADVERSE REACTIONS

Adverse drug reactions are frequently classified by mechanism as either *dose-related* ("toxic") or *unpredictable*. Unpredictable reactions are either idiosyncratic or allergic. Dose-related reactions include aminoglycoside-induced nephrotoxicity, linezolid-induced thrombocytopenia, penicillin-induced seizures, and vancomycin-induced anaphylactoid reactions. Many of these reactions can be avoided by reducing dosage in patients with impaired renal function, limiting the duration of therapy, or reducing the rate of administration. Adverse reactions to antibacterial agents are a common cause of morbidity, requiring alteration in therapy and additional expense, and they occasionally result in death. The elderly, often those with the more severe infections, may be especially prone to certain adverse reactions. The most clinically relevant adverse reactions to common antibacterial drugs are listed in **Table 36-7**.

DRUG INTERACTIONS

Antimicrobial drugs are a common cause of drug-drug interactions. **Table 36-8** lists the most common and best-documented interactions of antibacterial agents with other drugs and characterizes the clinical relevance of these interactions. Coadministration of drugs paired in the table does not necessarily result in clinically important adverse consequences in all cases. The information in Table 36-8 is intended only to heighten awareness of the potential for an interaction. Additional sources should be consulted to identify appropriate options.

MACROLIDES AND KETOLIDES

Erythromycin, clarithromycin, and telithromycin inhibit CYP3A4, the hepatic P450 enzyme that metabolizes many drugs. In ~10% of patients receiving digoxin, concentrations increase significantly when erythromycin or telithromycin is coadministered, and this increase may lead to digoxin toxicity. Azithromycin has little effect on the metabolism of other drugs.

Many drugs, such as the azole antifungals, can also increase erythromycin serum concentrations, leading to prolongation of the QT interval and a fivefold increase in mortality rate. This example serves as a reminder that the true significance of drug-drug interactions may be subtle yet profound and that close attention to the evolving safety literature is important.

QUINUPRISTIN/DALFOPRISTIN

Quinupristin/dalfopristin is an inhibitor of CYP3A4. Its interactions with other drugs are similar to those of erythromycin.

LINEZOLID

Linezolid is a monoamine oxidase inhibitor. Its concomitant administration with sympathomimetics (e.g., phenylpropanolamine) and with foods with high concentrations of tyramine should be avoided. Many case reports describe serotonin syndrome following coadministration of linezolid with selective serotonin reuptake inhibitors.

TETRACYCLINES

The most important interaction involving tetracyclines is reduced absorption when these drugs are coadministered with divalent and trivalent cations, such as antacids, iron compounds, or dairy products.

SULFONAMIDES

Sulfonamides, including TMP-SMX, increase the hypoprothrombinemic effect of warfarin by inhibition of its

TABLE 36-6

INFECTIONS FOR WHICH SPECIFIC ANTIBACTERIAL AGENTS ARE AMONG THE DRUGS OF CHOICE

AGENT	INFECTIONS	COMMON PATHOGEN(s) (RESISTANCE RATE,%)[a]
Penicillin G	Syphilis, yaws, leptospirosis, groups A and B streptococcal infections, pneumococcal infections, actinomycosis, oral and periodontal infections, meningococcal meningitis and meningococcemia, viridans streptococcal endocarditis, clostridial myonecrosis, tetanus, anthrax, rat-bite fever, *Pasteurella multocida* infections, and erysipeloid (*Erysipelothrix rhusiopathiae*)	*Neisseria meningitidis*[b] (intermediate,[c] 15–30; resistant, 0; geographic variation) Viridans streptococci (intermediate, 15–30; resistant, 5–10) *Streptococcus pneumoniae* (intermediate, 23; resistant, 17)
Ampicillin, amoxicillin	Salmonellosis, acute otitis media, *Haemophilus influenzae* meningitis and epiglottitis, *Listeria monocytogenes* meningitis, *Enterococcus faecalis* UTI	*Escherichia coli* (37) *H. influenzae* (35) *Salmonella* spp.[b] (30–50; geographic variation) *Enterococcus* spp. (24)
Nafcillin, oxacillin	*Staphylococcus aureus* (non-MRSA) bacteremia and endocarditis	*S. aureus* (46; MRSA) *Staphylococcus epidermidis* (78; MRSE)
Piperacillin plus tazobactam	Intraabdominal infections (facultative enteric gram-negative bacilli plus obligate anaerobes); infections caused by mixed flora (aspiration pneumonia, diabetic foot ulcers); infections caused by *Pseudomonas aeruginosa*	*P. aeruginosa* (6)
Cefazolin	*E. coli* UTI, surgical prophylaxis, *S. aureus* (non-MRSA) bacteremia and endocarditis	*E. coli* (7) *S. aureus* (46; MRSA)
Cefoxitin, cefotetan	Intraabdominal infections and pelvic inflammatory disease	*Bacteroides fragilis* (12)
Ceftriaxone	Gonococcal infections, pneumococcal meningitis, viridans streptococcal endocarditis, salmonellosis and typhoid fever, hospital-acquired infections caused by nonpseudomonal facultative gram-negative enteric bacilli	*S. pneumoniae* (intermediate, 16; resistant, 0) *E. coli* and *Klebsiella pneumoniae* (1; ESBL producers)
Ceftazidime, cefepime	Hospital-acquired infections caused by facultative gram-negative enteric bacilli and *Pseudomonas*	*P. aeruginosa* (16) (See ceftriaxone for ESBL producers)
Imipenem, meropenem	Intraabdominal infections, hospital-acquired infections (non-MRSA), infections caused by *Enterobacter spp*. and ESBL-producing gram-negative bacilli	*P. aeruginosa* (6) *Acinetobacter* spp. (35)
Aztreonam	Hospital-acquired infections caused by facultative gram-negative bacilli and *Pseudomonas* in penicillin-allergic patients	*P. aeruginosa* (16)
Vancomycin	Bacteremia, endocarditis, and other serious infections due to MRSA; pneumococcal meningitis; antibiotic-associated pseudomembranous colitis[d]	*Enterococcus* spp. (24)
Daptomycin	VRE infections; MRSA bacteremia	Rare
Gentamicin, amikacin, tobramycin	Combined with a penicillin for staphylococcal, enterococcal, or viridans streptococcal endocarditis; combined with a β-lactam antibiotic for gram-negative bacteremia; pyelonephritis	Gentamicin: *E. coli* (6) *P. aeruginosa* (17) *Acinetobacter* spp. (32)
Erythromycin, clarithromycin, azithromycin	*Legionella, Campylobacter,* and *Mycoplasma* infections; CAP; group A streptococcal pharyngitis in penicillin-allergic patients; bacillary angiomatosis (*Bartonella henselae*); gastric infections due to *Helicobacter pylori; Mycobacterium avium-intracellulare infections*	*S. pneumoniae* (28) *Streptococcus pyogenes*[b] (0–10; geographic variation) *H. pylori*[b] (2–20; geographic variation)
Clindamycin	Severe, invasive group A streptococcal infections; infections caused by obligate anaerobes; infections caused by susceptible staphylococci	*S. aureus* (nosocomial = 58; CA-MRSA = 10[b])

(*continued*)

TABLE 36-6

INFECTIONS FOR WHICH SPECIFIC ANTIBACTERIAL AGENTS ARE AMONG THE DRUGS OF CHOICE (*CONTINUED*)

AGENT	INFECTIONS	COMMON PATHOGEN(s) (RESISTANCE RATE,%)[a]
Doxycycline, minocycline	Acute bacterial exacerbations of chronic bronchitis, granuloma inguinale, brucellosis (with streptomycin), tularemia, glanders, melioidosis, spirochetal infections caused by *Borrelia* (Lyme disease and relapsing fever; doxycycline), infections caused by *Vibrio vulnificus*, some *Aeromonas* infections, infections due to *Stenotrophomonas* (minocycline), plague, ehrlichiosis, chlamydial infections (doxycycline), granulomatous skin infections due to *Mycobacterium marinum* (minocycline), rickettsial infections, mild CAP, skin and soft tissue infections caused by gram-positive cocci (CA-MRSA infections, leptospirosis, syphilis, actinomycosis in the penicillin-allergic patient)	*S. pneumoniae* (17) MRSA (5)
Trimethoprim-sulfamethoxazole	Community-acquired UTI; *S. aureus* skin and soft tissue infections (CA-MRSA)	*E. coli* (19) MRSA (3)
Sulfonamides	Nocardial infections, leprosy (dapsone, a sulfone), and toxoplasmosis (sulfadiazine)	UNK
Ciprofloxacin, levofloxacin, moxifloxacin	CAP (levofloxacin and moxifloxacin); UTI; bacterial gastroenteritis; hospital-acquired gram-negative enteric infections; *Pseudomonas* infections (ciprofloxacin and levofloxacin)	*S. pneumoniae* (1) *E. coli* (13) *P. aeruginosa* (23) *Salmonella* spp. (10–50; geographic variation) *Neisseria gonorrhoeae*[b] (0–5, non–West Coast U.S.; 10–15, California and Hawaii; 20–70, Asia, England, Wales)
Rifampin	Staphylococcal foreign body infections, in combination with other antistaphylococcal agents; *Legionella* pneumonia	Staphylococci rapidly develop resistance during rifampin monotherapy.
Metronidazole	Obligate anaerobic gram-negative bacteria (*Bacteroides* spp.): abscess in lung, brain, or abdomen; bacterial vaginosis; antibiotic-associated *Clostridium difficile* disease	UNK
Linezolid	VRE; staphylococcal skin and soft tissue infection (CA-MRSA)	Rare
Polymyxin E (colistin)	Hospital-acquired infection due to gram-negative bacilli resistant to all other chemotherapy: *P. aeruginosa, Acinetobacter spp., Stenotrophomonas maltophilia*	UNK
Quinupristin/dalfopristin	VRE	Vancomycin-resistant *E. faecalis*[b] (100) Vancomycin-resistant *E. faecium* (10)
Mupirocin	Topical application to nares to eradicate *S. aureus* carriage	UNK

[a]Unless otherwise noted, resistance rates are based on all isolates tested in 2008 in the clinical microbiology laboratory at Virginia Commonwealth University Medical Center. The rates are consistent with those reported by the National Nosocomial Infections Surveillance System (Am J Infect Control 32:470, 2004).
[b]Data from recent literature sources.
[c]Intermediate resistance.
[d]Drug is given orally for this indication.
Abbreviations: CA-MRSA, community-acquired methicillin-resistant *S. aureus;* CAP, community-acquired pneumonia; ESBL, extended-spectrum β-lactamase; MRSA, methicillin-resistant *S. aureus;* MRSE, methicillin-resistant *S. epidermidis*; UNK, resistance rates unknown; UTI, urinary tract infection; VRE, vancomycin-resistant enterococci.

metabolism or by protein-binding displacement. This interaction is a relatively common cause of bleeding in patients also taking warfarin, and the incidence may be increasing as more TMP-SMX is used to treat community-acquired infections caused by MRSA.

FLUOROQUINOLONES

Chelation of all fluoroquinolones with divalent and trivalent cations leads to a significant reduction in absorption. Scattered case reports suggest that quinolones can also potentiate the effects of warfarin, but this effect has not

TABLE 36-7

MOST CLINICALLY RELEVANT ADVERSE REACTIONS TO COMMON ANTIBACTERIAL DRUGS

DRUG	ADVERSE EVENT	COMMENTS
β-Lactams	Allergies in ~1–4% of treatment courses	Cephalosporins cause allergy in 2–4% of penicillin-allergic patients. Aztreonam is safe in β-lactam-allergic patients.
	Nonallergic skin reactions	Ampicillin "rash" is common among patients with Epstein-Barr virus infection.
	Diarrhea, including *Clostridium difficile* colitis (Chap. 47)	—
Vancomycin	Anaphylactoid reaction ("red man syndrome")	Give as a 1- to 2-h infusion.
	Nephrotoxicity, ototoxicity, allergy, neutropenia	Thought to be rare, but appear to be increasing as larger dosages are used
Telavancin	Taste disturbance, foamy urine, gastrointestinal distress	New drug; full spectrum of adverse reactions unclear
Aminoglycosides	Nephrotoxicity (generally reversible)	Greatest with prolonged therapy in the elderly or with preexisting renal insufficiency. Monitor serum creatinine every 2–3 days.
	Ototoxicity (often irreversible)	Risk factors similar to those for nephrotoxicity; both vestibular and hearing toxicities
Macrolides/ketolides	Gastrointestinal distress	Most common with erythromycin
	Ototoxicity	High-dose IV erythromycin
	Cardiac toxicity	QTc prolongation and torsades de pointes, especially when inhibitors of erythromycin metabolism are given simultaneously
	Hepatic toxicity (telithromycin)	Warning added to prescribing information (July 2006)
	Respiratory failure in patients with myasthenia gravis (telithromycin)	Warning added to prescribing information (July 2006)
Clindamycin	Diarrhea, including *C. difficile* colitis	—
Sulfonamides	Allergic reactions	Rashes (more common in HIV-infected patients); serious dermal reactions, including erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis
	Hematologic reactions	Uncommon; include agranulocytosis and granulocytopenia (more common in HIV-infected patients), hemolytic and megaloblastic anemia, thrombocytopenia
	Renal insufficiency	Crystalluria with sulfadiazine therapy
Fluoroquinolones	Diarrhea, including *C. difficile colitis*	—
	Contraindicated for general use in patients <18 years old and pregnant women	Appear safe in treatment of pulmonary infections in children with cystic fibrosis
	Central nervous system adverse effects (e.g., insomnia)	—
	Miscellaneous: allergies, tendon rupture, dysglycemias, QTc prolongation	Rare, although warnings for tendon rupture have been added to prescribing information
Rifampin	Hepatotoxicity	Rare
	Orange discoloration of urine and body fluids	Common
	Miscellaneous: flu-like symptoms, hemolysis, renal insufficiency	Uncommon; usually related to intermittent administration
Metronidazole	Metallic taste	Common
Tetracyclines/ glycylcyclines	Gastrointestinal distress	Up to 20% with tigecycline
	Esophageal ulceration	Doxycycline (take in A.M. with fluids)
Linezolid	Myelosuppression	Follows long-term treatment
	Ocular and peripheral neuritis	Follows long-term treatment
Daptomycin	Distal muscle pain or weakness	Weekly creatine phosphokinase measurements, especially in patients also receiving statins

TABLE 36-8

INTERACTIONS OF ANTIBACTERIAL AGENTS WITH OTHER DRUGS

ANTIBIOTIC	INTERACTS WITH	POTENTIAL CONSEQUENCE (CLINICAL SIGNIFICANCE[a])
Erythromycin/clarithromycin/ telithromycin	Theophylline	Theophylline toxicity (1)
	Carbamazepine	CNS depression (1)
	Digoxin	Digoxin toxicity (2)
	Triazolam/midazolam	CNS depression (2)
	Ergotamine	Ergotism (1)
	Warfarin	Bleeding (2)
	Cyclosporine/tacrolimus	Nephrotoxicity (1)
	Cisapride	Cardiac arrhythmias (1)
	Statins[b]	Rhabdomyolysis (2)
	Valproate	Valproate toxicity (2)
	Vincristine/vinblastine	Excess neurotoxicity (2)
Quinupristin/dalfopristin	Similar to erythromycin[c]	
Fluoroquinolones	Theophylline	Theophylline toxicity (2)[d]
	Antacids/sucralfate/iron	Subtherapeutic antibiotic levels (1)
Tetracycline	Antacids/sucralfate/iron	Subtherapeutic antibiotic levels (1)
Trimethoprim-sulfamethoxazole	Phenytoin	Phenytoin toxicity (2)
	Oral hypoglycemics	Hypoglycemia (2)
	Warfarin	Bleeding (1)
	Digoxin	Digoxin toxicity (2)
Metronidazole	Ethanol	Disulfiram-like reactions (2)
	Fluorouracil	Bone marrow suppression (1)
	Warfarin	Bleeding (2)
Rifampin	Warfarin	Clot formation (1)
	Oral contraceptives	Pregnancy (1)
	Cyclosporine/tacrolimus	Rejection (1)
	HIV-1 protease inhibitors	Increased viral load, resistance (1)
	Nonnucleoside reverse-transcriptase inhibitors	Increased viral load, resistance (1)
	Glucocorticoids	Loss of steroid effect (1)
	Methadone	Narcotic withdrawal symptoms (1)
	Digoxin	Subtherapeutic digoxin levels (1)
	Itraconazole	Subtherapeutic itraconazole levels (1)
	Phenytoin	Loss of seizure control (1)
	Statins	Hypercholesterolemia (1)
	Diltiazem	Subtherapeutic diltiazem levels (1)
	Verapamil	Subtherapeutic verapamil levels (1)

[a]1 = a well-documented interaction with clinically important consequences; 2 = an interaction of uncertain frequency but of potential clinical importance.
[b]Lovastatin and simvastatin are most affected; pravastatin and atorvastatin are less prone to clinically important effects.
[c]The macrolide antibiotics and quinupristin/dalfopristin inhibit the same human metabolic enzyme, CYP3A4, and similar interactions are anticipated.
[d]Ciprofloxacin only. Levofloxacin and moxifloxacin do not inhibit theophylline metabolism.
Note: New interactions are commonly reported after marketing. Consult the most recent prescribing information for updates. CNS, central nervous system.

been observed in most controlled trials. Patients receiving glucocorticoids are at increased risk of tendon rupture.

RIFAMPIN

Rifampin is an excellent inducer of many cytochrome P450 enzymes and increases the hepatic clearance of a large number of drugs. Before rifampin is prescribed for any patient, a review of concomitant drug therapy is essential.

METRONIDAZOLE

Metronidazole has been reported to cause a disulfiram-like syndrome when alcohol is ingested. The true frequency and significance of this reaction are unknown, and it is not well documented; however, patients for whom metronidazole is prescribed are usually instructed to avoid alcohol. Inhibition of the metabolism of warfarin by metronidazole leads to significant rises in prothrombin times.

PROPHYLAXIS OF BACTERIAL INFECTIONS

Antibacterial agents are occasionally indicated for use in patients who have no evidence of infection but who have been or are expected to be exposed to bacterial pathogens under circumstances that constitute a major risk of infection. The basic tenets of antimicrobial prophylaxis are as follows: (1) The risk or potential severity of infection should outweigh the risk of side effects from the antibacterial agent. (2) The antibacterial agent should be given for the shortest period necessary to prevent target infections. (3) The antibacterial agent should be given before the expected period of risk (e.g., within 1 h of incision before elective surgery) or as soon as possible after contact with an infected individual (e.g., prophylaxis for meningococcal meningitis).

Table 36-9 lists the major indications for antibacterial prophylaxis in adults. The table includes only those indications that are widely accepted, supported by well-designed studies, or recommended by expert panels. Prophylaxis is also used but is less widely accepted for recurrent cellulitis in conjunction with lymphedema, recurrent pneumococcal meningitis in conjunction with deficiencies in humoral immunity or CSF leaks, traveler's diarrhea, gram-negative sepsis in conjunction with neutropenia, and spontaneous bacterial peritonitis in conjunction with ascites. The use of antibacterial agents in children to prevent rheumatic fever is also common practice.

The major use of antibacterial prophylaxis is to prevent infections following surgical procedures. Antibacterial agents are administered just before the surgical procedure—and, for long operations, during the

TABLE 36-9

PROPHYLAXIS OF BACTERIAL INFECTIONS IN ADULTS

CONDITION	ANTIBACTERIAL AGENT	TIMING OR DURATION OF PROPHYLAXIS
Nonsurgical		
Cardiac lesions highly susceptible to bacterial endocarditis (prosthetic valves, previous endocarditis, congenital heart defects)	Amoxicillin	Before and after dental procedures that manipulate gingival tissue
Recurrent *S. aureus* infections	Mupirocin	5 days (intranasal)
Contact with patient with meningococcal meningitis	Rifampin Fluoroquinolone	2 days Single dose
Bite wounds[a]	Amoxicillin/clavulanic acid (alternatives: amoxicillin, doxycycline, or moxifloxacin)	3–5 days
Recurrent cystitis	Trimethoprim-sulfamethoxazole or a fluoroquinolone or nitrofurantoin	3 times per week for up to 1 year or after sexual intercourse
Surgical		
Clean (cardiac, vascular, neurologic, or orthopedic surgery)	Cefazolin (vancomycin)[b]	Before and during procedure
Ocular	Topical combinations and subconjunctival cefazolin	During and at end of procedure
Clean-contaminated (head and neck, high-risk gastroduodenal or biliary tract surgery; high-risk cesarean section; hysterectomy)	Cefazolin (or clindamycin for head and neck)	Before and during procedure
Clean-contaminated (vaginal or abdominal hysterectomy)	Cefazolin or cefoxitin or cefotetan or ampicillin-sulbactam	Before and during procedure
Clean-contaminated (high-risk genitourinary surgery)	Fluoroquinolone	Before and during procedure
Clean-contaminated (colorectal surgery or appendectomy)	Oral: neomycin plus erythromycin or metronidazole Parenteral: cefoxitin *or* cefotetan *or* cefazolin plus metronidazole *or* ampicillin-sulbactam	Before and during procedure
Dirty[a] (ruptured viscus)	Cefoxitin or cefotetan ± gentamicin, clindamycin + gentamicin, or another appropriate regimen directed at anaerobes and gram-negative aerobes	Before and for 3–5 days after procedure
Dirty[a] (traumatic wound)	Cefazolin	Before and for 3–5 days after trauma

[a]In these cases, use of antibacterial agents actually constitutes treatment of infection rather than prophylaxis.
[b]Vancomycin is recommended only in institutions that have a high incidence of infection with methicillin-resistant staphylococci.

procedure as well—to ensure high drug concentrations in serum and tissues during surgery. The objective is to eradicate bacteria originating from the air of the operating suite, the skin of the surgical team, or the patient's own flora that may contaminate the wound. In all but colorectal surgical procedures, prophylaxis is predominantly directed against staphylococci and cefazolin is the drug most commonly recommended. Prophylaxis is intended to prevent wound infection or infection of implanted devices, not all infections that may occur during the postoperative period (e.g., UTIs or pneumonia). Prolonged prophylaxis (beyond 24 h) merely alters the normal flora and favors infections with organisms resistant to the antibacterial agents used. National efforts to reduce surgical-site infections were begun in 2002 by the Surgical Infection Prevention Project (SIPP) sponsored by the Centers for Medicare and Medicaid Services. Additional initiatives by the American College of Surgeons–National Surgical Quality Improvement Program have been undertaken to further characterize best practices and to reduce surgical-site infections.

DURATION OF THERAPY AND TREATMENT FAILURE

Until recently, there was little incentive to establish the most appropriate duration of treatment; patients were instructed to take a 7- or 10-day course of treatment for most common infections. A number of recent investigations have evaluated shorter durations of therapy than have been used in the past, including treatment of patients with community-acquired pneumonia (5 days) and those with ventilator-associated pneumonia (7 or 8 days). **Table 36-10** lists common bacterial infections for which treatment duration guidelines have been established or for which there is sufficient clinical experience to establish treatment durations. The ultimate test of cure for a bacterial infection is the absence of relapse when therapy is discontinued. *Relapse* is defined as a recurrence of infection with the identical organism that caused the first infection. In general, therefore, the duration of therapy should be long enough to prevent relapse yet not excessive. Extension of therapy beyond the limit of effectiveness will increase the medication's side effects and encourage the selection of resistant bacteria. The art of treating bacterial infections lies in the ability to determine the appropriate duration of therapy for infections that are not covered by established guidelines. Re-treatment of serious infections for which therapy has failed usually requires a prolonged course (>4 weeks) with combinations of antibacterial agents.

TABLE 36-10

DURATION OF THERAPY FOR BACTERIAL INFECTIONS

DURATION OF THERAPY	INFECTIONS
Single dose	Gonococcal urethritis, streptococcal pharyngitis (penicillin G benzathine), primary and secondary syphilis (penicillin G benzathine)
3 days	Cystitis in young women, community- or travel-acquired diarrhea
3–10 days	Community-acquired pneumonia (3–5 days), community-acquired meningitis (pneumococcal or meningococcal), antibiotic-associated diarrhea (10 days), *Giardia* enteritis, cellulitis, epididymitis
2 weeks	*Helicobacter pylori*–associated peptic ulcer, neurosyphilis (penicillin IV), penicillin-susceptible viridans streptococcal endocarditis (penicillin plus aminoglycoside), disseminated gonococcal infection with arthritis, acute pyelonephritis, uncomplicated *S. aureus* catheter-associated bacteremia
3 weeks	Lyme disease, septic arthritis (nongonococcal)
4 weeks	Acute and chronic prostatitis, infective endocarditis (penicillin-resistant streptococcal)
>4 weeks	Acute and chronic osteomyelitis, *S. aureus* endocarditis, foreign-body infections (prosthetic-valve and joint infections), relapsing pseudomembranous colitis

STRATEGIES TO OPTIMIZE ANTIMICROBIAL USE

Antibiotic use is often not "rational," and it is easy to understand why. The diagnosis of bacterial infection is often uncertain, patients may expect or demand antimicrobial agents in this tenuous situation, and clinicians wish to provide effective therapy even when the cause remains uncertain. Furthermore, the rates of resistance for many bacterial pathogens are ever-changing, and even experts may not agree on the appropriate therapy or the clinical significance of resistance in some pathogens. Consequently, investigators report that ~50% of antibiotic use is in some way "inappropriate." Aside from the monetary cost of using unnecessary or expensive antibiotics, there are the more serious costs associated with excess morbidity from superinfections such as *C. difficile* disease, adverse drug reactions, drug interactions, and selection of resistant organisms. It is increasingly recognized that these costs add substantially to the overall costs of medical care.

At a time when fewer new antimicrobial drugs are entering the worldwide market than in the past, much has been written about the continued rise in rates of resistant microorganisms, its causes, and the solutions. The message seems clear: the use of existing and new antimicrobial agents must be more judicious and infection control efforts more effective if we are to slow or reverse trends in resistance. The phrase *antimicrobial*

stewardship is used to describe the new attitude toward antibacterial agents that must be adopted to preserve their usefulness, and hospitals have been encouraged by professional organizations to implement multidisciplinary antimicrobial stewardship programs. These programs are designed to improve the quality of patient care by adopting best practices at the local level to ensure that antimicrobial drugs are used only when necessary, at the most appropriate dosage, and for the most appropriate duration. While some newer antibacterial drugs undeniably represent important advances in therapy, many offer no advantage over older, less expensive agents. With rare exceptions, newer drugs are usually found to be no more effective than the comparison antibiotic in controlled trials, despite the "high prevalence of resistance" often touted to market the advantage of the new antibiotic over older therapies.

The following suggestions are intended to provide guidance through the antibiotic maze. First, objective evaluation of the merits of newer and older drugs is available. Online references such as the Johns Hopkins website (*www.hopkins-abxguide.org*) offer current and practical information regarding antimicrobial drugs and treatment regimens. Evidence-based practice guidelines for the treatment of most infections are available from the Infectious Diseases Society of America (*www.idsociety.org*). Furthermore, specialty texts such as *Principles and Practice of Infectious Diseases* are available online. Second, clinicians should become comfortable using a few drugs recommended by independent experts and professional organizations and should resist the temptation to use a new drug unless the merits are clear. A new antibacterial agent with a "broader spectrum and greater potency" or a "higher serum concentration-to-MIC ratio" will not necessarily be more clinically efficacious. Third, clinicians should become familiar with local bacterial susceptibility profiles available via annual "antibiograms" published by hospital clinical microbiology laboratories. It may not be necessary to use a new drug with "improved activity against *P. aeruginosa*" if that pathogen is rarely encountered or if it retains full susceptibility to older drugs. Fourth, a skeptical attitude toward manufacturers' claims is still appropriate. For example, rising rates of penicillin resistance in *S. pneumoniae* have been used to promote the use of broader-spectrum drugs, notably the fluoroquinolones. However, except in patients with meningitis, amoxicillin is still effective for infections caused by these "penicillin-resistant" strains. Finally, with regard to inpatient treatment with antibacterial drugs, a number of efforts to improve use are under study. The strategy of antibiotic "cycling" or rotation has not proved effective, but other strategies, such as reductions in the duration of therapy, hold promise. Adoption of other evidence-based strategies to improve antimicrobial use may be the best way to retain the utility of existing compounds. For example, appropriate empirical treatment of the seriously ill patient with one or more broad-spectrum agents is important for improving survival rates, but therapy may often be simplified by switching to a narrower-spectrum agent or even an oral drug once the results of cultures and susceptibility tests become available. While there is an understandable temptation not to alter effective empirical broad-spectrum therapy, switching to a more specific agent once the patient's clinical condition has improved does not compromise outcome. A promising and active area of research includes the use of shorter courses of antimicrobial therapy, perhaps guided by markers of infection such as serum concentrations of procalcitonin. Many antibiotics that once were given for 7–14 days can be given for 3–5 days with no apparent loss of efficacy and no increase in relapse rates (Table 36-10). Shorter durations of therapy, once proven as effective as longer durations, offer an opportunity to decrease overall drug use and may result in decreased resistance. Adoption of new guidelines for shorter-course therapy will not undermine the care of patients, many unnecessary complications and expenses will be avoided, and the useful life of these valuable drugs will perhaps be extended.

CHAPTER 37

PNEUMOCOCCAL INFECTIONS

David Goldblatt ■ Katherine L. O'Brien

In the late nineteenth century, pairs of micrococci were first recognized in the blood of rabbits injected with human saliva by both Louis Pasteur working in France and George Sternberg, an American army physician. The important role of these micrococci in human disease was not appreciated at that time. By 1886, when the organism was designated "pneumokokkus" and *Diplococcus pneumoniae*, the pneumococcus had been isolated by many independent investigators, and its role in the etiology of pneumonia was well known. In the 1930s, pneumonia was the third leading cause of death in the United States (after heart disease and cancer) and was responsible for ~7% of all deaths both in the United States and in Europe. While pneumonia was caused by a host of pathogens, lobar pneumonia—a pattern more likely to be caused by the pneumococcus—accounted for approximately one-half of all pneumonia deaths in the United States in 1929. In 1974, the organism was reclassified as *Streptococcus pneumoniae*.

MICROBIOLOGY

Etiologic agent

Pneumococci are spherical gram-positive bacteria of the genus *Streptococcus*. Within this genus, cell division occurs along a single axis, and bacteria grow in chains or pairs—hence the name *Streptococcus*, from the Greek *streptos*, meaning "twisted," and *kokkos*, meaning "berry." At least 22 streptococcal species are recognized and are divided further into groups based on their hemolytic properties. *S. pneumoniae* belongs to the α-hemolytic group that characteristically produces a greenish color on blood agar because of the reduction of iron in hemoglobin **(Fig. 37-1)**. The bacteria are fastidious and grow best in 5% CO_2 but require a source of catalase (e.g., blood) for growth on agar plates, where they develop mucoid (smooth/shiny) colonies. Pneumococci without a capsule produce colonies with a rough surface. Unlike that of other α-hemolytic streptococci, their growth is inhibited in the presence of optochin (ethyl hydrocuprein hydrochloride), and they are bile soluble.

In common with other gram-positive bacteria, pneumococci have a cell membrane beneath a cell wall, which in turn is covered by a polysaccharide capsule. Pneumococci are divided into serogroups or serotypes based on capsular polysaccharide structure, as distinguished with rabbit polyclonal antisera; capsules swell in the presence of specific antiserum (the Quellung reaction). The 91st and 92nd serotypes, 6C and 6D, have most recently been identified with monoclonal antibodies and by serologic, genetic, and biochemical means, respectively. Within the 92 serotypes there are 21 serogroups, each containing two to five serotypes with closely related capsules. The capsule protects the bacteria from

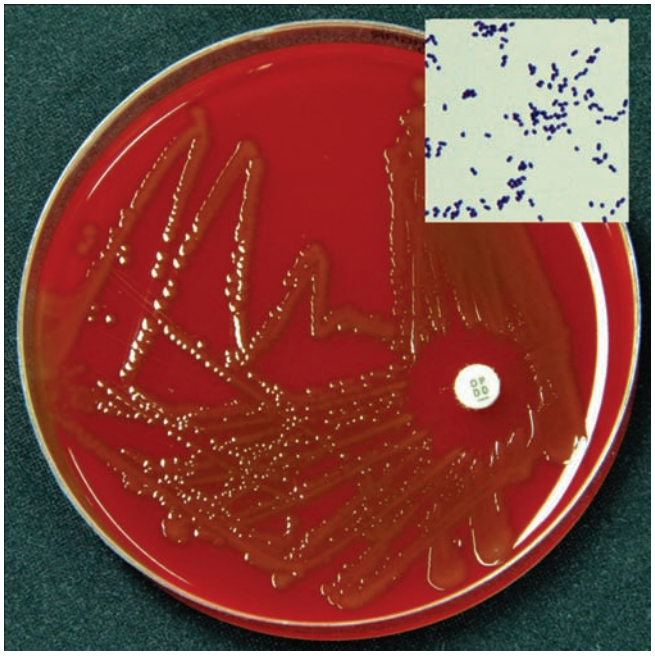


FIGURE 37-1
Pneumococci growing on blood agar, illustrating α hemolysis and optochin sensitivity (zone around optochin disk). *Inset:* Gram's stain, illustrating gram-positive diplococci. (*Photographs courtesy of Paul Turner, Shoklo Malaria Research Unit, Thailand.*)

phagocytosis by host cells in the absence of type-specific antibody and is arguably the most important determinant of pneumococcal virulence. Unencapsulated variants tend not to cause invasive disease.

Virulence factors

Within the cytoplasm, cell membrane, and cell wall, many molecules that may play a role in pneumococcal pathogenesis and virulence have been identified **(Fig. 37-2)**. These proteins are often involved in direct interactions with host tissues or in concealment of the bacterial surface from host defense mechanisms. Pneumolysin is a secreted cytotoxin thought to result in cytolysis of cells and tissues, and LytA enhances pathogenesis. A number of cell wall proteins interfere with the complement pathway, thus inhibiting complement deposition and preventing lysis and/or opsonophagocytosis. The pneumococcal H inhibitor (Hic) impedes the formation of C3 convertase, while pneumococcal surface protein C (PspC), also known as choline-binding protein A (CbpA), binds factor H and is thought to accelerate the breakdown of C3. PspA and CbpA inhibit the deposition of or degrade C3b. The numerous pneumococcal proteins thought to be involved in adhesion include the ubiquitous surface-anchored sialidase (neuraminidase) NanA, which cleaves sialic acid on host cells and proteins, and pneumococcal surface adhesin A (PsaA). Pili recently recognized by electron microscopy may also play an important role in binding to cells. Some of the antigens mentioned earlier are potential vaccine candidates (see "Prevention," later in the chapter).

Although the capsule surrounding the cell wall of *S. pneumoniae* is the basis for categorization by serotype, the behavior and pathogenic potential of a serotype may also be related to the genetic origin of the strain. Molecular typing is therefore of considerable interest. Initially, techniques such as pulsed-field gel electrophoresis were used to determine genetic relatedness; such techniques have been superseded by sequencing of housekeeping genes to define a clone (multilocus sequence typing, MLST). For *S. pneumoniae*, alleles at each of the loci *aroE*, *gdh*, *gki*, *recP*, *spi*, *xpt*, and *ddl* are sequenced and compared with all of the known alleles at that locus. Sequences identical to a known allele are assigned the same allele number, whereas those differing from any known allele—even at a single nucleotide site—are assigned new numbers. Software for assignment of alleles at each locus is available on the pneumococcal MLST web site (*http://spneumoniae.mlst.net/*), and the allelic profile of each isolate and its consequent sequence type are generated. With the advent of high-throughput

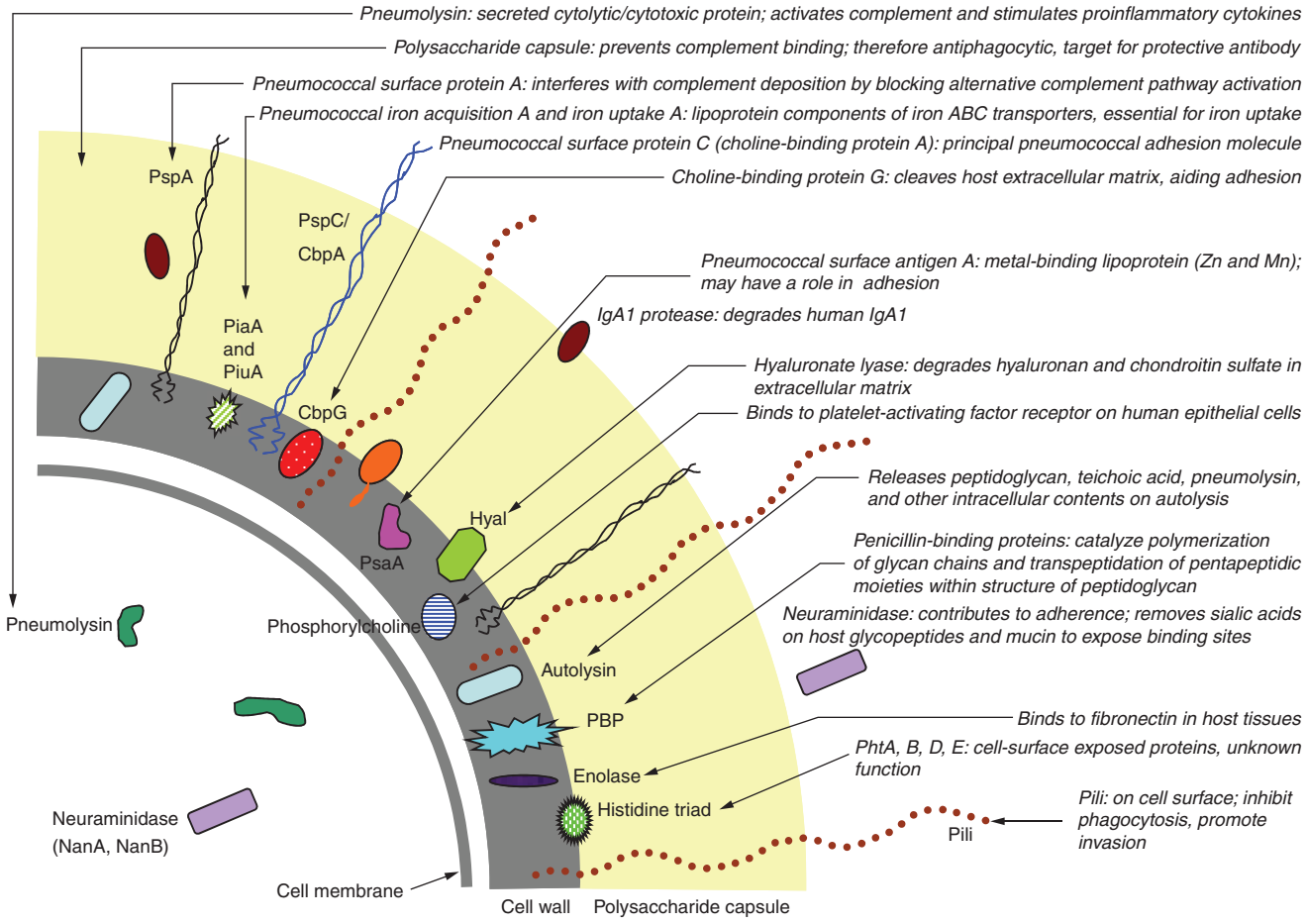


FIGURE 37-2
Schematic diagram of the pneumococcal cell surface, with key antigens and their roles highlighted.

and relatively inexpensive sequencing techniques, whole-genome sequencing will soon supersede MLST.

EPIDEMIOLOGY

Pneumococcal infections remain a significant global cause of morbidity and death, particularly among children and the elderly. Rapid and dramatic changes in the epidemiology of this disease during the past decade in several developed countries followed the licensure and routine childhood administration of pneumococcal polysaccharide–protein conjugate vaccine (PCV). With PCV introduction in developing and middle-income countries, additional profound changes in pneumococcal ecology and disease epidemiology are likely. The disease burden and serotype distribution in the PCV era may be different than expected because of concomitant secular trends in pneumococcal disease, the impact of antibiotic use on pneumococcal strain ecology, and surveillance system attributes that can themselves affect analysis of epidemiologic features.

Not all pneumococcal serotypes are equally likely to cause disease; serotype distribution varies by age, disease syndrome, and geography. Geographic differences may be driven by variation in the burden of disease rather than by true serotype distribution differences. Most data on serotype distribution are related to pediatric invasive pneumococcal disease (IPD, defined as infection of a normally sterile site); much less information on global distribution is available on disease in adults. Among children <5 years of age, five to seven serotypes cause >60% of IPD cases in most parts of the world, seven serotypes (1, 5, 6A, 6B, 14, 19F, and 23F) account for ~60% of cases in all areas of the world, but in any given region these seven serotypes may not all rank as the most common disease strains **(Fig. 37-3)**. Some serotypes (e.g., types 1 and 5) not only tend to cause disease in areas with a high disease burden but also cause waves of disease in lower-burden areas (e.g., Europe) or outbreaks (e.g., in military barracks; meningitis in sub-Saharan Africa). The broader range of serotypes causing disease among adults than among children is apparent from a comparison of the coverage of existing multiserotype vaccines in different age groups. For example, data from the United States for 2006–2007 on the serotypes causing IPD indicated that a polysaccharide vaccine containing 23 serotypes (PPV23) would cover 84% of cases among children <5 years of age and 76% of those among persons 18–64 years of age but only 65% of those among persons ≥65 years of age.

Pneumococci are intermittent inhabitants of the healthy human nasopharynx and are transmitted by respiratory droplets. In children, pneumococcal nasopharyngeal ecology varies by geographic region, socioeconomic status, climate, degree of crowding, and particularly intensity of exposure to other children, with children in day-care settings having higher rates of colonization. In developed-world settings, children serve as the major vectors of pneumococcal transmission. By 1 year of age, ~50% of children have had at least one episode of pneumococcal colonization. Cross-sectional prevalence data show rates of pneumococcal carriage ranging from 20% to 50% for children <5 years of age and from 5% to 15% for young and middle-aged adults; **Fig. 37-4** shows relevant data from the United Kingdom. Data on colonization rates among healthy elderly individuals are limited. In developing-world settings, pneumococcal acquisition occurs much earlier, sometimes within the first few days after birth, and nearly all infants have had at least one episode of colonization by 2 months of age. Cross-sectional studies show that up to the age of 5 years, 70–90% of children carry *S. pneumoniae* in the nasopharynx, and a significant proportion of adults (sometimes >40%) are also colonized. Their high rates of colonization make adults an important source of transmission and may affect community transmission dynamics.

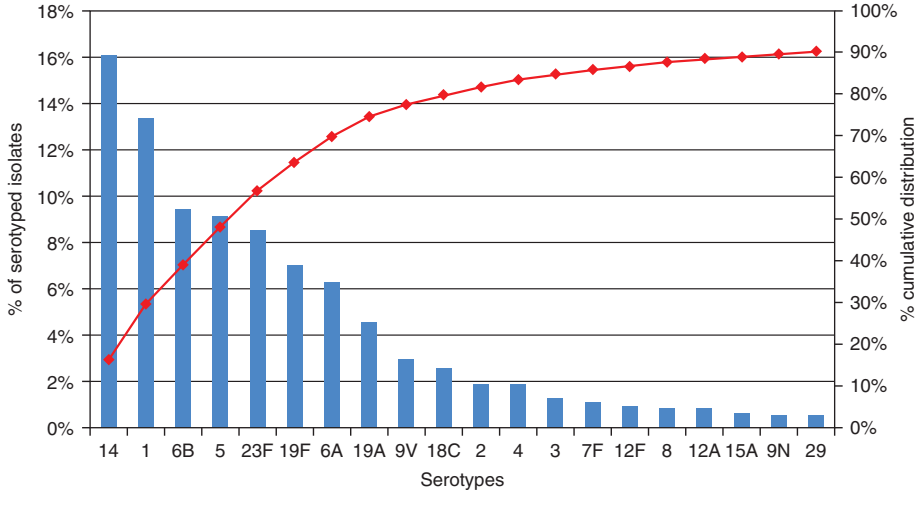


FIGURE 37-3
Meta-analysis of available global serotype data, adjusted for regional disease incidence. The red line shows cumulative incidence, as indicated on the right-hand Y axis. (*Source: Global Serotype Project Report for the Pneumococcal Advance Market Commitment Target Product Profile; available at http://www.vaccineamc.org/files/TPP_Codebook.pdf.*)

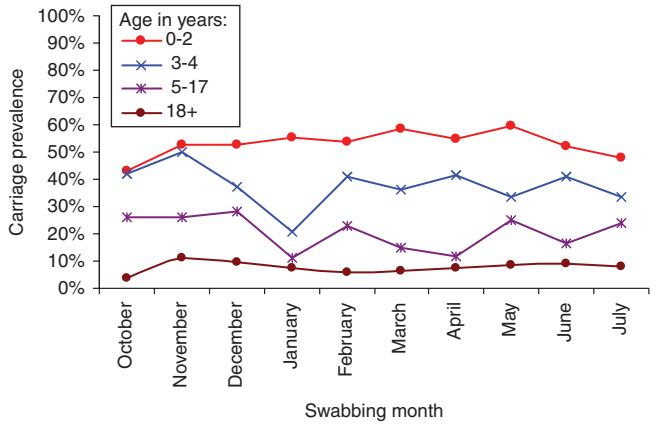


FIGURE 37-4

Prevalence of pneumococcal carriage in adults and children resident in the United Kingdom who had nasopharyngeal swabs collected monthly for 10 months (no seasonal trend; *t* test trend, >.05). (*Data adapted from D Goldblatt et al: J Infect Dis 192:387, 2005.*)

IPD develops when *S. pneumoniae* invades the bloodstream and seeds other organs or directly reaches the cerebrospinal fluid (CSF) by local extension. Pneumonia may follow aspiration of pneumococci, although only 10–30% of such cases are associated with a positive blood culture (and thus contribute to the measured burden of IPD). The dramatic variation of IPD rates with age is illustrated by data from the United States for 1998–1999, a period prior to PCV introduction. Rates of IPD were highest among children <2 years of age and among adults ≥65 years of age (188 and 60 cases per 100,000, respectively; **Fig. 37-5**). Since the introduction of PCV, IPD rates among infants and children in the United States have fallen by >75%, a decrease driven by the near elimination of vaccine-serotype IPD. A similar impact of PCV on vaccine-serotype IPD rates has been consistently observed in countries where PCV has been introduced into the routine pediatric vaccination schedule. However, changes in the non-vaccine-serotype IPD rate in various countries have been heterogeneous; the interpretation of this heterogeneity is a complex issue. In the United States, Canada, and Australia, rates of non-vaccine-serotype IPD have increased but the magnitude of the increase is generally small relative to the substantial reductions in vaccine-serotype IPD. In contrast, in other settings (e.g., Alaska Native communities and the United Kingdom), the reduction in vaccine-serotype IPD has been offset by notable increases in rates of disease caused by non-vaccine serotypes. Explanations for the heterogeneity of findings include replacement disease resulting from vaccine pressure, changes in clinical case investigation, secular trends unrelated to PCV use, antibiotic pressure selecting for resistant organisms, changes in surveillance or reporting systems, rapidity of introduction, and inclusion of a catch-up campaign. The roles and relative importance of these hypothesized mechanisms in driving the observed non-vaccine-serotype IPD trends and in explaining the observed heterogeneity among populations are not yet fully understood.

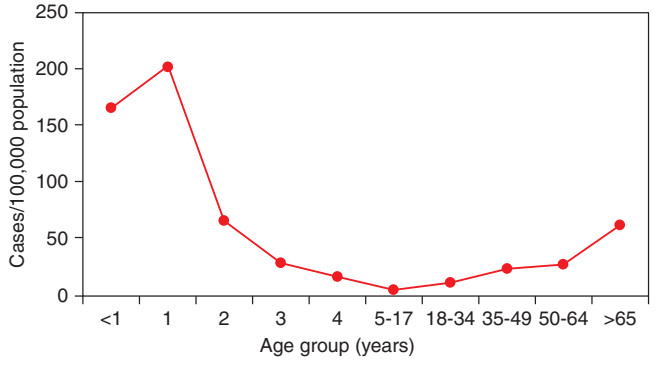


FIGURE 37-5

Rates of invasive pneumococcal disease before the introduction of pneumococcal conjugate vaccine, by age group: United States, 1998. (*Source: CDC, Active Bacterial Core Surveillance/Emerging Infectious Program Network, 2000. Data adapted from MMWR 49[RR-9], 2000.*)

Pneumonia is the most common of the serious pneumococcal disease syndromes and poses special challenges from a clinical and public health perspective. Most cases of pneumococcal pneumonia are not associated with bacteremia, and in these cases a definitive etiologic diagnosis is difficult. As a result, estimates of disease burden focus primarily on IPD rates and fail to include the major portion of the burden of serious pneumococcal disease. Among children, PCV trials designed to collect efficacy data on syndrome-based outcomes (e.g., radiographically confirmed pneumonia, clinically diagnosed pneumonia) have revealed the burden of culture-negative pneumococcal pneumonia.

The case-fatality ratios (CFRs) for pneumococcal pneumonia and IPD vary by age, underlying medical condition, and access to care. In addition, the CFR for pneumococcal pneumonia varies with the severity of disease at presentation (rather than according to whether or not the pneumonia episode is associated with bacteremia) and with the patient's age (from <5% among hospitalized patients 18–44 years old to >12% among those >65 years old, even when appropriate and timely management is available). Notably, the likelihood of death in the first 24 h of hospitalization did not change substantially with the introduction of antibiotics; this surprising observation highlights the fact that the pathophysiology of severe pneumococcal pneumonia among adults reflects a rapidly progressive cascade of events that often unfolds irrespective of antibiotic administration. Management in an intensive care unit can provide critical support for the patient through the acute period, with lower CFRs.

Rates of pneumococcal disease vary by season, with higher rates in colder than in warmer months in temperate climates; by gender, with males more often affected than females; and by risk group, with risk factors including underlying medical conditions, behavioral issues, and ethnic group. In the United States, some Native American populations (including Alaska natives)

and African Americans have higher rates of disease than the general population; the increased risk is probably attributable to socioeconomic conditions and the prevalence of underlying risk factors for pneumococcal disease. Medical conditions that increase the risk of pneumococcal infection are listed in **Table 37-1**. Outbreaks of disease are well recognized in crowded settings with susceptible individuals, such as infant day-care facilities, military barracks, and nursing homes. Furthermore, there is a clear association between preceding viral respiratory disease (especially but not exclusively influenza) and risk of secondary pneumococcal infections. The significant role of pneumococcal pneumonia in the morbidity and mortality associated with seasonal and pandemic influenza is increasingly recognized.

TABLE 37-1

CLINICAL RISK GROUPS FOR PNEUMOCOCCAL INFECTION

CLINICAL RISK GROUP	EXAMPLES
Asplenia or splenic dysfunction	Sickle cell disease, celiac disease
Chronic respiratory disease	Chronic obstructive pulmonary disease, bronchiectasis, cystic fibrosis, interstitial lung fibrosis, pneumoconiosis, bronchopulmonary dysplasia, aspiration risk, neuromuscular disease (e.g., cerebral palsy), severe asthma
Chronic heart disease	Ischemic heart disease, congenital heart disease, hypertension with cardiac complications, chronic heart failure
Chronic kidney disease	Nephrotic syndrome, chronic renal failure, renal transplantation
Chronic liver disease	Cirrhosis, biliary atresia, chronic hepatitis
Diabetes mellitus	Diabetes mellitus requiring insulin or oral hypoglycemic drugs
Immunocompromise/ immunosuppression	HIV infection, common variable immunodeficiency, leukemia, lymphoma, Hodgkin's disease, multiple myeloma, generalized malignancy, chemotherapy, organ or bone marrow transplantation, systemic glucocorticoid treatment for >1 month at a dose equivalent to ≥20 mg/day (children, ≥1 mg/kg per day)
Cochlear implants	. . .
Cerebrospinal fluid leaks	. . .
Miscellaneous	Infancy and old age; prior hospitalization; alcoholism; malnutrition; cigarette smoking; day-care center attendance; residence in military training camps, prisons, homeless shelters

Note: Groups for whom pneumococcal vaccines are recommended by the Advisory Committee on Immunization Practices can be found at *http://www.cdc.gov/vaccines/recs/schedules/default.htm.*

Reduced pneumococcal susceptibility to penicillin was first noted in 1967, but not until the 1990s did reduced antibiotic susceptibility emerge as a significant clinical and public health issue, with an increasing prevalence of pneumococcal isolates resistant to single or multiple classes of antibiotics and a rising absolute magnitude of minimal inhibitory concentrations (MICs). Strains with reduced susceptibility to penicillin G, cefotaxime, ceftriaxone, macrolides, and other antibiotics are now found worldwide and account for a significant proportion of disease-causing strains in many locations, especially among children. Vancomycin resistance has not yet been observed in clinical pneumococcal strains. Lack of antimicrobial susceptibility is clearly related to a subset of serotypes, many of which disproportionately cause disease among children. The vicious cycle of antibiotic exposure, selection of resistant organisms in the nasopharynx, and transmission of these organisms within the community leading to difficult-to-treat infections and increased antibiotic exposure has been interrupted to some extent by the introduction and routine use of PCV. The clinical implications of pneumococcal antimicrobial nonsusceptibility are addressed later in the section on treatment.

PATHOGENESIS

Pneumococci colonize the human nasopharynx from an early age; colonization acquisition events are generally described as asymptomatic, but evidence exists to associate acquisition with mild respiratory symptoms, especially in the very young. From the nasopharynx, the bacteria spread either via the bloodstream to distant sites (e.g., brain, joint, bones, peritoneal cavity) or locally to mucosal surfaces where they can cause otitis media or pneumonia. Direct spread from the nasopharynx to the central nervous system (CNS) can occur in rare cases of skull base fracture, although most cases of pneumococcal meningitis are secondary to hematogenous spread. Pneumococci can cause disease in almost any organ or part of the body; however, otitis media, pneumonia, bacteremia, and meningitis are most common. Colonization is a relatively frequent event, yet disease is rare. In the nasopharynx, pneumococci survive in mucus secreted by epithelial cells, where they can avoid local immune factors such as leukocytes and complement. The mucus itself is a component of local defense mechanisms, and the flow of mucus (driven in part by cilia in what is known as the *mucociliary escalator*) effects mechanical clearance of pneumococci. While many colonization episodes are of short duration, longitudinal studies in adults and children have revealed persistent colonization with a specific serotype over many months. Colonization eventually results in the development of capsule-specific serum IgG, which is thought to play a role in mediating clearance of bacteria from the nasopharynx. IgG antibodies to surface exposed

cell wall or secreted proteins also appear in the circulation in an age-dependent fashion or after colonization; the biological role of these antibodies is less clear. Recent acquisition of a new colonizing serotype is more likely to be associated with subsequent invasion, presumably as a result of the absence of type-specific immunity. Intercurrent viral infections make the host more susceptible to pneumococcal colonization, and pneumococcal disease in a colonized individual often follows perturbation of the nasopharyngeal mucosa by such infections. Local cytokine production after a viral infection is thought to upregulate adhesion factors in the respiratory epithelium, allowing pneumococci to adhere via a variety of surface adhesin molecules, including PsaA, PspA, CbpA, PspC, Hyl, pneumolysin, and the neuraminidases (Fig. 37-2). Adhesion coupled with inflammation induced by pneumococcal factors such as peptidoglycans and teichoic acids results in invasion. It is the inflammation induced by various bacterium-derived factors that is responsible for the pathology associated with pneumococcal infection. Cell wall–derived teichoic acids and peptidoglycans induce a variety of cytokines, including the proinflammatory cytokines interleukin (IL) 1, IL-6, and tumor necrosis factor (TNF), and activate complement via the alternative pathway. Polymorphonuclear leukocytes are thus attracted, and an intense inflammatory response is initiated. Pneumolysin is also important in local pathology, inducing proinflammatory cytokine production by local monocytes.

The pneumococcal capsule, consisting of polysaccharides with antiphagocytic properties due to resistance to the deposition of complement, plays an important role in pathogenesis. While most capsular types can cause human disease, certain capsular types are more commonly isolated from sites of infection. The reason for the dominance of some serotypes over others in IPD, as depicted in Fig. 37-3, is unclear.

HOST DEFENSE MECHANISMS

Innate immunity

As described earlier, intact respiratory epithelium and a host of nonspecific or innate immune factors (e.g., mucus, splenic function, complement, neutrophils, and macrophages) constitute the first line of defense against pneumococci. Physical factors such as the cough reflex and the mucociliary escalator are important in clearing bacteria from the lungs. Immunologic factors are critical as well: C-reactive protein (CRP) binds phosphorylcholine in the pneumococcal cell wall, inducing complement activation and leading to bacterial clearance; Toll-like receptor 2 (TLR2) recognizes both pneumococcal lipoteichoic acid and cell wall peptidoglycan; and in animal models, the absence of host TLR2 leads to more severe infection and impaired clearance of nasopharyngeal colonization. TLR4 appears to be necessary for the proinflammatory effect of pneumolysin on macrophages. The importance of TLR recognition is underlined by descriptions of an inherited deficiency of human IL-1 receptor–associated kinase 4 (IRAK-4) that manifests as an unusual susceptibility to infection with bacteria, including *S. pneumoniae*. IRAK-4 is essential for the normal functioning of several TLRs. Other factors that interfere with these nonspecific mechanisms (e.g., viral infections, cystic fibrosis, bronchiectasis, complement deficiency, and chronic obstructive pulmonary disease) all predispose to the development of pneumococcal pneumonia. Patients who lack a spleen or have abnormal splenic function (e.g., persons with sickle cell disease) are at high risk of developing overwhelming pneumococcal disease.

Acquired immunity

Acquired immunity induced via contact following colonization or through cross-reactive antigens rests largely on the development of serum IgG antibody specific for the pneumococcal capsular polysaccharide. Nearly all polysaccharides are T cell–independent antigens; B cells can make antibodies to such antigens without T cell help. However, in children <1–2 years old, such B cell responses are poorly developed. This delayed ontogeny of capsule-specific IgG in young children is associated with susceptibility to pneumococcal infection (Fig. 37-5). The extremely high risk of pneumococcal infection in the absence of serum immunoglobulin (i.e., in conditions such as agammaglobulinemia) highlights the important role of capsular antibody in protection against disease. Each serotype's capsule is chemically distinct; thus immunity tends to be serotype specific, although some cross-immunity exists. For example, conjugate vaccine–induced antibodies to serotype 6B prevent infection due to serotype 6A. However, cross-protection against serotypes within serogroups is not universal; for instance, antibodies to serotype 19F do not appear to confer protection against disease caused by serotype 19A. Antibodies to surface exposed or secreted pneumococcal proteins (such as pneumolysin, PsaA, and PspA) also appear in the circulation with increasing age of the host, but their functional significance remains unclear. Although data from murine models suggest that CD4+ T cells may play a role in preventing pneumococcal colonization and disease, these data have not yet been replicated in humans.

APPROACH TO THE PATIENT **Pneumococcal Infections**

There is no pathognomonic presentation of pneumococcal disease; patients may present with a range of syndromes and with more than one clinical syndrome (e.g., pneumonia and meningitis). *S. pneumoniae* can infect nearly any body tissue, manifesting as disease ranging in severity from mild and self-limited to life-threatening. The differential diagnosis of common clinical syndromes such as pneumonia, otitis media, fever of unknown origin, and meningitis should always include pneumococcal infection. A microbiologically confirmed diagnosis is made in only a minority of pneumococcal cases since, in most circumstances (and especially in pneumonia and otitis media), fluid from the site of infection is not available for etiologic determination. Empirical therapy that includes appropriate treatment for *S. pneumoniae* is often indicated.

Algorithms for assessment and management of ill children have been developed for use in the developing world or in other settings where evaluation by a trained physician may not be feasible. Children who present with ominous signs such as inability to drink, convulsions, lethargy, and severe malnutrition are categorized as having very severe disease without further evaluation by the community health care worker, are given antibiotics, and are immediately referred to a hospital for diagnosis and management. Children who present with cough and tachypnea (the latter defined according to specific age strata) are further stratified into severity categories based on the presence or absence of lower chest wall indrawing and are managed accordingly with either antibiotics alone or antibiotics and referral to a hospital facility. Children with cough but no tachypnea are categorized as having a nonpneumonia respiratory illness.

CLINICAL MANIFESTATIONS

The clinical manifestations of pneumococcal disease depend on the site of infection and the duration of illness. Clinical syndromes are classified as noninvasive (e.g., otitis media and nonbacteremic pneumonia) or invasive (e.g., bacteremic pneumonia). The pathogenesis of noninvasive illness involves contiguous spread from the nasopharynx or skin; invasive disease involves infection of a normally sterile body fluid or follows bacteremia.

Pneumonia

Pneumonia is the most common serious pneumococcal syndrome and is considered invasive when associated with a positive blood culture. Pneumococcal pneumonia can present as a mild community-acquired infection at one extreme and as a life-threatening disease requiring intubation and intensive support at the other.

Presenting manifestations

The presentation of pneumococcal pneumonia does not reliably distinguish it from pneumonia of other etiologies. In a subset of cases, pneumococcal pneumonia is recognized at the outset as associated with a viral upper respiratory infection and is characterized by the abrupt onset of cough and dyspnea accompanied by fever, shaking chills, and myalgias. The cough evolves from nonpurulent to productive of sputum that is purulent and sometimes tinged with blood. Patients may describe stabbing pleuritic chest pain and significant dyspnea indicating involvement of the parietal pleura. Among the elderly, the presenting clinical symptoms may be less specific, with confusion or malaise but without fever or cough. In such cases, a high index of suspicion is required because failure to treat pneumococcal pneumonia promptly in an elderly patient is likely to result in rapid evolution of the infection, with increased severity, morbidity, and risk of death.

Findings on physical examination

The clinical signs associated with pneumococcal pneumonia among adults include tachypnea (>30 breaths/min) and tachycardia, hypotension in severe cases, and fever in most cases (although not in all elderly patients). Respiratory signs are varied, including dullness to percussion in areas of the chest with significant consolidation, crackles on auscultation, reduced expansion of the chest in some cases as a result of splinting to reduce pain, bronchial breathing in a minority of cases, pleural rub in occasional cases, and cyanosis in cases with significant hypoxemia. Among infants with severe pneumonia, chest wall indrawing and nasal flaring are common. Nonrespiratory findings can include upper abdominal pain if the diaphragmatic pleura is involved as well as mental status changes, particularly confusion among elderly patients.

Differential diagnosis

The differential diagnosis of pneumococcal pneumonia includes cardiac conditions such as myocardial infarction and heart failure with atypical pulmonary edema; pulmonary conditions such as atelectasis; and pneumonia caused by viral pathogens, mycoplasmas, *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Legionella*, or (in HIV-infected and otherwise immunocompromised hosts) *Pneumocystis*. In cases including abdominal symptoms, the differential diagnosis includes cholecystitis, appendicitis, perforated peptic ulcer disease, and subphrenic abscesses. The challenge in cases with abdominal symptoms is to remember to include pneumococcal pneumonia—a nonabdominal process—in the differential diagnosis.

Diagnosis

Some authorities advocate treating uncomplicated, nonsevere, community-acquired pneumonia without determining the microbiologic etiology, given that this information is unlikely to alter clinical management. However, efforts to identify the cause of pneumonia are important when the disease is more severe and when the diagnosis of pneumonia is not clearly established. The gold standard for etiologic diagnosis of pneumococcal pneumonia is pathologic examination of lung tissue. In lieu of that procedure, evidence of an infiltrate on chest radiography warrants a diagnosis of pneumonia. However, cases of pneumonia without radiographic evidence do occur. An infiltrate can be absent either early in the course of the illness or with dehydration; upon rehydration, an infiltrate usually appears. The radiographic appearance of pneumococcal pneumonia is varied; it classically consists of lobar or segmental consolidation **(Fig. 37-6)** but in some cases is patchy. More than one lobe is involved in ~30% of cases. Consolidation may be associated with a small pleural effusion or empyema in complicated cases. In children, "round pneumonia," a distinctly spherical consolidation on chest radiography, is associated with a pneumococcal etiology. Round pneumonia is uncommon in adults. *S. pneumoniae* is not the only cause of such lesions; other causes, especially cancer, should be considered.

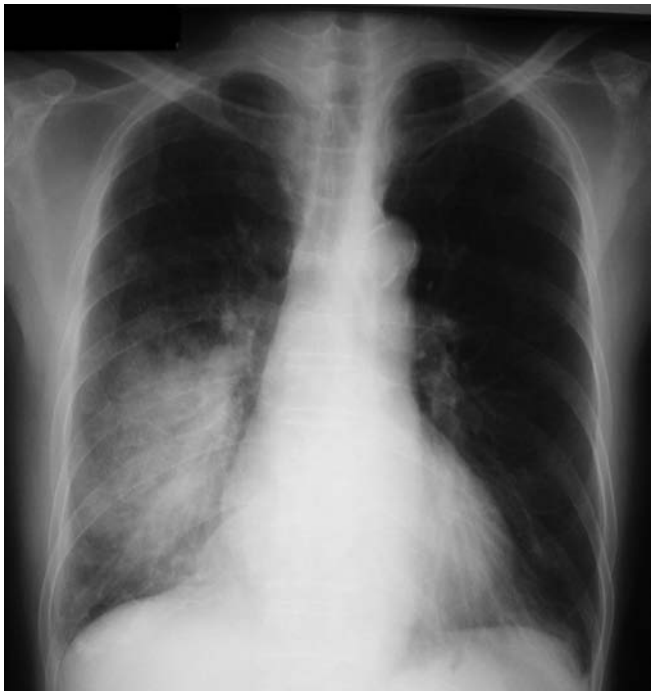


FIGURE 37-6
Chest radiograph depicting classic lobar pneumonia in the right lower lobe of an elderly patient's lung.

Blood drawn from patients with suspected pneumococcal pneumonia can be used for supportive or definitive diagnostic tests. Blood cultures are positive for pneumococci in a minority (<30%) of cases of pneumococcal pneumonia. Nonspecific findings include an elevated polymorphonuclear leukocyte count (>15,000/μL in most cases and upward of 40,000/μL in some), leukopenia in <10% of cases (a poor prognostic sign associated with a fatal outcome), and elevated values in liver function tests (e.g., both conjugated and unconjugated hyperbilirubinemia). Anemia, low serum albumin levels, hyponatremia, and elevated serum creatinine levels are all found in ~20–30% of patients.

Urinary pneumococcal antigen assays have facilitated etiologic diagnosis. In adults, among whom the prevalence of pneumococcal nasopharyngeal colonization is relatively low, a positive pneumococcal urinary antigen test has a high predictive value. The same is not true for children, in whom a positive urinary antigen test can reflect the mere presence of *S. pneumoniae* in the nasopharynx.

Most cases of pneumococcal pneumonia are diagnosed by Gram's staining and culture of sputum. The utility of a sputum specimen is directly related to its quality and the patient's antibiotic treatment status.

Complications

Empyema is the most common focal complication of pneumococcal pneumonia, occurring in <5% of cases. When fluid in the pleural space is accompanied by fever and leukocytosis (even low-grade) after 4–5 days of appropriate antibiotic treatment for pneumococcal pneumonia, empyema should be considered. Parapneumonic effusions are more common than empyema, representing a self-limited inflammatory response to pneumonia. Pleural fluid with frank pus, bacteria (detected by microscopic examination), or a pH of ≥7.1 indicates empyema and demands aggressive and complete drainage, usually through chest tube insertion.

Meningitis

Pneumococcal meningitis typically presents as a pyogenic condition that is clinically indistinguishable from meningitis of other bacterial etiologies. Meningitis can be the primary presenting pneumococcal syndrome or a complication of other conditions such as skull fracture, otitis media, bacteremia, or mastoiditis. Now that *H. influenzae* type b vaccine is routinely used, *S. pneumoniae* and *Neisseria meningitidis* are the most common bacterial causes of meningitis in both adults and children. Pyogenic meningitis, including that due to *S. pneumoniae*, is associated clinically with findings that include severe, generalized, gradual-onset headache, fever, and nausea as well as specific CNS manifestations such as stiff neck, photophobia, seizures, and confusion. Clinical signs include a toxic appearance, altered consciousness, bradycardia, and hypertension indicative of increased intracranial pressure. A small proportion of adult patients have Kernig's or Brudzinski's sign or cranial nerve palsies (particularly of the 3rd and 6th cranial nerves).

A definitive diagnosis of pneumococcal meningitis rests on the examination of CSF for (1) evidence of turbidity (visual inspection); (2) elevated protein level, elevated white blood cell count, and reduced glucose concentration (quantitative measurement); and (3) specific identification of the etiologic agent (culture, Gram's staining, antigen testing, or PCR). A blood culture positive for *S. pneumoniae* in conjunction with clinical manifestations of meningitis is also considered confirmatory. Among adults, detection of pneumococcal antigen in urine is considered highly specific because of the low prevalence of nasopharyngeal colonization in this age group.

The mortality rate for pneumococcal meningitis is ~20%. In addition, up to 50% of survivors experience acute or chronic complications, including deafness, hydrocephalus, and mental retardation in children and diffuse brain swelling, subarachnoid bleeding, hydrocephalus, cerebrovascular complications, and hearing loss in adults.

Other invasive syndromes

S. pneumoniae can cause other invasive syndromes involving virtually any body site. These syndromes include primary bacteremia without other sites of infection (bacteremia without a source; occult bacteremia), osteomyelitis, septic arthritis, endocarditis, pericarditis, and peritonitis. The essential diagnostic approach is collection of fluid from the site of infection by sterile technique and examination by Gram's staining, culture, and—when relevant—capsular antigen assay or PCR. Hemolytic-uremic syndrome can complicate invasive pneumococcal disease.

Noninvasive syndromes

The two major noninvasive syndromes caused by *S. pneumoniae* are sinusitis and otitis media; the latter is

the most common pneumococcal syndrome and most often affects young children. The manifestations of otitis media include the acute onset of severe pain, fever, deafness, and tinnitus, most frequently in the setting of a recent upper respiratory tract infection. Clinical signs include a red, swollen, often bulging tympanic membrane with reduced movement on insufflation or tympanography. Redness of the tympanic membrane is not sufficient for the diagnosis of otitis media.

Pneumococcal sinusitis is also a complication of upper respiratory tract infections and presents with facial pain, congestion, fever, and—in many cases—persistent nighttime cough. A definitive diagnosis is made by aspiration and culture of sinus material; however, presumptive treatment is most commonly initiated after application of a strict set of clinical diagnostic criteria.

TREATMENT Pneumococcal Infections

Historically, the activity of penicillin against pneumococci made parenteral penicillin G the drug of choice for disease caused by susceptible organisms, including community-acquired pneumonia. For susceptible strains, penicillin G remains the most commonly used agent, with daily doses ranging from 50,000 U/kg for minor infections to 300,000 U/kg for meningitis. Other parenteral β-lactam drugs, such as ampicillin, cefotaxime, ceftriaxone, and cefuroxime, can be used against penicillin-susceptible strains but offer little advantage over penicillin. Macrolides and cephalosporins are alternatives for penicillin-allergic patients. While agents such as clindamycin, tetracycline, and trimethoprim-sulfamethoxazole exhibit some activity against pneumococci, resistance to these agents is frequently encountered in different parts of the world.

Penicillin-resistant pneumococci were first described in the mid-1960s, at which point tetracycline- and macrolide-resistant strains had already been reported. Multidrug-resistant strains were first described in the 1970s, but it was during the 1990s that pneumococcal drug resistance reached pandemic proportions. The use of antibiotics selects for resistant pneumococci, and strains resistant to β-lactam agents and to multiple drugs are now found all over the world. The emergence of high rates of macrolide and fluoroquinolone resistance has also been described.

The molecular basis of penicillin resistance in *S. pneumoniae* is the alteration of penicillin-binding protein (PBP) genes by transformation and horizontal transfer of DNA from related streptococcal species. Such alteration of PBPs results in lower affinity for penicillins. Depending on the specific PBP(s) and the number of PBPs altered, the level of resistance ranges from intermediate to high. For many years, penicillin susceptibility breakpoints have been defined by MICs as follows: susceptible, ≥0.06 μg/mL; intermediate, 0.12–1.0 μg/mL; and resistant, ≥2.0 μg/mL. However, in vitro results often were not predictive of the response of a patient to treatment for pneumococcal diseases other than meningitis. New recommendations have been based on the revised penicillin G breakpoints established in 2008 by the Clinical and Laboratory Standards Institute. For IV treatment of meningitis with at least 24 million units per day in 8 divided doses, the susceptibility breakpoint remains ≥0.06 μg/mL, and MICs of ≥0.12 μg/mL indicate resistance. For IV treatment of nonmeningeal infections with 12 million units per day in 6 divided doses, the breakpoints are ≥2 μg/mL for susceptible organisms, 4 μg/mL for intermediate organisms, and ≥ 8 μg/mL for resistant organisms; a dosage of 18–24 million units per day is recommended for strains with MICs in the intermediate category. The original breakpoints remain the same for oral treatment of nonmeningeal infections with penicillin V.

Although guidelines for antibiotic therapy should be driven in part by local patterns of resistance, guidelines from national organizations in many countries (e.g., the Infectious Diseases Society of America/American Thoracic Society, the British Thoracic Society, and the European Respiratory Society) lay out evidence-based approaches. The following guidelines for individual sepsis syndromes are based on those advocated by the American Academy of Pediatrics and published in the 2009 *Red Book*.

MENINGITIS LIKELY OR PROVEN TO BE DUE TO *S. PNEUMONIAE* As a result of the increased prevalence of resistant pneumococci, first-line therapy for persons ≥1 month of age is a combination of vancomycin (adults, 30–60 mg/kg per day; infants and children, 60 mg/kg per day) and cefotaxime (adults, 8–12 g/d in 4–6 divided doses; children, 225–300 mg/kg per day in 1 dose or 2 divided doses) or ceftriaxone (adults, 4 g/d in 1 dose or 2 divided doses; children, 100 mg/kg per day in 1 dose or 2 divided doses). If children are hypersensitive to β-lactam agents (penicillins and cephalosporins), rifampin (adults, 600 mg/d; children, 20 mg/d in 1 dose or 2 divided doses) can be substituted for cefotaxime or ceftriaxone. A lumbar puncture should be considered after 48 h if the organism is not susceptible to penicillin and information on cephalosporin sensitivity is not yet available, if the patient's clinical condition does not improve or deteriorates, or if dexamethasone has been administered and may be compromising clinical evaluation. When antibiotic sensitivity data become available, treatment should be modified accordingly. If the isolate is sensitive to penicillin, vancomycin can be discontinued and penicillin can replace the cephalosporin, or cefotaxime or ceftriaxone can be continued alone. If the isolate displays any resistance to penicillin but is susceptible to the cephalosporins, vancomycin can be discontinued and cefotaxime or ceftriaxone continued. If the isolate exhibits any resistance to penicillin and is not susceptible to cefotaxime and ceftriaxone, vancomycin and high-dose cefotaxime or ceftriaxone can be continued; rifampin may be added as well if the isolate is susceptible and the patient's clinical condition is worsening, if the CSF remains

positive for bacteria, or if the MIC of the cephalosporin in question against the infecting strain is high. Some physicians advocate the use of glucocorticoids in children >6 months old, but this recommendation remains controversial and is not universally considered the standard of care. Glucocorticoids significantly reduce rates of mortality, severe hearing loss, and neurologic sequelae in adults and should be administered to those with community-acquired bacterial meningitis. If dexamethasone is given to either adults or children, it should be administered before or in conjunction with the first antibiotic dose.

INVASIVE INFECTIONS (EXCLUDING MENINGITIS) In previously well children with noncritical illness, antibiotic therapy with a recommended antibiotic should be instigated at the following dosages: penicillin G, 250,000–400,000 units/kg per day (in divided doses 4–6 h apart); cefotaxime, 75–100 mg/d (doses 8 h apart); or ceftriaxone, 50–75 mg/d (doses 12–24 h apart). For critically ill children, including those who have myocarditis or multilobular pneumonia with hypoxia or hypotension, vancomycin may be added if the isolate may possibly be resistant to β-lactam drugs, with its use reviewed once susceptibility data become available. If the organism is resistant to β-lactam agents, therapy should be modified on the basis of clinical response and susceptibility to other antibiotics. Clindamycin or vancomycin can be used as a first-line agent for children with severe β-lactam hypersensitivity, but vancomycin should not be continued if the organism is shown to be sensitive to other non-β-lactam antibiotics.

For outpatient management, amoxicillin (1 g every 8 h) provides effective treatment for virtually all cases of pneumococcal pneumonia. Neither cephalosporins nor quinolones, which are far more expensive, offer any advantage over amoxicillin. Levofloxacin (500–750 mg/d as a single dose) and moxifloxacin (400 mg/d as a single dose) are also highly likely to be effective in the United States except in patients who come from closed populations where these drugs are used widely or who have themselves been treated recently with a quinolone. Clindamycin (600–1200 mg/d every 6 h) is effective in 90% of cases and azithromycin (500 mg on day 1 followed by 250–500 mg/d) or clarithromycin (500–750 mg/d as a single dose) in 80% of cases. Treatment failure resulting in bacteremic disease due to macrolide-resistant isolates has been amply documented in patients given azithromycin empirically. As noted earlier, rates of resistance to all these antibiotics are relatively low in some countries and much higher in others; high-dose amoxicillin remains the best option worldwide.

The optimal duration of treatment for pneumococcal pneumonia is uncertain, but its continuation for at least 5 days once the patient becomes afebrile appears to be a prudent approach. Cases with a second focus of infection (e.g., empyema or septic arthritis) require longer therapy.

ACUTE OTITIS MEDIA Amoxicillin (80–90 mg/kg per day) is recommended for children with acute otitis media except in situations where observation and symptom-based treatment without antibiotics are advocated. These situations include nonsevere illness and an uncertain diagnosis in children 6 months to 2 years of age and nonsevere illness (even if the diagnosis seems certain) in children >2 years of age. Although the optimal duration of therapy has not been conclusively established, a 10-day course is recommended for younger children and for children with severe disease at any age. For children >6 years old who have mild or moderate disease, a course of 5–7 days is considered adequate. Patients whose illness fails to respond should be reassessed at 48–72 h. If acute otitis media is confirmed and antibiotic treatment has not been started, administration of amoxicillin should be commenced. If antibiotic therapy fails, a change is indicated. Failure to respond to second-line antibiotics as well indicates that myringotomy or tympanocentesis may need to be undertaken in order to obtain samples for culture.

The earlier recommendations can also be followed for the treatment of sinusitis. Detailed information on the further management of these conditions in children has been published by the American Academy of Pediatrics and the American Academy of Family Physicians.

PREVENTION

Measures to prevent pneumococcal disease include vaccination against *S. pneumoniae* and influenza viruses, reduction of comorbidities that increase the risk of pneumococcal disease, and prevention of antibiotic overuse, which fuels pneumococcal resistance.

Capsular polysaccharide vaccines

The 23-valent pneumococcal polysaccharide vaccine (PPV23), containing 25 μg of each capsular polysaccharide, has been licensed for use since 1983. Recommendations for its use vary by country. The U.S. Advisory Committee on Immunization Practices recommends PPV23 for all persons ≥65 years of age and for those 2–64 years of age who have underlying medical conditions that put them at increased risk for pneumococcal disease or severity (Table 37-1; see also *http://www.cdc.gov/vaccines/recs/schedules/default.htm*). Revaccination 5 years after the first dose is recommended for persons >2 years of age who have underlying medical conditions but not routinely for those whose only indication is an age of ≥65 years. PPV23 does not induce an anamnestic response, and antibody concentrations wane over time; thus revaccination is particularly important for individuals with conditions resulting in loss of antibody. Concerns about repeated revaccination have focused on safety (i.e., local reactions) and the induction of immune hyporesponsiveness. Neither the clinical relevance nor the biological basis of hyporesponsiveness is clear, but, given the possibility of its occurrence, more than one revaccination has not been recommended.

The effectiveness of PPV23 against IPD, pneumococcal pneumonia, all-cause pneumonia, and death is

controversial, with wide variation in observations. The many published meta-analyses of PPV efficacy have often reached opposing conclusions with regard to a given clinical entity. Generally, observational studies cite greater effectiveness than do controlled clinical trials. The consensus is that PPV is effective against IPD but is less effective or ineffective against nonbacteremic pneumococcal pneumonia. However, published trials, observational studies, and meta-analyses contradict this view. Efficacy is often lower in the elderly and in immunodeficient patients whose condition is associated with reduced antibody responses to vaccines than in younger, healthier populations. When PPV is effective, the duration of protection following a single dose of vaccine is estimated to be ~5 years.

What is not disputed is that improved pneumococcal vaccines are needed for adults. Even in the setting of routine vaccination of infants (which indirectly protects adults from vaccine-serotype strains), disease caused by serotypes not represented in the vaccine continues to be responsible for a significant burden of disease among adults.

Polysaccharide–protein conjugate vaccines

Infants and young children respond poorly to PPV, which contains T cell–independent antigens. Consequently, another class of pneumococcal vaccines, the PCVs, were developed specifically for infants and young children. The first product, a 7-valent PCV, was licensed in 2000 in the United States. As of 2010, three PCV products—containing 7, 10, and 13 serotypes, respectively—were commercially available. The serotypes included in these PCV formulations are important causes of IPD and antibiotic resistance among young children. Randomized controlled trials have demonstrated a high degree of efficacy of PCVs against vaccine-serotype IPD as well as efficacy against pneumonia, otitis media, nasopharyngeal colonization, and all-cause mortality. PCVs are recommended by the World Health Organization for inclusion in routine childhood immunization schedules worldwide, especially in countries with high infant mortality rates.

The United States was the first country to introduce PCV and therefore has the longest experience with its community-wide effects. The introduction of PCV in the United States has resulted in a >90% reduction in vaccine-serotype IPD among the whole population **(Fig. 37-7)**. This decline has been noted not only in those age groups immunized but also in adults and is attributable to the near elimination of vaccine-serotype nasopharyngeal colonization in immunized infants, which reduces spread to adults. This protection of unimmunized community members through vaccination of a subset of the community is termed *the indirect effect*. Increases in colonization with—and concomitantly in disease due to—non-vaccine-serotype strains (i.e., replacement colonization and disease) have been seen; however, the absolute rate increases in IPD caused by non-vaccine serotypes are generally small, especially relative to decreases in vaccine-serotype IPD (see "Epidemiology," earlier in chapter). Since vaccine-serotype strains are more commonly resistant to antibiotics than

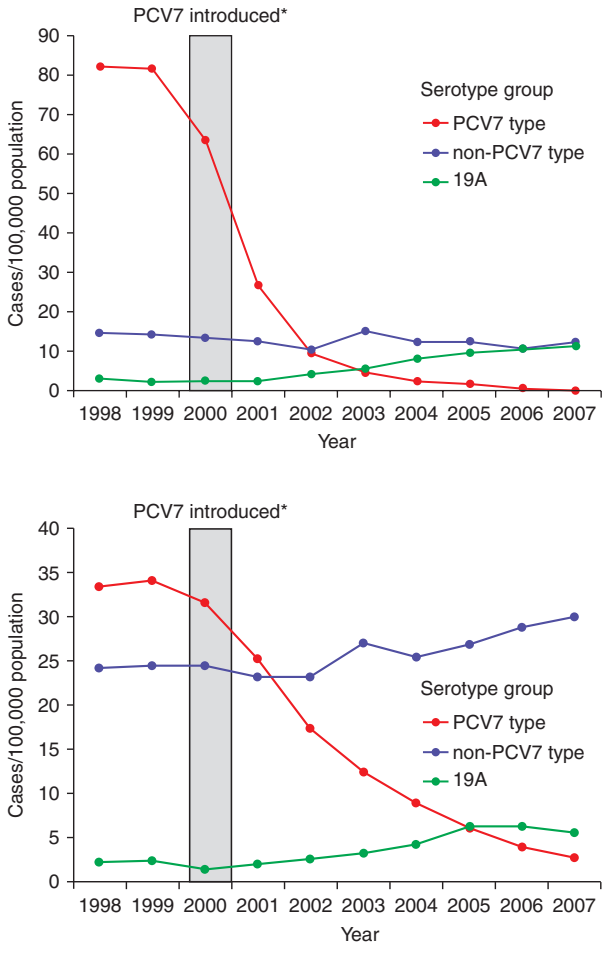


FIGURE 37-7
Changes in invasive pneumococcal disease (IPD) incidence, by serotype group, among children <5 years old (*top*) and adults >65 years old (*bottom*), 1998–2007. *7-Valent pneumococcal conjugate vaccine (PCV7) was introduced in the United States for routine administration to infants and young children during the second half of 2000. (*Reprinted with permission from T Pilishvili et al: J Infect Dis 201:32, 2010.*)

are non-vaccine serotypes, use of PCV has also resulted in dramatic declines in the proportion and absolute rates of drug-resistant pneumococcal disease. The recommendations of the Advisory Committee on Immunization Practices for the use of conjugate vaccines can be found at *http://www.cdc.gov/MMWR/pdf/wk/mm5909.pdf*. Recently, PCV has been shown to prevent pneumococcal infection in HIV-infected adults.

Other prevention strategies

Pneumococcal disease can also be averted through the prevention of illnesses that predispose individuals to pneumococcal infections. Relevant measures include influenza vaccination and improved management and control of diabetes, HIV infection, heart disease, and lung disease. Finally, the reduction of antibiotic misuse is a strategy for the prevention of pneumococcal disease in that antimicrobial resistance directly and indirectly perpetuates organism transmission and disease in the community.

CHAPTER 38

STAPHYLOCOCCAL INFECTIONS

Franklin D. Lowy

Staphylococcus aureus, the most virulent of the many staphylococcal species, has demonstrated its versatility by remaining a major cause of morbidity and mortality despite the availability of numerous effective antistaphylococcal antibiotics. *S. aureus* is a pluripotent pathogen, causing disease through both toxin-mediated and non-toxin-mediated mechanisms. This organism is responsible for both nosocomial and community-based infections that range from relatively minor skin and soft tissue infections primarily to life-threatening systemic infections.

The "other" staphylococci, collectively designated *coagulase-negative staphylococci* (CoNS), are considerably less virulent than *S. aureus* but remain important pathogens in infections primarily associated with prosthetic devices.

MICROBIOLOGY AND TAXONOMY

Staphylococci, gram-positive cocci in the family Micrococcaceae, form grapelike clusters on Gram's stain (Fig. 38-1). These organisms are catalase-positive (unlike streptococcal species), nonmotile, aerobic, and facultatively anaerobic. They are capable of prolonged survival on environmental surfaces in varying conditions.

More than 30 staphylococcal species are pathogenic. A simple strategy for identification of the more clinically important species is outlined in Fig. 38-2. Automated diagnostic systems, kits for biochemical characterization, and DNA-based assays are available for species identification. With few exceptions, *S. aureus* is distinguished from other staphylococcal species by its production of coagulase, a surface enzyme that converts fibrinogen to fibrin. Latex kits designed to detect both protein A and clumping factor also distinguish *S. aureus* from other staphylococcal species. *S. aureus* ferments mannitol, is positive for protein A, and produces DNAse. On blood agar plates, *S. aureus* tends to form golden β-hemolytic colonies; in contrast, CoNS produce small white nonhemolytic colonies.

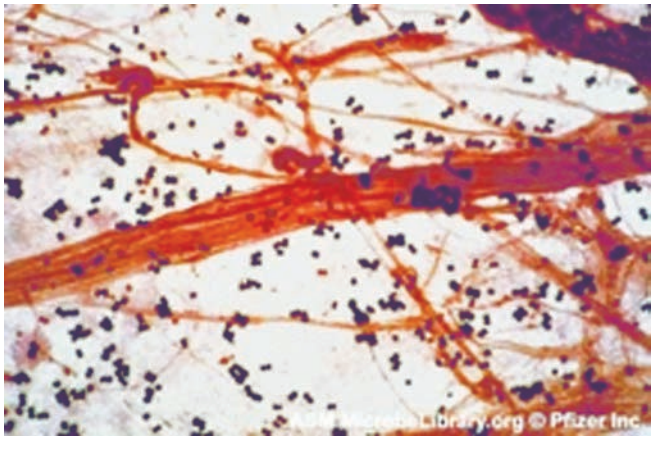


FIGURE 38-1
Gram's stain of *S. aureus* in a sputum sample with polymorphonuclear leukocytes. (*From ASM MicrobeLibrary.org. © Pfizer, Inc.*)

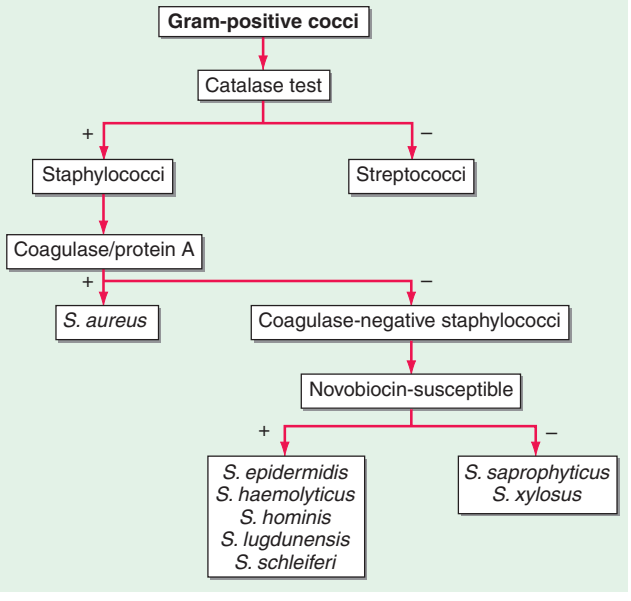


FIGURE 38-2
Biochemical characterization of staphylococci: algorithm of biochemical tests used to discriminate among the clinically important staphylococci. Additional tests are necessary to identify all of the different species.

Determining whether multiple staphylococcal isolates from different patients are the same or different is often relevant when there is concern that a nosocomial outbreak is due to a common point source (e.g., a contaminated medical instrument). Molecular typing methods, such as pulsed-field gel electrophoresis and sequence-based techniques [e.g., staphylococcal protein A (*spa*) typing], have increasingly been used for this purpose.

S. AUREUS INFECTIONS

EPIDEMIOLOGY

S. aureus is a part of the normal human flora; ~25–50% of healthy persons may be persistently or transiently colonized. The rate of colonization is higher among insulin-dependent diabetics, HIV-infected patients, patients undergoing hemodialysis, and individuals with skin damage. The anterior nares are a frequent site of human colonization, although the skin (especially when damaged), vagina, axilla, perineum, and oropharynx may also be colonized. These colonization sites serve as a reservoir of strains for future infections, and persons colonized with *S. aureus* are at greater risk of subsequent infection than are noncolonized individuals.

Some diseases increase the risk of *S. aureus* infection; diabetes, for example, combines an increased rate of *S. aureus* colonization and the use of injectable insulin with the possibility of impaired leukocyte function. Individuals with congenital or acquired qualitative or quantitative defects of polymorphonuclear leukocytes (PMNs) are at increased risk of *S. aureus* infections; this group includes neutropenic patients (e.g., those receiving chemotherapeutic agents), those with chronic granulomatous disease, and those with Job's or Chédiak-Higashi syndrome. Other groups at risk include individuals with skin abnormalities and those with prosthetic devices.

Overall, *S. aureus* is a leading cause of nosocomial infections. It is the most common cause of surgical wound infections and is second only to CoNS as a cause of primary bacteremia. Increasingly, nosocomial isolates are resistant to multiple antibiotics. In the community, *S. aureus* remains an important cause of skin and soft tissue infections, respiratory infections, and (among injection drug users) infective endocarditis. The increasing prevalence of home infusion therapy is another cause of community-acquired staphylococcal infections.

Most individuals who develop *S. aureus* infections are infected with their own colonizing strains. However, *S. aureus* may also be acquired from other people or from environmental exposures. Transmission most frequently results from transient colonization of the hands of hospital personnel, who then transfer strains from one patient to another. Spread of staphylococci in aerosols of respiratory or nasal secretions from heavily colonized individuals has also been reported.

In the past 10 years, numerous outbreaks of community-based infection caused by methicillin-resistant *S. aureus* (MRSA) in individuals with no prior medical exposure have been reported. These outbreaks have taken place in both rural and urban settings in widely separated regions throughout the world. The reports document a dramatic change in the epidemiology of MRSA infections. The outbreaks have occurred among such diverse groups as children, prisoners, athletes, Native Americans, and drug users. Risk factors common to these outbreaks include poor hygienic conditions, close contact, contaminated material, and damaged skin. The community-associated infections have been caused by a limited number of MRSA strains. In the United States, strain USA300 (defined by pulsed-field gel electrophoresis) has been the predominant clone. While the majority of infections caused by this community-based clone of MRSA have involved the skin and soft tissue, 5–10% have been invasive. USA300 is also responsible for an increasing number of nosocomial infections. Of concern has been the apparent capacity of community-acquired MRSA (CA-MRSA) strains to cause serious disease in immunocompetent individuals.

PATHOGENESIS

General concepts

S. aureus is a pyogenic pathogen known for its capacity to induce abscess formation at sites of both local and metastatic infections. This classic pathologic response to *S. aureus* defines the framework within which the infection will progress. The bacteria elicit an inflammatory response characterized by an initial intense infiltration of PMNs and a subsequent infiltration of macrophages and fibroblasts. Either the host cellular response (including the deposition of fibrin and collagen) contains the infection, or infection spreads to the adjoining tissue or the bloodstream.

In toxin-mediated staphylococcal disease, infection is not invariably present. For example, once toxin has been elaborated into food, staphylococcal food poisoning can develop in the absence of viable bacteria. In staphylococcal toxic shock syndrome (TSS), conditions allowing toxin elaboration at colonization sites (e.g., the presence of a superabsorbent tampon) suffice for initiation of clinical illness.

The S. aureus genome

The entire genome has been sequenced for numerous strains of *S. aureus*. Among the interesting revelations are (1) a high degree of nucleotide sequence similarity among the different strains; (2) acquisition of a relatively large amount of genetic information by horizontal transfer from other bacterial species; and (3) the presence of unique "pathogenicity" or "genomic" islands—mobile genetic elements that contain clusters of enterotoxin and exotoxin genes or antimicrobial resistance determinants. Among the genes in these islands are those carrying *mecA*, the gene responsible for methicillin resistance. Methicillin resistance–containing islands have been designated staphylococcal cassette chromosome *mecs* (SCC*mecs*) and range in size from ~20 to 60 kb. To date, eight SCC*mec*s have been

identified. Types 1–3 are traditionally associated with nosocomial MRSA isolates, while types 4–6 have been associated with the epidemic CA-MRSA strains.

A limited number of MRSA clones have been responsible for most community and hospital-associated infections worldwide. A comparison of these strains with those from earlier outbreaks (e.g., the phage 80/81 strains from the 1950s) has revealed preservation of the nucleotide sequence over time. This observation suggests that these strains possess determinants that facilitate survival and spread.

Regulation of virulence gene expression

In both toxin-mediated and non-toxin-mediated diseases due to *S. aureus*, the expression of virulence determinants associated with infection depends on a series of regulatory genes [e.g., accessory gene regulator (*agr*) and staphylococcal accessory regulator (*sar*)] that coordinately control the expression of many virulence genes. The regulatory gene *agr* is part of a quorum-sensing signal transduction pathway that senses and responds to bacterial density. Staphylococcal surface proteins are synthesized during the bacterial exponential growth phase in vitro. In contrast, many secreted proteins, such as α toxin, the enterotoxins, and assorted enzymes, are released during the postexponential growth phase in response to transcription of the effector molecule of *agr*, RNAIII.

It has been hypothesized that these regulatory genes serve a similar function in vivo. Successful invasion requires the sequential expression of these different bacterial elements. Bacterial adhesins are needed to initiate colonization of host tissue surfaces. The subsequent release of various enzymes enables the colony to obtain nutritional support and permits bacteria to spread to adjacent tissues. Studies with strains in which these regulatory genes are inactivated show reduced virulence in several animal models of *S. aureus* infection.

Pathogenesis of invasive S. aureus infection

Staphylococci are opportunists. For these organisms to invade the host and cause infection, some or all of the following steps are necessary: contamination and colonization of tissue surfaces, establishment of a localized infection, invasion, evasion of the host response, and metastatic spread. The initiation of staphylococcal infection requires a breach in cutaneous or mucosal barriers. Colonizing strains or strains transferred from other individuals are introduced into damaged skin, a wound, or the bloodstream. Recurrences of *S. aureus* infections are common, apparently because of the capacity of these pathogens to survive, to persist in a quiescent state in various tissues, and then to cause recrudescent infections when suitable conditions arise.

S. aureus colonization of body surfaces

The anterior nares are a principal site of staphylococcal colonization in humans. Colonization appears to involve the attachment of *S. aureus* to keratinized epithelial cells of the anterior nares. Other factors that may contribute to colonization include the influence of other resident nasal flora and their bacterial density, host factors, and nasal mucosal damage (e.g., that resulting from inhalational drug use). Other colonized body sites, such as damaged skin, the groin, and the oropharynx, may be particularly important reservoirs for CA-MRSA strains.

Inoculation and colonization of tissue surfaces

Staphylococci may be introduced into tissue as a result of minor abrasions, administration of medications such as insulin, or establishment of IV access with catheters. After their introduction into a tissue site, bacteria replicate and colonize the host tissue surface. A family of structurally related *S. aureus* surface proteins referred to as MSCRAMMs (microbial surface components recognizing adhesive matrix molecules) plays an important role in mediating adherence to these sites. By adhering to exposed matrix molecules (e.g., fibrinogen, fibronectin), MSCRAMMs such as clumping factor and collagen-binding protein enable the bacteria to colonize different tissue surfaces; these proteins contribute to the pathogenesis of invasive infections such as endocarditis and arthritis by facilitating the adherence of *S. aureus* to surfaces with exposed fibrinogen or collagen.

Although CoNS are classically known for their ability to elaborate biofilms and to colonize prosthetic devices, *S. aureus* also possesses the genes responsible for biofilm formation, such as the intercellular adhesion (*ica*) locus. Binding to these devices occurs in a stepwise fashion, involving staphylococcal adherence to serum constituents that have coated the device surface and subsequent biofilm elaboration. *S. aureus* is thus a frequent cause of biomedical-device infections.

Invasion

After colonization, staphylococci replicate at the initial site of infection, elaborating enzymes that include serine proteases, hyaluronidases, thermonucleases, and lipases. These enzymes facilitate bacterial survival and local spread across tissue surfaces, although their precise role in infections is not well defined. The lipases may facilitate survival in lipid-rich areas such as the hair follicles, where *S. aureus* infections are often initiated. The *S. aureus* toxin Panton-Valentine leukocidin is cytolytic to PMNs, macrophages, and monocytes. Strains elaborating this toxin have been epidemiologically linked with cutaneous and more serious infections caused by strains of CA-MRSA.

Constitutional findings may result from either localized or systemic infections. The staphylococcal cell wall—consisting of alternating N-acetyl muramic acid and N-acetyl glucosamine units in combination with an additional cell wall component, lipoteichoic acid—can initiate an inflammatory response that includes the sepsis syndrome. Staphylococcal α toxin, which causes pore formation in various eukaryotic cells, can also initiate an inflammatory response with findings suggestive of sepsis.

Evasion of host defense mechanisms

Evasion of host defense mechanisms is critical to invasion. Staphylococci possess an antiphagocytic polysaccharide microcapsule. Most human *S. aureus* infections are

due to capsular types 5 and 8. The *S. aureus* capsule also plays a role in the induction of abscess formation. The capsular polysaccharides are zwitterionic: they have both negative and positive charges—a feature that is critical to abscess formation. Protein A, an MSCRAMM unique to *S. aureus*, acts as an Fc receptor, binding the Fc portion of IgG subclasses 1, 2, and 4 and preventing opsonophagocytosis by PMNs. Both chemotaxis inhibitory protein of staphylococci (CHIPS, a secreted protein) and extracellular adherence protein (EAP, a surface protein) interfere with PMN migration to sites of infection.

An additional potential mechanism of *S. aureus* evasion is its capacity for intracellular survival. Both professional and nonprofessional phagocytes internalize staphylococci. Internalization by endothelial cells may provide a sanctuary that protects bacteria against the host's defenses. It also results in cellular changes, such as the expression of integrins and Fc receptors that may contribute to systemic manifestations of disease, including sepsis and vasculitis. The intracellular environment favors the phenotypic expression of *S. aureus* small-colony variants. These menadione- and hemin-auxotrophic mutants are generally deficient in α toxin and can persist within endothelial cells. Small-colony variants are often selected after aminoglycoside therapy and are more commonly found in sites of persistent infections (e.g., chronic bone infections) and in respiratory secretions from patients with cystic fibrosis. These variants may facilitate prolonged staphylococcal survival and enhance the likelihood of recurrences. Finally, *S. aureus* can survive within PMNs and may use these cells to spread and to seed other tissue sites.

Pathogenesis of community-acquired MRSA infections

A number of different virulence determinants have been identified as contributing to the pathogenesis of CA-MRSA infections. There is a strong epidemiologic association linking the presence of the gene for the Panton-Valentine leukocidin with skin and soft tissue infections as well as with invasive infections such as necrotizing pneumonia. Other determinants that may play a role in the pathogenesis of these infections include the arginine catabolic mobile element (ACME), a cluster of unique genes that may facilitate evasion of host defense mechanisms; phenol-soluble modulins, a family of cytolytic peptides; and alpha toxin.

Host response to S. aureus infection

The primary host response to *S. aureus* infection is the recruitment of PMNs. These cells are attracted to infection sites by bacterial components such as formylated peptides or peptidoglycan as well as by the cytokines tumor necrosis factor (TNF) and interleukins (ILs) 1 and 6, which are released by activated macrophages and endothelial cells.

Although most individuals have antistaphylococcal antibodies, it is not clear that the antibody levels are qualitatively or quantitatively sufficient to protect against infection. Although anticapsular and anti-MSCRAMM antibodies facilitate opsonization in vitro and have been protective against infection in several animal models, they have not yet successfully prevented staphylococcal infections in clinical trials.

Pathogenesis of toxin-mediated disease

S. aureus produces three types of toxin: cytotoxins, pyrogenic toxin superantigens, and exfoliative toxins. Both epidemiologic data and studies in animals suggest that antitoxin antibodies are protective against illness in TSS, staphylococcal food poisoning, and staphylococcal scalded-skin syndrome (SSSS). Illness develops after toxin synthesis and absorption and the subsequent toxin-initiated host response.

Enterotoxin and toxic shock syndrome toxin 1 (TSST-1)

The pyrogenic toxin superantigens are a family of small-molecular-size, structurally similar proteins that are responsible for two diseases: TSS and food poisoning. TSS results from the ability of enterotoxins and TSST-1 to function as T cell mitogens. In the normal process of antigen presentation, the antigen is first processed within the cell, and peptides are then presented in the major histocompatibility complex (MHC) class II groove, initiating a measured T cell response. In contrast, enterotoxins bind directly to the invariant region of MHC—outside the MHC class II groove. The enterotoxins can then bind T cell receptors via the vβ chain, and this binding results in a dramatic overexpansion of T cell clones (up to 20% of the total T cell population). The consequence of this T cell expansion is a "cytokine storm," with the release of inflammatory mediators that include interferon γ, IL-1, IL-6, TNF-α, and TNF-β. The resulting multisystem disease produces a constellation of findings that mimic those in endotoxin shock; however, the pathogenic mechanisms differ. The release of endotoxin from the gastrointestinal tract may synergistically enhance the toxin's effects.

A different region of the enterotoxin molecule is responsible for the symptoms of food poisoning. The enterotoxins are heat stable and can survive conditions that kill the bacteria. Illness results from the ingestion of preformed toxin. As a result, the incubation period is short (1–6 h). The toxin stimulates the vagus nerve and the vomiting center of the brain. It also appears to stimulate intestinal peristaltic activity.

Exfoliative toxins and the staphylococcal scalded-skin syndrome

The exfoliative toxins are responsible for SSSS. The toxins that produce disease in humans are of two serotypes: ETA and ETB. These toxins disrupt the desmosomes that link adjoining cells. Although the mechanism of this disruption remains uncertain, studies suggest that the toxins possess serine protease activity, which—through undefined mechanisms—triggers exfoliation. The result is a split in the epidermis at the granular level, and this event is responsible for the superficial desquamation of the skin that typifies this illness.

DIAGNOSIS

Staphylococcal infections are readily diagnosed by Gram's stain (Fig. 38-1) and microscopic examination of abscess contents or of infected tissue. Routine culture of infected material usually yields positive results, and blood cultures are sometimes positive even when infections are localized to extravascular sites. Polymerase chain reaction (PCR)–based assays have been applied to the rapid diagnosis of *S. aureus* infection and are increasingly used in clinical microbiology laboratories. To date, serologic assays have not proved useful for the diagnosis of staphylococcal infections. Determining whether patients with documented *S. aureus* bacteremia also have infective endocarditis or a metastatic focus of infection remains a diagnostic challenge. Uniformly positive blood cultures suggest an endovascular infection such as endocarditis (see "Bacteremia, Sepsis, and Infective Endocarditis," later in the chapter).

CLINICAL SYNDROMES

(Table 38-1)

Skin and soft tissue infections

S. aureus causes a variety of cutaneous infections, many of which can also be caused by group A streptococci or (less commonly) other streptococcal species. Common factors predisposing to *S. aureus* cutaneous infection include chronic skin conditions (e.g., eczema), skin damage (e.g., insect bites, minor trauma), injections (e.g., in diabetes, injection drug use), and poor personal hygiene. These infections are characterized by the formation of pus-containing blisters, which often begin in hair follicles and spread to adjoining tissues. *Folliculitis* is a superficial infection that involves the hair follicle, with a central area of purulence (pus) surrounded by induration and erythema. *Furuncles* (boils) are more extensive, painful lesions that tend to occur in hairy, moist regions of the body and extend from the hair follicle to become a true abscess with an area of central purulence. *Carbuncles* are most often located in the lower neck and are even more severe and painful, resulting from the coalescence of other lesions that extend to a deeper layer of the subcutaneous tissue. In general, furuncles and carbuncles are readily apparent, with pus often expressible or discharging from the abscess.

Mastitis develops in 1–3% of nursing mothers. This infection of the breast, which generally presents within 2–3 weeks after delivery, is characterized by findings that range from cellulitis to abscess formation. Systemic signs, such as fever and chills, are often present in more severe cases. Other cutaneous *S. aureus* infections include impetigo, cellulitis, and hidradenitis suppurativa (a recurrent follicular infection in regions with apocrine glands, such as the axilla). *S. aureus* is one of the most common causes of surgical wound infection.

Musculoskeletal infections

S. aureus is among the most common causes of bone infections—both those resulting from hematogenous dissemination and those arising from contiguous spread from a soft tissue site. *Hematogenous osteomyelitis* in children most often involves the long bones. Infections present as fever and bone pain or with a child's reluctance to bear weight. The white blood cell count and erythrocyte sedimentation rate are often elevated. Blood cultures are positive in ~50% of cases. When necessary, bone biopsies for culture and histopathologic examination are usually diagnostic. Routine x-rays may be normal for up to 14 days after the onset of symptoms. ^{99m}Tc-phosphonate scanning often detects early evidence of infection. MRI is more sensitive than other techniques in establishing a radiologic diagnosis.

In adults, hematogenous osteomyelitis involving the long bones is less common. However, *vertebral osteomyelitis* is among the more common clinical presentations.

TABLE 38-1

COMMON ILLNESSES CAUSED BY *STAPHYLOCOCCUS AUREUS*

- **Skin and Soft Tissue Infections**
  - Folliculitis
  - Furuncle, carbuncle
  - Cellulitis
  - Impetigo
  - Mastitis
  - Surgical wound infections
  - Hidradenitis suppurativa
- **Musculoskeletal Infections**
  - Septic arthritis
  - Osteomyelitis
  - Pyomyositis
  - Psoas abscess
- **Respiratory Tract Infections**
  - Ventilator-associated or nosocomial pneumonia
  - Septic pulmonary emboli
  - Postviral pneumonia (e.g., influenza)
  - Empyema
- **Bacteremia and Its Complications**
  - Sepsis, septic shock
  - Metastatic foci of infection (kidney, joints, bone, lung)
  - Infective endocarditis
- **Infective Endocarditis**
  - Injection drug use–associated
  - Native-valve
  - Prosthetic-valve
  - Nosocomial
- **Device-Related Infections** (e.g., intravascular catheters, prosthetic joints)
- **Toxin-Mediated Illnesses**
  - Toxic shock syndrome
  - Food poisoning
  - Staphylococcal scalded-skin syndrome
- **Invasive Infections Associated with Community-Acquired MRSA**
  - Necrotizing fasciitis
  - Waterhouse-Friderichsen syndrome
  - Necrotizing pneumonia
  - Purpura fulminans

Vertebral bone infections are most often seen in patients with endocarditis, those undergoing hemodialysis, diabetics, and injection drug users. These infections may present as intense back pain and fever but may also be clinically occult, presenting as chronic back pain and low-grade fever. *S. aureus* is the most common cause of epidural abscess, a complication that can result in neurologic compromise. Patients complain of difficulty voiding or walking and of radicular pain in addition to the symptoms associated with their osteomyelitis. Surgical intervention in this setting often constitutes a medical emergency. MRI most reliably establishes the diagnosis **(Fig. 38-3)**.

Bone infections that result from contiguous spread tend to develop from soft tissue infections, such as those associated with diabetic or vascular ulcers, surgery, or trauma. Exposure of bone, a draining fistulous tract, failure to heal, or continued drainage suggests involvement of underlying bone. Bone involvement is established by bone culture and histopathologic examination (revealing, for example, evidence of PMN infiltration). Contamination of culture material from adjacent tissue can make the diagnosis of osteomyelitis difficult in the absence of pathologic confirmation. In addition, it is sometimes hard to distinguish radiologically between osteomyelitis and overlying soft tissue infection with underlying osteitis.

In both children and adults, *S. aureus* is the most common cause of *septic arthritis* in native joints. This infection is rapidly progressive and may be associated with extensive joint destruction if left untreated. It presents as intense pain on motion of the affected joint, swelling, and fever. Aspiration of the joint reveals turbid fluid, with >50,000 PMNs/μL and gram-positive cocci in clusters on Gram's stain (Fig. 38-1). In adults, arthritis may result from trauma, surgery, or hematogenous dissemination. The most commonly involved joints include the knees, shoulders, hips, and phalanges. Infection frequently develops in joints previously damaged by osteoarthritis or rheumatoid arthritis. Iatrogenic infections resulting from aspiration or injection of agents into the joint also occur. In these settings, the patient experiences increased pain and swelling in the involved joint in association with fever.

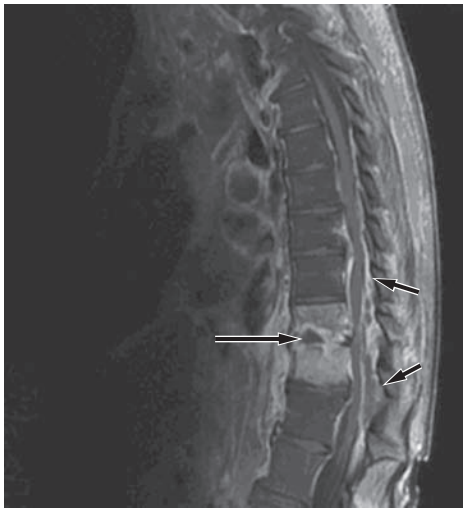


FIGURE 38-3
S. aureus **vertebral osteomyelitis and epidural abscess involving the thoracic disk between T9 and T10.** Sagittal postcontrast MRI of the spine illustrates destruction of the T9–T10 intervertebral space with enhancement (*arrow*). There is impingement on the thoracic cord and an epidural collection extending from T9 through T11 (*short arrows*).

Pyomyositis is an unusual infection of skeletal muscles that is seen primarily in tropical climates but also occurs in immunocompromised and HIV-infected patients. Pyomyositis presents as fever, swelling, and pain overlying the involved muscle. Aspiration of fluid from the involved tissue reveals pus. Although a history of trauma may be associated with the infection, its pathogenesis is poorly understood.

Respiratory tract infections

Respiratory tract infections caused by *S. aureus* occur in selected clinical settings. *S. aureus* is a cause of serious respiratory tract infections in newborns and infants; these infections present as shortness of breath, fever, and respiratory failure. Chest x-ray may reveal pneumatoceles (shaggy, thin-walled cavities). Pneumothorax and empyema are recognized complications of this infection.

In adults, nosocomial *S. aureus* pulmonary infections are commonly seen in intubated patients in intensive care units. Nasally colonized patients are at increased risk of these infections. The clinical presentation is no different from that encountered in pulmonary infections of other bacterial etiologies. Patients produce increased volumes of purulent sputum and develop respiratory distress, fever, and new pulmonary infiltrates. Distinguishing bacterial pneumonia from respiratory failure of other causes or new pulmonary infiltrates in critically ill patients is often difficult and relies on a constellation of clinical, radiologic, and laboratory findings.

Community-acquired respiratory tract infections due to *S. aureus* usually follow viral infections—most commonly influenza. Patients may present with fever, bloody sputum production, and midlung-field pneumatoceles or multiple, patchy pulmonary infiltrates **(Fig. 38-4)**. Diagnosis is made by sputum Gram's stain and culture. Blood cultures, although useful, are usually negative.

Bacteremia, sepsis, and infective endocarditis

S. aureus bacteremia may be complicated by sepsis, endocarditis, vasculitis, or metastatic seeding (establishment of suppurative collections at other tissue sites). The frequency of metastatic seeding during bacteremia has been estimated to be as high as 31%. Among the more commonly seeded tissue sites are bones, joints, kidneys, and lungs.

Recognition of these complications by clinical and laboratory diagnostic methods alone is often difficult. Comorbid conditions that are frequently seen in association with *S. aureus* bacteremia and that increase the risk of complications include diabetes, HIV infection, and renal insufficiency. Other host factors associated

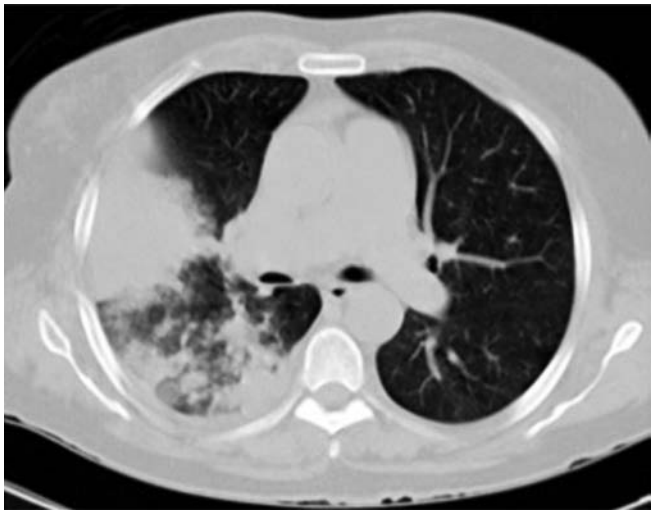


FIGURE 38-4
CT illustrating necrotizing pneumonia due to community-acquired MRSA in a diabetic woman who originally presented with a cutaneous abscess.

with an increased risk of complications include presentation with community-acquired *S. aureus* bacteremia (except in injection drug users), lack of an identifiable primary focus of infection, and the presence of prosthetic devices or material.

Clinically, *S. aureus* sepsis presents in a manner similar to that documented for sepsis due to other bacteria. The well-described progression of hemodynamic changes—beginning with respiratory alkalosis and clinical findings of hypotension and fever—is commonly seen. The microbiologic diagnosis is established by positive blood cultures.

The overall incidence of *S. aureus* endocarditis has increased over the past 20 years. *S. aureus* is now the leading cause of endocarditis worldwide, accounting for 25–35% of cases. This increase is due, at least in part, to the increased use of intravascular devices; transesophageal echocardiography studies found an infective endocarditis incidence of 25% among patients with *S. aureus* bacteremia and intravascular catheters. Other factors associated with an increased risk of endocarditis are injection drug use, hemodialysis, the presence of intravascular prosthetic devices at the time of bacteremia, and immunosuppression. Despite the availability of effective antibiotics, mortality rates from these infections continue to range from 20% to 40%, depending on both the host and the nature of the infection. Complications of *S. aureus* endocarditis include cardiac valvular insufficiency, peripheral emboli, metastatic seeding, and central nervous system (CNS) involvement (e.g., mycotic aneurysms, embolic strokes).

S. aureus endocarditis is encountered in four clinical settings: (1) right-sided endocarditis in association with injection drug use, (2) left-sided native-valve endocarditis, (3) prosthetic-valve endocarditis, and (4) nosocomial endocarditis. In each of these settings, the diagnosis is established by recognition of clinical stigmata suggestive of endocarditis. These findings include cardiac manifestations, such as new or changing cardiac valvular murmurs; cutaneous evidence, such as vasculitic lesions, Osler's nodes, or Janeway lesions; evidence of right- or left-sided embolic disease; and a history suggesting a risk for *S. aureus* bacteremia. In the absence of antecedent antibiotic therapy, blood cultures are almost uniformly positive. Transthoracic echocardiography, while less sensitive than transesophageal echocardiography, is less invasive and often establishes the presence of valvular vegetations. The Duke criteria (see Table 20-3) are now commonly used to help establish the likelihood of this diagnosis.

Acute right-sided tricuspid valvular *S. aureus* endocarditis is most often seen in injection drug users. The classic presentation includes a high fever, a toxic clinical appearance, pleuritic chest pain, and the production of purulent (sometimes bloody) sputum. Chest x-rays reveal evidence of septic pulmonary emboli (small, peripheral, circular lesions that may cavitate with time). A high percentage of affected patients have no history of antecedent valvular damage. At the outset of their illness, patients may present with fever alone, without cardiac or other localizing findings. As a result, a high index of clinical suspicion is essential for diagnosis.

Individuals with antecedent cardiac valvular damage more commonly present with left-sided native-valve endocarditis involving the previously affected valve. These patients tend to be older than those with right-sided endocarditis, their prognosis is worse, and their incidence of complications (including peripheral emboli, cardiac decompensation, and metastatic seeding) is higher.

S. aureus is one of the more common causes of prosthetic-valve endocarditis. This infection is especially fulminant in the early postoperative period and is associated with a high mortality rate. In most instances, medical therapy alone is not sufficient and urgent valve replacement is necessary. Patients are prone to develop valvular insufficiency or myocardial abscesses originating from the region of valve implantation.

The increased frequency of nosocomial endocarditis (15–30% of cases, depending on the series) reflects in part the increased use of intravascular devices. This form of endocarditis is most commonly caused by *S. aureus*. Because patients often are critically ill, are receiving antibiotics for various other indications, and have comorbid conditions, the diagnosis is often missed.

Urinary tract infections

Urinary tract infections (UTIs) are infrequently caused by *S. aureus*. In contrast with that of most other urinary pathogens, the presence of *S. aureus* in the urine suggests hematogenous dissemination. Ascending *S. aureus* infections occasionally result from instrumentation of the genitourinary tract.

Prosthetic device–related infections

S. aureus accounts for a large proportion of prosthetic device–related infections. These infections often involve intravascular catheters, prosthetic valves, orthopedic devices, peritoneal catheters, pacemakers,

left-ventricular-assist devices, and vascular grafts. In contrast with the more indolent presentation of CoNS infections, *S. aureus* device-related infections often present more acutely, with both localized and systemic manifestations. The latter infections also tend to progress more rapidly. It is relatively common for a pyogenic collection to be present at the device site. Aspiration of these collections and performance of blood cultures are important components in establishing a diagnosis. *S. aureus* infections tend to occur more commonly soon after implantation unless the device is used for access (e.g., intravascular or hemodialysis catheters). In the latter instance, infections can occur at any time. As in most prosthetic-device infections, successful therapy usually involves removal of the device. Left in place, the device is a potential nidus for either persistent or recurrent infections.

Infections associated with community-acquired MRSA

While the skin and soft tissues are the most common sites of infection associated with CA-MRSA, 5–10% of these infections are invasive and can even be life-threatening. The latter infections include necrotizing fasciitis, necrotizing pneumonia, and sepsis with Waterhouse-Friderichsen syndrome or purpura fulminans. These life-threatening infections reflect the increased virulence of MRSA strains.

Toxin-mediated diseases

Food poisoning

S. aureus is among the most common causes of foodborne outbreaks of infection in the United States. Staphylococcal food poisoning results from the inoculation of toxin-producing *S. aureus* into food by colonized food handlers. Toxin is then elaborated in such growth-promoting food as custards, potato salad, or processed meats. Even if the bacteria are killed by warming, the heat-stable toxin is not destroyed. The onset of illness is rapid, occurring within 1–6 h of ingestion. The illness is characterized by nausea and vomiting, although diarrhea, hypotension, and dehydration may also occur. The differential diagnosis includes diarrhea of other etiologies, especially that caused by similar toxins (e.g., the toxins elaborated by *Bacillus cereus*). The rapidity of onset, the absence of fever, and the epidemic nature of the presentation (without 2° spread) arouse suspicion of staphylococcal food poisoning. Symptoms generally resolve within 8–10 h. The diagnosis can be established by the demonstration of bacteria or the documentation of enterotoxin in the implicated food. Treatment is entirely supportive.

Toxic shock syndrome

TSS gained attention in the early 1980s, when a nationwide outbreak occurred among young, otherwise healthy, menstruating women. Epidemiologic investigation demonstrated that these cases were associated with the use of a highly absorbent tampon that had recently been introduced to the market. Subsequent studies established the role of TSST-1 in these illnesses. Withdrawal of the tampon from the market resulted in a rapid decline in the incidence of this disease. However, menstrual and nonmenstrual cases continue to be reported.

The clinical presentation is similar in menstrual and nonmenstrual TSS, although the nature of the risk differs. Evidence of clinical *S. aureus* infection is not a prerequisite. TSS results from the elaboration of an enterotoxin or the structurally related enterotoxin-like TSST-1. More than 90% of menstrual cases are caused by TSST-1, whereas a high percentage of nonmenstrual cases are caused by enterotoxins. TSS begins with relatively nonspecific flulike symptoms. In menstrual cases, the onset usually comes 2 or 3 days after the start of menstruation. Patients present with fever, hypotension, and erythroderma of variable intensity. Mucosal involvement is common (e.g., conjunctival hyperemia). The illness can rapidly progress to symptoms that include vomiting, diarrhea, confusion, myalgias, and abdominal pain. These symptoms reflect the multisystemic nature of the disease, with involvement of the liver, kidneys, gastrointestinal tract, and/or CNS. Desquamation of the skin occurs during convalescence, usually 1–2 weeks after the onset of illness. Laboratory findings may include azotemia, leukocytosis, hypoalbuminemia, thrombocytopenia, and liver function abnormalities.

Diagnosis of TSS still depends on a constellation of findings rather than one specific finding and on a lack of evidence of other possible infections (e.g., Rocky Mountain spotted fever; **Table 38-2**). Other diagnoses

TABLE 38-2

CASE DEFINITION OF *S. AUREUS* TOXIC SHOCK SYNDROME

1. Fever: temperature of ≥38.9°C (≥102°F)
2. Hypotension: systolic blood pressure of ≤90 mmHg, or orthostatic hypotension (orthostatic drop in diastolic blood pressure by ≥15 mmHg, orthostatic syncope, or orthostatic dizziness)
3. Diffuse macular rash, with desquamation 1–2 weeks after onset (including the palms and soles)
4. Multisystem involvement
   a. Hepatic: bilirubin or aminotransferase levels ≥2 times normal
   b. Hematologic: platelet count ≤100,000/μL
   c. Renal: blood urea nitrogen or serum creatinine level ≥2 times the normal upper limit
   d. Mucous membranes: vaginal, oropharyngeal, or conjunctival hyperemia
   e. Gastrointestinal: vomiting or diarrhea at onset of illness
   f. Muscular: severe myalgias or serum creatine phosphokinase level ≥2 times the upper limit
   g. Central nervous system: disorientation or alteration in consciousness without focal neurologic signs and in the absence of fever and hypotension
5. Negative serologic or other tests for measles, leptospirosis, and Rocky Mountain spotted fever as well as negative blood or cerebrospinal fluid cultures for organisms other than *S. aureus*

Source: M Wharton et al: Case definitions for public health surveillance. MMWR 39:1, 1990; with permission.

to be considered are drug toxicities, viral exanthems, sepsis, and Kawasaki disease. Illness occurs only in persons who lack antibody to TSST-1. Recurrences are possible if antibody fails to develop after the illness.

Staphylococcal scalded-skin syndrome

SSSS most often affects newborns and children. The illness may vary from localized blister formation to exfoliation of much of the skin surface. The skin is usually fragile and often tender, with thin-walled, fluid-filled bullae. Gentle pressure results in rupture of the lesions, leaving denuded underlying skin (Nikolsky's sign; **Fig. 38-5**). The mucous membranes are usually spared. In more generalized infection, there are often constitutional symptoms, including fever, lethargy, and irritability with poor feeding. Significant amounts of fluid can be lost in more extensive cases. Illness usually follows localized infection at one of a number of possible sites. SSSS is much less common among adults but can follow infections caused by exfoliative toxin–producing strains.

PREVENTION

Prevention of the spread of *S. aureus* infections in the hospital setting involves hand washing and careful attention to appropriate isolation procedures. Through careful screening for MRSA carriage and strict isolation practices, some Scandinavian countries have been remarkably successful at preventing the introduction and dissemination of MRSA in hospitals. Other countries, such as the United States and Great Britain, have been less successful.

The use of topical antimicrobial agents (e.g., mupirocin) to eliminate nasal colonization and/or chlorhexidine to eliminate cutaneous colonization with *S. aureus* and to prevent subsequent infection has been investigated in a number of clinical settings. Elimination of nasal carriage of *S. aureus* has reduced the incidence of infections among patients undergoing hemodialysis and peritoneal dialysis. Mupirocin effectively eliminates nasal colonization with *S. aureus*. An analysis of clinical trials suggests that there may also be a reduction in the incidence of postsurgical infections in those nasally colonized with *S. aureus*.

"Bundling" (the application of selected medical interventions in a sequence of prescribed steps) has reduced rates of nosocomial infections related to such procedures as the insertion of intravenous catheters, in which staphylococci are among the most common pathogens (see Table 14-3). A number of immunization strategies to prevent *S. aureus* infections—both active (e.g., capsular polysaccharide–protein conjugate vaccine) and passive (e.g., clumping factor antibody)—have been assessed. However, none has been successful for either prophylaxis or therapy.

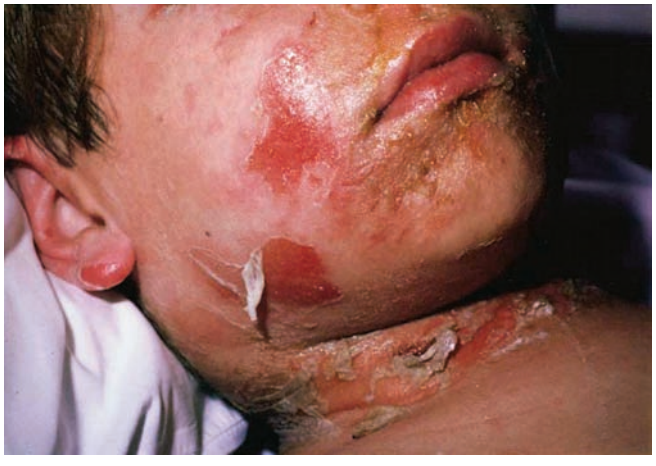


FIGURE 38-5
Evidence of staphylococcal scalded-skin syndrome in a 6-year-old boy. Nikolsky's sign, with separation of the superficial layer of the outer epidermal layer, is visible. (*Reprinted with permission from LA Schenfeld et al: N Engl J Med 342:1178, 2000. © 2000 Massachusetts Medical Society. All rights reserved.*)

COAGULASE-NEGATIVE STAPHYLOCOCCAL INFECTIONS

CoNS, although considerably less virulent than *S. aureus*, are among the most common causes of prosthetic-device infections. Approximately half of the identified CoNS species have been associated with human infections. Of these species, *S. epidermidis* is the most common human pathogen. This component of the normal human flora is found on the skin (where it is the most abundant bacterial species) as well as in the oropharynx and vagina. *S. saprophyticus*, a novobiocin-resistant species, is a pathogen in UTIs.

PATHOGENESIS

Among CoNS, *S. epidermidis* is the species most commonly associated with prosthetic-device infections. Infection is a two-step process, with initial adhesion to the device followed by colonization. *S. epidermidis* is uniquely adapted to colonize these devices by its capacity to elaborate the extracellular polysaccharide (glycocalyx or slime) that facilitates formation of a protective biofilm on the device surface.

Implanted prosthetic material is often coated with host serum or tissue constituents such as fibrinogen or fibronectin. These molecules serve as potential bridging ligands, facilitating initial bacterial attachment to the device surface. A number of surface-associated proteins, such as autolysin (AtlE), fibrinogen-binding protein, and accumulation-associated protein (AAP), may play a role in attachment to either modified or unmodified prosthetic surfaces. The polysaccharide intercellular adhesin facilitates subsequent staphylococcal colonization and accumulation on the device surface. In *S. epidermidis*, intercellular adhesin (*ica*) genes are more commonly found in strains associated with device infections than in strains associated with colonization of mucosal surfaces. Biofilm appears

to act as a barrier protecting bacteria from host defense mechanisms as well as from antibiotics, while providing a suitable environment for bacterial survival. Poly-γ-DL-glutamic acid is secreted by *S. epidermidis* and promotes protection against neutrophil phagocytosis.

Two additional staphylococcal species, *S. lugdunensis* and *S. schleiferi*, produce more serious infections (native-valve endocarditis and osteomyelitis) than do other CoNS. The basis for this enhanced virulence is not known, although both species appear to share more virulence determinants with *S. aureus* (e.g., clumping factor and lipase) than do other CoNS.

The capacity of *S. saprophyticus* to cause UTIs in young women appears to be related to its enhanced capacity to adhere to uroepithelial cells. A 160-kDa hemagglutinin/adhesin may contribute to this affinity.

DIAGNOSIS

While the detection of CoNS at sites of infection or in the bloodstream is not difficult by standard microbiologic culture methods, interpretation of these results is frequently problematic. Since these organisms are present in large numbers on the skin, they often contaminate cultures. It has been estimated that only 10–25% of blood cultures positive for CoNS reflect true bacteremia. Similar problems arise with cultures of other sites. Among the clinical findings suggestive of true bacteremia are fever, evidence of local infection (e.g., erythema or purulent drainage at the IV catheter site), leukocytosis, and systemic signs of sepsis. Laboratory findings suggestive of true bacteremia include multiple isolations of the same strain (i.e., the same species with the same antibiogram or a closely related DNA fingerprint) from separate cultures, growth of the strain within 48 h, and bacterial growth in both aerobic and anaerobic bottles.

CLINICAL SYNDROMES

CoNS cause diverse prosthetic device–related infections, including those that involve prosthetic cardiac valves and joints, vascular grafts, intravascular devices, and CNS shunts. In all of these settings, the clinical presentation is similar. The signs of localized infection are often subtle, the rate of disease progression is slow, and the systemic findings are often limited. Signs of infection, such as purulent drainage, pain at the site, or loosening of prosthetic implants, are sometimes evident. Fever is frequently but not always present, and there may be mild leukocytosis. Acute-phase reactant levels, the erythrocyte sedimentation rate, and the C-reactive protein concentration may be elevated.

Infections that are not associated with prosthetic devices are infrequent, although native-valve endocarditis due to CoNS has accounted for ~5% of cases in some reviews. *S. lugdunensis* appears to be a more aggressive pathogen in this setting, causing greater mortality and rapid valvular destruction with abscess formation.

TREATMENT Staphylococcal Infections

GENERAL PRINCIPLES OF THERAPY Surgical incision and drainage of all suppurative collections constitute the most important therapeutic intervention for staphylococcal infections. The emergence of MRSA in the community has increased the importance of culturing all collections in order to identify pathogens and to determine antimicrobial susceptibility. Prosthetic-device infections are unlikely to be successfully managed unless the device is removed. In the limited number of situations in which removal is not possible or the infection is due to CoNS, an initial attempt at medical therapy without device removal may be warranted. Because of the well-recognized risk of complications associated with *S. aureus* bacteremia (e.g., endocarditis, metastatic foci of infection), therapy is generally prolonged (4–8 weeks) unless the patient is identified as being among the small percentage of individuals who are at low risk for complications.

DURATION OF ANTIMICROBIAL THERAPY Debate continues regarding the duration of therapy for bacteremic *S. aureus* infections. Among the findings associated with an increased risk of complicated bacteremia are persistently positive blood cultures 48–96 h after institution of therapy, acquisition of the infection in the community, failure to remove a removable focus of infection (i.e., an intravascular catheter), and infection with cutaneous or embolic manifestations. For immunocompetent patients in whom short-course therapy is planned, transesophageal echocardiography to rule out endocarditis is warranted since neither clinical nor laboratory findings are adequate to detect cardiac involvement. In addition, an aggressive radiologic investigation to identify potential metastatic collections is often indicated. All symptomatic sites must be carefully evaluated.

CHOICE OF ANTIMICROBIAL AGENTS The choice of antimicrobial agents to treat both coagulase-positive and coagulase-negative staphylococcal infections has become increasingly problematic because of the prevalence of multidrug-resistant strains. Staphylococcal resistance to most antibiotic families, including β-lactams, aminoglycosides, fluoroquinolones, and (to a lesser extent) glycopeptides, has increased. This trend is more apparent with CoNS: >80% of nosocomial isolates are resistant to methicillin, and these methicillin-resistant strains are usually resistant to most other antibiotics as well. Because the selection of antimicrobial agents for *S. aureus* infections is similar to that for CoNS infections, treatment options for these pathogens are discussed together and are summarized in Table 38-3.

As a result of the widespread dissemination of plasmids containing the enzyme penicillinase, few strains of staphylococci (≥5%) remain susceptible to penicillin.

TABLE 38-3

ANTIMICROBIAL THERAPY FOR STAPHYLOCOCCAL INFECTIONS[a]

SENSITIVITY/ RESISTANCE OF ISOLATE	DRUG OF CHOICE	ALTERNATIVE(S)	COMMENTS
Parenteral Therapy for Serious Infections			
Sensitive to penicillin	Penicillin G (4 mU q4h)	Nafcillin or oxacillin (2 g q4h), cefazolin (2 g q8h), vancomycin (1 g q12h[b])	Fewer than 5% of isolates are sensitive to penicillin.
Sensitive to methicillin	Nafcillin or oxacillin (2 g q4h)	Cefazolin (2 g q8h[b]), vancomycin (15–20 mg/kg q8–12h[b])	Patients with penicillin allergy can be treated with a cephalosporin if the allergy does not involve an anaphylactic or accelerated reaction; desensitization to β-lactams may be indicated in selected cases of serious infection when maximal bactericidal activity is needed (e.g., prosthetic valve endocarditis[d]). Type A β-lactamase may rapidly hydrolyze cefazolin and reduce its efficacy in endocarditis. Vancomycin is a less effective option.
Resistant to methicillin	Vancomycin (15–20 mg/kg q8–12h[b])	Daptomycin (6 mg/kg q24h[b,c]) for bacteremia, endocarditis, and complicated skin infections; linezolid (600 mg q12h except: 400 mg q12h for uncomplicated skin infections); quinupristin/dalfopristin (7.5 mg/kg q8h)	Sensitivity testing is necessary before an alternative drug is used. Adjunctive drugs (those that should be used only in combination with other antimicrobial agents) include gentamicin (1 mg/kg q8h[b]), rifampin (300 mg PO q8h), and fusidic acid (500 mg q8h; not readily available in the United States). For some serious infections, higher doses of daptomycin have been used. Quinupristin/dalfopristin is bactericidal against methicillin-resistant isolates unless the strain is resistant to erythromycin or clindamycin. The efficacy of adjunctive therapy is not well established in many settings. Both linezolid and quinupristin/dalfopristin have had in vitro activity against most VISA and VRSA strains. See footnote for treatment of prosthetic-valve endocarditis.[d]
Resistant to methicillin with intermediate or complete resistance to vancomycin[e]	Uncertain	Same as for methicillin-resistant strains; check antibiotic susceptibilities	Same as for methicillin-resistant strains; check antibiotic susceptibilities
Not yet known (i.e., empirical therapy)	Vancomycin (15–20 mg/kg q8–12h[b])	–	Empirical therapy is given when the susceptibility of the isolate is not known. Vancomycin with or without an aminoglycoside is recommended for suspected community- or hospital-acquired *Staphylococcus aureus* infections because of the increased frequency of methicillin-resistant strains in the community.
Oral Therapy for Skin and Soft Tissue Infections			
Sensitive to methicillin	Dicloxacillin (500 mg qid), cephalexin (500 mg qid)	Minocycline or doxycycline (100 mg q12h[b]), TMP-SMX (1 or 2 ds tablets bid), clindamycin (300–450 mg/kg tid)	It is important to know the antibiotic susceptibility of isolates in the specific geographic region. All drainage should be cultured.

(*continued*)

TABLE 38-3

ANTIMICROBIAL THERAPY FOR STAPHYLOCOCCAL INFECTIONS[a] (*CONTINUED*)

SENSITIVITY/ RESISTANCE OF ISOLATE	DRUG OF CHOICE	ALTERNATIVE(S)	COMMENTS
Oral Therapy for Skin and Soft Tissue Infections (*continued*)			
Resistant to methicillin	Clindamycin (300–450 mg/kg tid), TMP-SMX (1 or 2 ds tablets bid), minocycline or doxycycline (100 mg q12h[b]), linezolid (400–600 mg bid)		It is important to know the antibiotic susceptibility of isolates in the specific geographic region. All drainage should be cultured.

[a]Recommended dosages are for adults with normal renal and hepatic function.
[b]The dosage must be adjusted for patients with reduced creatinine clearance.
[c]Daptomycin cannot be used for pneumonia.
[d]For the treatment of prosthetic valve endocarditis, the addition of gentamicin (1 mg/kg q8h) and rifampin (300 mg PO q8h) is recommended, with adjustment of the gentamicin dosage if the creatinine clearance rate is reduced.
[e]Vancomycin-resistant *S. aureus* isolates from clinical infections have been reported.
Abbreviations: TMP-SMX, trimethoprim-sulfamethoxazole; VISA, vancomycin-intermediate *S. aureus;* VRSA, vancomycin-resistant *S. aureus.*
Source: Modified with permission from FD Lowy: N Engl J Med 339:520, 1998 (© 1998 Massachusetts Medical Society. All rights reserved.) and from DL Stevens et al: Clin Infect Dis 41:1373, 2006, and Med Lett 48:13, 2006.

However, against susceptible strains, penicillin remains the drug of choice. Penicillin-resistant isolates are treated with semisynthetic penicillinase-resistant penicillins (SPRPs), such as oxacillin or nafcillin. Methicillin, the first of the SPRPs, is now used infrequently. Cephalosporins are alternative therapeutic agents for these infections. Second- and third-generation cephalosporins do not have a therapeutic advantage over first-generation cephalosporins for the treatment of staphylococcal infections. The carbapenems have excellent activity against methicillin-sensitive *S. aureus* but not against MRSA.

The isolation of MRSA was reported within 1 year of the introduction of methicillin. The prevalence of MRSA has since increased steadily. In many hospitals, 40–50% of *S. aureus* isolates are now resistant to methicillin. Resistance to methicillin indicates resistance to all SPRPs as well as to all cephalosporins. Production of a novel penicillin-binding protein (PBP 2a or 2′) is responsible for methicillin resistance. This protein is synthesized by the *mecA* gene, which (as stated earlier) is part of a large mobile genetic element—a pathogenicity or genomic island—called SCC*mec*. It is hypothesized that this genetic material was acquired via horizontal transfer from a related staphylococcal species, such as *S. sciuri*. Phenotypic expression of methicillin resistance may be constitutive (i.e., expressed in all organisms in a population) or heterogeneous (i.e., displayed by only a proportion of the total organism population). Detection of methicillin resistance in the clinical microbiology laboratory can be difficult if the strain expresses heterogeneous resistance. Therefore, susceptibility studies are routinely performed at reduced temperatures (≥35°C for 24 h), with increased concentrations of salt in the medium to enhance the expression of resistance. In addition to PCR-based techniques, a number of rapid methods for the detection of methicillin resistance have been developed.

Vancomycin remains the drug of choice for the treatment of MRSA infections. Because it is less bactericidal than the β-lactams, it should be used only after careful consideration in patients with a history of β-lactam allergies. Three types of staphylococcal resistance to vancomycin have emerged. (1) Minimum inhibitory concentration (MIC) "creep" refers to the incremental increase in vancomycin MICs that has been detected in various geographic areas. Studies suggest that infections due to *S. aureus* strains with vancomycin MICs of >1 μg/mL may not respond as well to vancomycin therapy as those due to strains with MICs of <1 μg/mL. Some authorities (e.g., *The Medical Letter*) have recommended choosing an alternative agent in this setting. (2) In 1997, an *S. aureus* strain with reduced susceptibility to vancomycin (VISA) was reported from Japan. Subsequently, additional clinical isolates of VISA were reported. These strains were all resistant to methicillin and many other antimicrobial agents. The VISA strains appear to evolve (under vancomycin selective pressure) from strains that are susceptible to vancomycin but are heterogeneous, with a small proportion of the bacterial population expressing the resistance phenotype. The mechanism of VISA resistance is due to an abnormally large cell wall. Vancomycin is trapped by the abnormal peptidoglycan cross-linking and is unable to gain access to its target site. (3) In 2002, the first clinical isolate of fully vancomycin-resistant *S. aureus* was reported. Resistance in this and six

subsequently reported clinical isolates was due to the presence of *vanA*, the gene responsible for expression of vancomycin resistance in enterococci. This observation suggested that resistance was acquired as a result of horizontal conjugal transfer from a vancomycin-resistant strain of *Enterococcus faecalis*. Several patients had both MRSA and vancomycin-resistant enterococci cultured from infection sites. The *vanA* gene is responsible for the synthesis of the dipeptide D-Ala-D-Lac in place of D-Ala-D-Ala. Vancomycin cannot bind to the altered peptide.

Telavancin is a parenteral lipoglycopeptide derivative of vancomycin that was recently approved by the U.S. Food and Drug Administration for the treatment of complicated skin and soft tissue infections. This drug has two targets: the cell wall and the cell membrane. It remains active against VISA strains.

Daptomycin, a parenteral bactericidal agent with antistaphylococcal activity, is approved for the treatment of bacteremia (including right-sided endocarditis) and complicated skin infections. It is not effective in respiratory infections. This drug has a novel mechanism of action: it disrupts the cytoplasmic membrane. Staphylococcal resistance to daptomycin, sometimes developing during therapy, has been reported.

Linezolid—the first oxazolidinone—is bacteriostatic against staphylococci and offers the advantage of comparable bioavailability after oral or parenteral administration. Cross-resistance with other inhibitors of protein synthesis has not been detected. However, resistance to linezolid has been reported. Serious adverse reactions to linezolid include thrombocytopenia, occasional cases of neutropenia, and rare instances of peripheral neuropathy.

The parenteral streptogramin antibiotic quinupristin/dalfopristin displays bactericidal activity against all staphylococci, including VISA strains. This drug has been used successfully to treat serious MRSA infections. In cases of resistance to erythromycin or clindamycin, quinupristin/dalfopristin is bacteriostatic against staphylococci. There are limited data on the efficacy of either quinupristin/dalfopristin or linezolid for the treatment of infective endocarditis.

Although the quinolones are reasonably active against staphylococci in vitro, the frequency of staphylococcal resistance to these agents has increased progressively, especially among methicillin-resistant isolates. Of particular concern in MRSA is the possible emergence of quinolone resistance during therapy. Resistance to the quinolones is most commonly chromosomal and results from mutations of the topoisomerase IV or DNA gyrase genes, although multidrug efflux pumps may also contribute. While the newer quinolones exhibit increased in vitro activity against staphylococci, it is uncertain whether this increase translates into enhanced in vivo activity.

Tigecycline, a broad-spectrum minocycline analogue, has bacteriostatic activity against MRSA and is approved for use in skin and soft tissue infections as well as intraabdominal infections caused by *S. aureus*. Other antibiotics, such as minocycline and trimethoprim-sulfamethoxazole, have been used successfully to treat MRSA infections in cases of vancomycin toxicity or intolerance.

Combinations of antistaphylococcal agents are sometimes used to enhance bactericidal activity in the treatment of serious infections such as endocarditis or osteomyelitis. In selected instances (e.g., right-sided endocarditis), drug combinations are also used to shorten the duration of therapy. Among the antimicrobial agents used in combinations are rifampin, aminoglycosides (e.g., gentamicin), and fusidic acid (which is not readily available in the United States). While these agents are not effective singly because of the frequent emergence of resistance, they may be useful in combination with other agents because of their bactericidal activity against staphylococci. So far, however, clinical studies have not documented a therapeutic benefit, and recent reports have raised concern with regard to the potential nephrotoxicity of gentamicin and adverse drug reactions from the addition of rifampin.

ANTIMICROBIAL THERAPY FOR SELECTED SETTINGS When necessary, the use of oral antistaphylococcal agents for uncomplicated skin and soft tissue infections is usually successful. For other infections, parenteral therapy is indicated.

S. aureus endocarditis is usually an acute, life-threatening infection. Thus prompt collection of blood for cultures must be followed immediately by empirical antimicrobial therapy. For life-threatening *S. aureus* native-valve endocarditis, many clinicians begin therapy with a 3- to 5-day course of a β-lactam and an aminoglycoside (gentamicin, 1 mg/kg IV every 8 h), although limited clinical data support this choice. If a MRSA strain is isolated, vancomycin (15–20 mg/kg every 8–12 h, given in equal doses up to a total of 2 g) is recommended. The vancomycin dose should be adjusted on the basis of trough vancomycin levels. Patients are generally treated for 4–6 weeks, with duration depending on whether there are complications. In prosthetic-valve endocarditis, surgery in addition to antibiotic therapy is often necessary. The combination of a β-lactam agent—or, if the isolate is β-lactam-resistant, vancomycin (30 mg/kg every 24 h, given in doses up to a total of 2 g)—with an aminoglycoside (gentamicin, 1 mg/kg IV every 8 h) and rifampin (300 mg orally or IV every 8 h) is recommended. This combination is used to avoid the possible emergence of rifampin resistance during therapy if only two drugs are used.

For hematogenous osteomyelitis or septic arthritis in children, a 4-week course of therapy is usually adequate. In adults, treatment is often more prolonged. For chronic forms of osteomyelitis, surgical debridement is necessary in combination with antimicrobial therapy. For joint infections, a critical component of therapy is the repeated aspiration or arthroscopy of the affected joint to prevent damage from leukocytes. The combination of rifampin with ciprofloxacin has been used successfully to treat prosthetic-joint infections, especially when the device cannot be removed. The efficacy of this combination may reflect enhanced activity against staphylococci in biofilms as well as the attainment of effective intracellular concentrations.

The choice of empirical therapy for staphylococcal infections depends in part on susceptibility data for the local geographic area. Increasingly, vancomycin (in combination with an aminoglycoside or rifampin for serious infections) is the drug of choice for both community- and hospital-acquired infections. The increase in CA-MRSA skin and soft tissue infections has drawn attention to the need for initiation of appropriate empirical therapy. Oral agents that have been effective against these isolates include clindamycin, trimethoprim-sulfamethoxazole, doxycycline, and linezolid.

THERAPY FOR TOXIC SHOCK SYNDROME Supportive therapy with reversal of hypotension is the mainstay of therapy for TSS. Both fluids and pressors may be necessary. Tampons or other packing material should be promptly removed. The role of antibiotics is less clear. Some investigators recommend a combination of clindamycin and a semisynthetic penicillin or vancomycin (if the isolate is resistant to methicillin). Clindamycin is advocated because, as a protein synthesis inhibitor, it reduces toxin synthesis in vitro. Linezolid also appears to be effective as a toxin synthesis inhibitor. A semisynthetic penicillin or glycopeptide is suggested to eliminate any potential focus of infection as well as to eradicate persistent carriage that might increase the likelihood of recurrent illness. Anecdotal reports document the successful use of IV immunoglobulin to treat TSS. The role of glucocorticoids in the treatment of this disease is uncertain.

THERAPY FOR OTHER TOXIN-MEDIATED DISEASES Therapy for staphylococcal food poisoning is entirely supportive. For SSSS, antistaphylococcal therapy targets the primary site of infection.

CHAPTER 39

STREPTOCOCCAL INFECTIONS

Michael R. Wessels

Many varieties of streptococci are found as part of the normal flora colonizing the human respiratory, gastrointestinal, and genitourinary tracts. Several species are important causes of human disease. Group A *Streptococcus* (GAS, *S. pyogenes*) is responsible for streptococcal pharyngitis, one of the most common bacterial infections of school-age children, and for the postinfectious syndromes of acute rheumatic fever (ARF) and poststreptococcal glomerulonephritis (PSGN). Group B *Streptococcus* (GBS, *S. agalactiae*) is the leading cause of bacterial sepsis and meningitis in newborns and a major cause of endometritis and fever in parturient women. Viridans streptococci are the most common cause of bacterial endocarditis. Enterococci, which are morphologically similar to streptococci, are now considered a separate genus on the basis of DNA homology studies. Thus, the species previously designated as *S. faecalis* and *S. faecium* have been renamed *Enterococcus faecalis* and *E. faecium*, respectively. The enterococci are discussed in Chap. 40.

Streptococci are gram-positive, spherical to ovoid bacteria that characteristically form chains when grown in liquid media. Most streptococci that cause human infections are facultative anaerobes, although some are strict anaerobes. Streptococci are relatively fastidious organisms, requiring enriched media for growth in the laboratory. Clinicians and clinical microbiologists identify streptococci by several classification systems, including hemolytic pattern, Lancefield group, species name, and common or trivial name. Many streptococci associated with human infection produce a zone of complete (β) hemolysis around the bacterial colony when cultured on blood agar. The β-hemolytic streptococci can be classified by the Lancefield system, a serologic grouping based on the reaction of specific antisera with bacterial cell-wall carbohydrate antigens. With rare exceptions, organisms belonging to Lancefield groups A, B, C, and G are all β-hemolytic, and each is associated with characteristic patterns of human infection. Other streptococci produce a zone of partial (α) hemolysis, often imparting a greenish appearance to the agar. These α-hemolytic streptococci are further identified by biochemical testing and include *S. pneumoniae* (Chap. 37), an important cause of

TABLE 39-1

CLASSIFICATION OF STREPTOCOCCI

LANCEFIELD GROUP	REPRESENTATIVE SPECIES	HEMOLYTIC PATTERN	TYPICAL INFECTIONS
A	*S. pyogenes*	β	Pharyngitis, impetigo, cellulitis, scarlet fever
B	*S. agalactiae*	β	Neonatal sepsis and meningitis, puerperal infection, urinary tract infection, diabetic ulcer infection, endocarditis
C, G	*S. dysgalactiae* subsp. *equisimilis*	β	Cellulitis, bacteremia, endocarditis
D	Enterococci[a]: *E. faecalis; E. faecium*	Usually nonhemolytic	Urinary tract infection, nosocomial bacteremia, endocarditis
	Nonenterococci: *S. bovis*	Usually nonhemolytic	Bacteremia, endocarditis
Variable or nongroupable	Viridans streptococci: *S. sanguis; S. mitis*	α	Endocarditis, dental abscess, brain abscess
	Intermedius or *milleri* group: *S. intermedius, S. anginosus, S. constellatus*	Variable	Brain abscess, visceral abscess
	Anaerobic streptococci[b]: *Peptostreptococcus magnus*	Usually nonhemolytic	Sinusitis, pneumonia, empyema, brain abscess, liver abscess

[a]See Chap. 40.
[b]See Chap. 69.

pneumonia, meningitis, and other infections, and the several species referred to collectively as the *viridans streptococci*, which are part of the normal oral flora and are important agents of subacute bacterial endocarditis. Finally, some streptococci are nonhemolytic, a pattern sometimes called γ *hemolysis*. Among the organisms classified serologically as group D streptococci, the enterococci are classified as a distinct genus (Chap. 40). The classification of the major streptococcal groups causing human infections is outlined in **Table 39-1**.

GROUP A STREPTOCOCCI

Lancefield's group A consists of a single species, *S. pyogenes*. As its species name implies, this organism is associated with a variety of suppurative infections. In addition, GAS can trigger the postinfectious syndromes of ARF (which is uniquely associated with *S. pyogenes* infection; Chap. 41) and PSGN.

Worldwide, GAS infections and their postinfectious sequelae (primarily ARF and rheumatic heart disease) account for an estimated 500,000 deaths per year. Although data are incomplete, the incidence of all forms of GAS infection and that of rheumatic heart disease are thought to be tenfold higher in resource-limited countries than in developed countries **(Fig. 39-1)**.

PATHOGENESIS

GAS elaborates a number of cell-surface components and extracellular products important in both the pathogenesis of infection and the human immune response. The cell wall contains a carbohydrate antigen that may be released by acid treatment. The reaction of such acid extracts with group A–specific antiserum is the basis for definitive identification of a streptococcal strain as *S. pyogenes*. The major surface protein of GAS is M protein, which occurs in more than 100 antigenically distinct types and is the basis for the serotyping of strains with specific antisera. The M protein molecules are fibrillar structures anchored in the cell wall of the organism that extend as hairlike projections away from the cell surface. The amino acid sequence of the distal or amino-terminal portion of the M protein molecule is quite variable, accounting for the antigenic variation of the different M types, while more proximal regions of the protein are relatively conserved. A newer technique for assignment of M type to GAS isolates uses the polymerase chain reaction to amplify the variable region of the *emm* gene, which encodes M protein. DNA sequence analysis of the amplified gene segment can be compared with an extensive database [developed at the Centers for Disease Control and Prevention (CDC)] for assignment of *emm* type. This method eliminates the need for typing sera, which are available in only a few reference laboratories. The presence of M protein on a GAS isolate correlates with its capacity to resist phagocytic killing in fresh human blood. This phenomenon appears to be due, at least in part, to the binding of plasma fibrinogen to M protein molecules on the streptococcal surface, which interferes with complement activation and deposition of opsonic complement fragments on the bacterial cell. This resistance to phagocytosis may be overcome by M protein–specific antibodies; thus individuals with antibodies to a given M type acquired as a result of prior infection are protected against subsequent infection with organisms of the same M type but not against that with different M types.

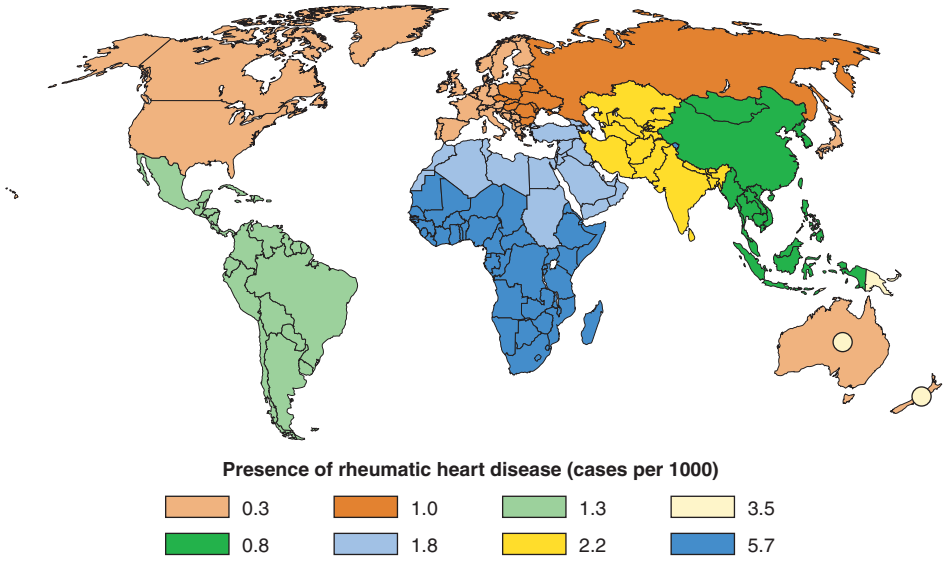


FIGURE 39-1
Prevalence of rheumatic heart disease in children 5–14 years old. The circles within Australia and New Zealand represent indigenous populations (and also Pacific Islanders in New Zealand). (*From JR Carapetis et al: Lancet Infect Dis 5:685, 2005, with permission.*)

GAS also elaborates, to varying degrees, a polysaccharide capsule composed of hyaluronic acid. The production of large amounts of capsule by certain strains imparts a characteristic mucoid appearance to the colonies. The capsular polysaccharide plays an important role in protecting GAS from ingestion and killing by phagocytes. In contrast to M protein, the hyaluronic acid capsule is a weak immunogen, and antibodies to hyaluronate have not been shown to be important in protective immunity. The presumed explanation is the apparent structural identity between streptococcal hyaluronic acid and the hyaluronic acid of mammalian connective tissues. The capsular polysaccharide may also play a role in GAS colonization of the pharynx by binding to CD44, a hyaluronic acid–binding protein expressed on human pharyngeal epithelial cells.

GAS produces a large number of extracellular products that may be important in local and systemic toxicity and in the spread of infection through tissues. These products include streptolysins S and O, toxins that damage cell membranes and account for the hemolysis produced by the organisms; streptokinase; DNAses; SpyCEP, a serine protease that cleaves and inactivates the chemoattractant cytokine interleukin 8, thereby inhibiting neutrophil recruitment to the site of infection; and several pyrogenic exotoxins. Previously known as erythrogenic toxins, the pyrogenic exotoxins cause the rash of scarlet fever. Since the mid-1980s, pyrogenic exotoxin–producing strains of GAS have been linked to unusually severe invasive infections, including necrotizing fasciitis and the streptococcal toxic shock syndrome (TSS). Several extracellular products stimulate specific antibody responses useful for serodiagnosis of recent streptococcal infection. Tests for these antibodies are used primarily for detection of preceding streptococcal infection in cases of suspected ARF or PSGN.

CLINICAL MANIFESTATIONS

Pharyngitis

Although seen in patients of all ages, GAS pharyngitis is one of the most common bacterial infections of childhood, accounting for 20–40% of all cases of exudative pharyngitis in children; it is rare among those under the age of 3. Younger children may manifest streptococcal infection with a syndrome of fever, malaise, and lymphadenopathy without exudative pharyngitis. Infection is acquired through contact with another individual carrying the organism. Respiratory droplets are the usual mechanism of spread, although other routes, including food-borne outbreaks, have been well described. The incubation period is 1–4 days. Symptoms include sore throat, fever and chills, malaise, and sometimes abdominal complaints and vomiting, particularly in children. Both symptoms and signs are quite variable, ranging from mild throat discomfort with minimal physical findings to high fever and severe sore throat associated with intense erythema and swelling of the pharyngeal mucosa and the presence of purulent exudate over the posterior pharyngeal wall and tonsillar pillars. Enlarged, tender anterior cervical lymph nodes commonly accompany exudative pharyngitis.

The differential diagnosis of streptococcal pharyngitis includes the many other bacterial and viral etiologies (Table 39-2). Streptococcal infection is an unlikely cause when symptoms and signs suggestive of viral infection are prominent (conjunctivitis, coryza, cough, hoarseness, or discrete ulcerative lesions of the buccal or pharyngeal mucosa). Because of the range of clinical presentations of streptococcal pharyngitis and the large number of other agents that can produce the same clinical picture, diagnosis of streptococcal pharyngitis on clinical grounds alone is not reliable. The throat culture remains the diagnostic gold standard. Culture of a

TABLE 39-2

INFECTIOUS ETIOLOGIES OF ACUTE PHARYNGITIS

ORGANISM	ASSOCIATED CLINICAL SYNDROME(S)
Viruses	
Rhinovirus	Common cold
Coronavirus	Common cold
Adenovirus	Pharyngoconjunctival fever
Influenza virus	Influenza
Parainfluenza virus	Cold, croup
Coxsackievirus	Herpangina, hand-foot-and-mouth disease
Herpes simplex virus	Gingivostomatitis (primary infection)
Epstein-Barr virus	Infectious mononucleosis
Cytomegalovirus	Mononucleosis-like syndrome
HIV	Acute (primary) infection syndrome
Bacteria	
Group A streptococci	Pharyngitis, scarlet fever
Group C or G streptococci	Pharyngitis
Mixed anaerobes	Vincent's angina
Arcanobacterium haemolyticum	Pharyngitis, scarlatiniform rash
Neisseria gonorrhoeae	Pharyngitis
Treponema pallidum	Secondary syphilis
Francisella tularensis	Pharyngeal tularemia
Corynebacterium diphtheriae	Diphtheria
Yersinia enterocolitica	Pharyngitis, enterocolitis
Yersinia pestis	Plague
Chlamydiae	
Chlamydia pneumoniae	Bronchitis, pneumonia
Chlamydia psittaci	Psittacosis
Mycoplasmas	
Mycoplasma pneumoniae	Bronchitis, pneumonia

throat specimen that is properly collected (i.e., by vigorous rubbing of a sterile swab over both tonsillar pillars) and properly processed is the most sensitive and specific means of definitive diagnosis. A rapid diagnostic kit for latex agglutination or enzyme immunoassay of swab specimens is a useful adjunct to throat culture. While precise figures on sensitivity and specificity vary, rapid diagnostic kits generally are >95% specific. Thus a positive result can be relied upon for definitive diagnosis and eliminates the need for throat culture. However, because rapid diagnostic tests are less sensitive than throat culture (relative sensitivity in comparative studies, 55–90%), a negative result should be confirmed by throat culture.

TREATMENT GAS Pharyngitis

In the usual course of uncomplicated streptococcal pharyngitis, symptoms resolve after 3–5 days. The course is shortened little by treatment, which is given primarily to prevent suppurative complications and ARF. Prevention of ARF depends on eradication of the organism from the pharynx, not simply on resolution of symptoms, and requires 10 days of penicillin treatment (Table 39-3). A first-generation cephalosporin, such as cephalexin or cefadroxil, may be substituted for penicillin in cases of penicillin allergy if the nature of the allergy is not an immediate hypersensitivity reaction (anaphylaxis or urticaria) or another potentially life-threatening manifestation (e.g., severe rash and fever). Alternative agents are erythromycin and azithromycin. Azithromycin is more expensive but offers the advantages of better gastrointestinal tolerability, once-daily dosing, and a 5-day treatment course at a dose of 12 mg/kg once daily (maximum, 500 mg).

Resistance to erythromycin and other macrolides is common among isolates from several countries, including Spain, Italy, Finland, Japan, and Korea. Macrolide resistance may be becoming more prevalent elsewhere with the increasing use of this class of antibiotics. In areas with resistance rates exceeding 5–10%, macrolides should be avoided unless results of susceptibility testing are known. Follow-up culture after

TABLE 39-3

TREATMENT OF GROUP A STREPTOCOCCAL INFECTIONS

INFECTION	TREATMENT[a]
Pharyngitis	Benzathine penicillin G, 1.2 mU IM; *or* penicillin V, 250 mg PO tid or 500 mg PO bid × 10 days (Children <27 kg: Benzathine penicillin G, 600,000 units IM; *or* penicillin V, 250 mg PO bid or tid × 10 days)
Impetigo	Same as pharyngitis
Erysipelas/cellulitis	Severe: Penicillin G, 1–2 mU IV q4h Mild to moderate: Procaine penicillin, 1.2 mU IM bid
Necrotizing fasciitis/myositis	Surgical debridement; *plus* penicillin G, 2–4 mU IV q4h; *plus* clindamycin,[b] 600–900 mg q8h
Pneumonia/empyema	Penicillin G, 2–4 mU IV q4h; *plus* drainage of empyema
Streptococcal toxic shock syndrome	Penicillin G, 2–4 mU IV q4h; *plus* clindamycin,[b] 600–900 mg q8h; *plus* IV immunoglobulin,[b] 2 g/kg as a single dose

[a]Penicillin allergy: A first-generation cephalosporin, such as cephalexin or cefadroxil, may be substituted for penicillin in cases of penicillin allergy if the nature of the allergy is not an immediate hypersensitivity reaction (anaphylaxis or urticaria) or another potentially life-threatening manifestation (e.g., severe rash and fever). Alternative agents for oral therapy are erythromycin (10 mg/kg PO qid, up to a maximum of 250 mg per dose) and azithromycin (a 5-day treatment course at a dose of 12 mg/kg once daily, up to a maximum of 500 mg per day). Vancomycin is an alternative for parenteral therapy.
[b]Efficacy unproven, but recommended by several experts. See text for discussion.

treatment is no longer routinely recommended but may be warranted in selected cases, such as those involving patients or families with frequent streptococcal infections or those occurring in situations in which the risk of ARF is thought to be high (e.g., when cases of ARF have recently been reported in the community).

Complications

Suppurative complications of streptococcal pharyngitis have become uncommon with the widespread use of antibiotics for most symptomatic cases. These complications result from the spread of infection from the pharyngeal mucosa to deeper tissues by direct extension or by the hematogenous or lymphatic route and may include cervical lymphadenitis, peritonsillar or retropharyngeal abscess, sinusitis, otitis media, meningitis, bacteremia, endocarditis, and pneumonia. Local complications, such as peritonsillar or parapharyngeal abscess formation, should be considered in a patient with unusually severe or prolonged symptoms or localized pain associated with high fever and a toxic appearance. Nonsuppurative complications include ARF (Chap. 41) and PSGN, both of which are thought to result from immune responses to streptococcal infection. Penicillin treatment of streptococcal pharyngitis has been shown to reduce the likelihood of ARF but not that of PSGN.

Bacteriologic treatment failure and the asymptomatic carrier state

Surveillance cultures have shown that up to 20% of individuals in certain populations may have asymptomatic pharyngeal colonization with GAS. There are no definitive guidelines for management of these asymptomatic carriers or of asymptomatic patients who still have a positive throat culture after a full course of treatment for symptomatic pharyngitis. A reasonable course of action is to give a single 10-day course of penicillin for symptomatic pharyngitis and, if positive cultures persist, not to re-treat unless symptoms recur. Studies of the natural history of streptococcal carriage and infection have shown that the risk both of developing ARF and of transmitting infection to others is substantially lower among asymptomatic carriers than among individuals with symptomatic pharyngitis. Therefore, overly aggressive attempts to eradicate carriage probably are not justified under most circumstances. An exception is the situation in which an asymptomatic carrier is a potential source of infection to others. Outbreaks of food-borne infection and nosocomial puerperal infection have been traced to asymptomatic carriers who may harbor the organisms in the throat, vagina, or anus or on the skin.

TREATMENT **Asymptomatic Pharyngeal Colonization with GAS**

When a carrier is transmitting infection to others, attempts to eradicate carriage are warranted. Data are limited on the best regimen to clear GAS after penicillin alone has failed. The combination of penicillin V (500 mg four times daily for 10 days) and rifampin (600 mg twice daily for the last 4 days) has been used to eliminate pharyngeal carriage. A 10-day course of oral vancomycin (250 mg four times daily) and rifampin (600 mg twice daily) has eradicated rectal colonization.

Scarlet fever

Scarlet fever consists of streptococcal infection, usually pharyngitis, accompanied by a characteristic rash (Fig. 39-2). The rash arises from the effects of one of three toxins, currently designated streptococcal pyrogenic exotoxins A, B, and C and previously known as erythrogenic or scarlet fever toxins. In the past, scarlet fever was thought to reflect infection of an individual lacking toxin-specific immunity with a toxin-producing strain of GAS. Susceptibility to scarlet fever was correlated with results of the Dick test, in which a small amount of erythrogenic toxin injected intradermally produced local erythema in susceptible individuals but elicited no reaction in those with specific immunity. Subsequent studies have suggested that development of the scarlet fever rash may reflect a hypersensitivity reaction requiring prior exposure to the toxin. For reasons that are not clear, scarlet fever has become less common in recent years, although strains of GAS that produce pyrogenic exotoxins continue to be prevalent in the population. The symptoms of scarlet fever are the same as those of pharyngitis alone. The rash typically begins on the first or second day of illness over the upper trunk, spreading to involve the extremities but sparing

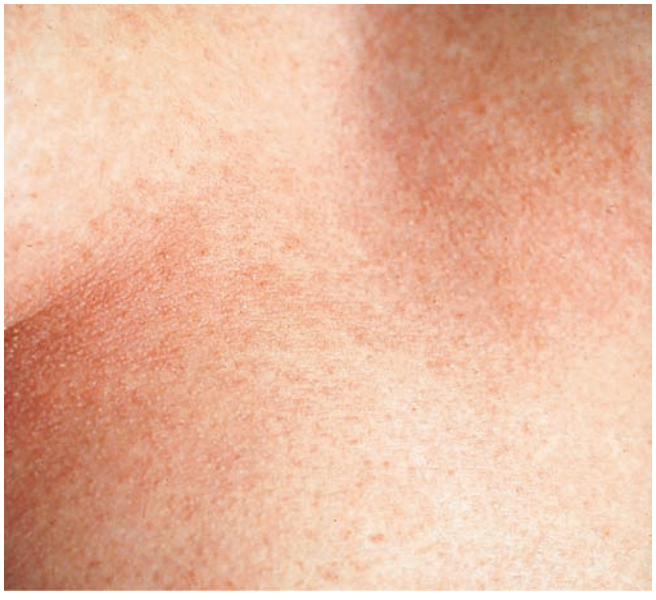


FIGURE 39-2
Scarlet fever exanthem. Finely punctate erythema has become confluent (scarlatiniform); petechiae can occur and have a linear configuration within the exanthem in body folds (Pastia's lines). (*From Fitzpatrick, Johnson, Wolff: Color Atlas and Synopsis of Clinical Dermatology, 4th ed, New York, McGraw-Hill, 2001, with permission.*)

the palms and soles. The rash is made up of minute papules, giving a characteristic "sandpaper" feel to the skin. Associated findings include circumoral pallor, "strawberry tongue" (enlarged papillae on a coated tongue, which later may become denuded), and accentuation of the rash in skinfolds (Pastia's lines). Subsidence of the rash in 6–9 days is followed after several days by desquamation of the palms and soles. The differential diagnosis of scarlet fever includes other causes of fever and generalized rash, such as measles and other viral exanthems, Kawasaki disease, toxic shock syndrome, and systemic allergic reactions (e.g., drug eruptions).

Skin and soft tissue infections

GAS—and occasionally other streptococcal species—can cause a variety of infections involving the skin, subcutaneous tissues, muscles, and fascia. While several clinical syndromes offer a useful means for classification of these infections, not all cases fit exactly into one category. The classic syndromes are general guides to predicting the level of tissue involvement in a particular patient, the probable clinical course, and the likelihood that surgical intervention or aggressive life support will be required.

Impetigo (pyoderma)

Impetigo, a superficial infection of the skin, is caused primarily by GAS and occasionally by other streptococci or *Staphylococcus aureus*. Impetigo is seen most often in young children, tends to occur during warmer months, and is more common in semitropical or tropical climates than in cooler regions. Infection is more common among children living under conditions of poor hygiene. Prospective studies have shown that colonization of unbroken skin with GAS precedes clinical infection. Minor trauma, such as a scratch or an insect bite, may then serve to inoculate organisms into the skin. Impetigo is best prevented, therefore, by attention to adequate hygiene. The usual sites of involvement are the face (particularly around the nose and mouth) and the legs, although lesions may occur at other locations. Individual lesions begin as red papules, which evolve quickly into vesicular and then pustular lesions that break down and coalesce to form characteristic honeycomb-like crusts **(Fig. 39-3)**. Lesions generally are not painful, and patients do not appear ill. Fever is not a feature of impetigo and, if present, suggests either infection extending to deeper tissues or another diagnosis. The classic presentation of impetigo usually poses little diagnostic difficulty. Cultures of impetiginous lesions often yield *S. aureus* as well as GAS. In almost all cases, streptococci are isolated initially and staphylococci appear later, presumably as secondary colonizing flora. In the past, penicillin was nearly always effective against these infections. However, an increasing frequency of penicillin treatment failure suggests that *S. aureus* may have become more prominent as a cause of impetigo. *Bullous impetigo* due to *S. aureus* is distinguished from typical streptococcal infection by more extensive, bullous lesions that break down and leave thin paper-like crusts instead of the thick amber crusts of streptococcal impetigo. Other skin lesions that may be confused with impetigo include herpetic lesions—either those of orolabial herpes simplex or those of chickenpox or zoster. Herpetic lesions can generally be distinguished by their appearance as more discrete, grouped vesicles and by a positive Tzanck test. In difficult cases, cultures of vesicular fluid should yield GAS in impetigo and the responsible virus in *Herpesvirus* infections.

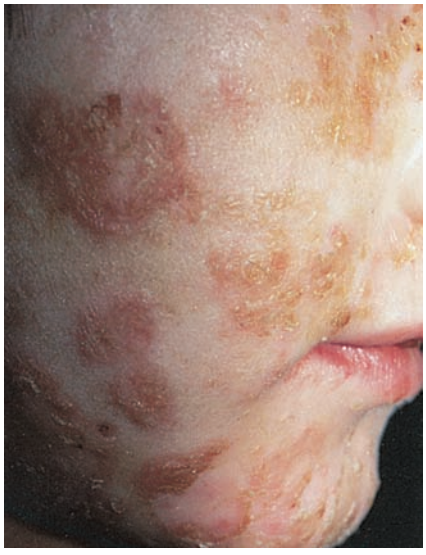


FIGURE 39-3
Impetigo contagiosa is a superficial streptococcal or *Staphylococcus aureus* infection consisting of honey-colored crusts and erythematous weeping erosions. Occasionally, bullous lesions may be seen. (*Courtesy of Mary Spraker, MD; with permission.*)

TREATMENT **Streptococcal Impetigo**

Treatment of streptococcal impetigo is the same as that for streptococcal pharyngitis. In view of evidence that *S. aureus* has become a relatively frequent cause of impetigo, empirical regimens should cover both streptococci and *S. aureus*. For example, either dicloxacillin or cephalexin can be given at a dose of 250 mg four times daily for 10 days. Topical mupirocin ointment is also effective. Culture may be indicated to rule out methicillin-resistant *S. aureus*, especially if the response to empirical treatment is unsatisfactory. ARF is not a sequela to streptococcal skin infections, although PSGN may follow either skin or throat infection. The reason for this difference is not known. One hypothesis is that the immune response necessary for development of ARF occurs only after infection of the pharyngeal mucosa. In addition, the strains of GAS that cause pharyngitis are generally of different M protein types than those associated with skin infections; thus the strains that cause pharyngitis may have rheumatogenic potential, while the skin-infecting strains may not.

Cellulitis

Inoculation of organisms into the skin may lead to *cellulitis*: infection involving the skin and subcutaneous tissues. The portal of entry may be a traumatic or surgical wound, an insect bite, or any other break in skin integrity. Often, no entry site is apparent. One form of streptococcal cellulitis, *erysipelas*, is characterized by a bright red appearance of the involved skin, which forms a plateau sharply demarcated from surrounding normal skin **(Fig. 39-4)**. The lesion is warm to the touch, may be tender, and appears shiny and swollen. The skin often has a *peau d'orange* texture, which is thought to reflect involvement of superficial lymphatics; superficial blebs or bullae may form, usually 2–3 days after onset. The lesion typically develops over a few hours and is associated with fever and chills. Erysipelas tends to occur on the malar area of the face (often with extension over the bridge of the nose to the contralateral malar region) and the lower extremities. After one episode, recurrence at the same site—sometimes years later—is not uncommon. Classic cases of erysipelas, with typical features, are almost always due to β-hemolytic streptococci, usually GAS and occasionally group C or G. Often, however, the appearance of streptococcal cellulitis is not sufficiently distinctive to permit a specific diagnosis on clinical grounds. The area involved may not be typical for erysipelas, the lesion may be less intensely red than usual and may fade into surrounding skin, and/or the patient may appear only mildly ill. In such cases, it is prudent to broaden the spectrum of empirical antimicrobial therapy to include other pathogens, particularly *S. aureus*, that can produce cellulitis with the same appearance. Staphylococcal infection should be suspected if cellulitis develops around a wound or an ulcer.

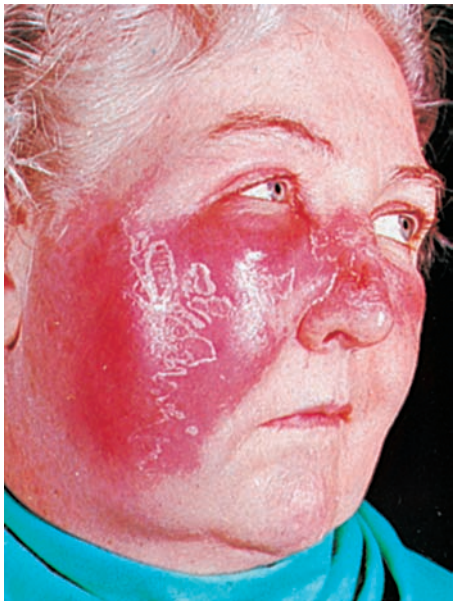


FIGURE 39-4
Erysipelas is a streptococcal infection of the superficial dermis and consists of well-demarcated, erythematous, edematous, warm plaques.

Streptococcal cellulitis tends to develop at anatomic sites in which normal lymphatic drainage has been disrupted, such as sites of prior cellulitis, the arm ipsilateral to a mastectomy and axillary lymph node dissection, a lower extremity previously involved in deep venous thrombosis or chronic lymphedema, or the leg from which a saphenous vein has been harvested for coronary artery bypass grafting. The organism may enter via a dermal breach some distance from the eventual site of clinical cellulitis. For example, some patients with recurrent leg cellulitis following saphenous vein removal stop having recurrent episodes only after treatment of tinea pedis on the affected extremity. Fissures in the skin presumably serve as a portal of entry for streptococci, which then produce infection more proximally in the leg at the site of previous injury. Streptococcal cellulitis may also involve recent surgical wounds. GAS is among the few bacterial pathogens that typically produce signs of wound infection and surrounding cellulitis within the first 24 h after surgery. These wound infections are usually associated with a thin exudate and may spread rapidly, either as cellulitis in the skin and subcutaneous tissue or as a deeper tissue infection (see next). Streptococcal wound infection or localized cellulitis may also be associated with *lymphangitis*, manifested by red streaks extending proximally along superficial lymphatics from the infection site.

TREATMENT **Streptococcal Cellulitis**

See Table 39-3 and Chap. 22.

Deep soft tissue infections

Necrotizing fasciitis (*hemolytic streptococcal gangrene*) involves the superficial and/or deep fascia investing the muscles of an extremity or the trunk. The source of the infection is either the skin, with organisms introduced into tissue through trauma (sometimes trivial), or the bowel flora, with organisms released during abdominal surgery or from an occult enteric source, such as a diverticular or appendiceal abscess. The inoculation site may be inapparent and is often some distance from the site of clinical involvement; e.g., the introduction of organisms via minor trauma to the hand may be associated with clinical infection of the tissues overlying the shoulder or chest. Cases associated with the bowel flora are usually polymicrobial, involving a mixture of anaerobic bacteria (such as *Bacteroides fragilis* or anaerobic streptococci) and facultative organisms (usually gram-negative bacilli). Cases unrelated to contamination from bowel organisms are most commonly caused by GAS alone or in combination with other organisms (most often *S. aureus*). Overall, GAS is implicated in ~60% of cases of necrotizing fasciitis. The onset of symptoms is usually quite acute and is marked by severe pain at the site of involvement, malaise, fever, chills, and a toxic appearance. The physical findings, particularly early on, may not be

striking, with only minimal erythema of the overlying skin. Pain and tenderness are usually severe. In contrast, in more superficial cellulitis, the skin appearance is more abnormal, but pain and tenderness are only mild or moderate. As the infection progresses (often over several hours), the severity and extent of symptoms worsen, and skin changes become more evident, with the appearance of dusky or mottled erythema and edema. The marked tenderness of the involved area may evolve into anesthesia as the spreading inflammatory process produces infarction of cutaneous nerves.

Although myositis is more commonly due to *S. aureus* infection, GAS occasionally produces abscesses in skeletal muscles (*streptococcal myositis*), with little or no involvement of the surrounding fascia or overlying skin. The presentation is usually subacute, but a fulminant form has been described in association with severe systemic toxicity, bacteremia, and a high mortality rate. The fulminant form may reflect the same basic disease process seen in necrotizing fasciitis, but with the necrotizing inflammatory process extending into the muscles themselves rather than remaining limited to the fascial layers.

TREATMENT **Deep Soft Tissue Infections**

Once necrotizing fasciitis is suspected, early surgical exploration is both diagnostically and therapeutically indicated. Surgery reveals necrosis and inflammatory fluid tracking along the fascial planes above and between muscle groups, without involvement of the muscles themselves. The process usually extends beyond the area of clinical involvement, and extensive debridement is required. Drainage and debridement are central to the management of necrotizing fasciitis; antibiotic treatment is a useful adjunct (Table 39-3), but surgery is life-saving. Treatment for streptococcal myositis consists of surgical drainage—usually by an open procedure that permits evaluation of the extent of infection and ensures adequate debridement of involved tissues—and high-dose penicillin (Table 39-3).

Pneumonia and empyema

GAS is an occasional cause of pneumonia, generally in previously healthy individuals. The onset of symptoms may be abrupt or gradual. Pleuritic chest pain, fever, chills, and dyspnea are the characteristic manifestations. Cough is usually present but may not be prominent. Approximately one-half of patients with GAS pneumonia have an accompanying pleural effusion. In contrast to the sterile parapneumonic effusions typical of pneumococcal pneumonia, those complicating streptococcal pneumonia are almost always infected. The empyema fluid is usually visible by chest radiography on initial presentation, and its volume may increase rapidly. These pleural collections should be drained early, as they tend to become loculated rapidly, resulting in a chronic fibrotic reaction that may require thoracotomy for removal.

Bacteremia, puerperal sepsis, and streptococcal toxic shock syndrome

GAS bacteremia is usually associated with an identifiable local infection. Bacteremia occurs rarely with otherwise uncomplicated pharyngitis, occasionally with cellulitis or pneumonia, and relatively frequently with necrotizing fasciitis. Bacteremia without an identified source raises the possibility of endocarditis, an occult abscess, or osteomyelitis. A variety of focal infections may arise secondarily from streptococcal bacteremia, including endocarditis, meningitis, septic arthritis, osteomyelitis, peritonitis, and visceral abscesses. GAS is occasionally implicated in infectious complications of childbirth, usually endometritis and associated bacteremia. In the preantibiotic era, puerperal sepsis was commonly caused by GAS; currently, it is more often caused by GBS. Several nosocomial outbreaks of puerperal GAS infection have been traced to an asymptomatic carrier, usually someone present at delivery. The site of carriage may be the skin, throat, anus, or vagina.

Beginning in the late 1980s, several reports described patients with GAS infections associated with shock and multisystem organ failure. This syndrome was called the streptococcal TSS because it shares certain features with staphylococcal TSS. In 1993, a case definition for streptococcal TSS was formulated **(Table 39-4)**. The general features of the illness include fever, hypotension, renal impairment, and respiratory distress syndrome. Various types of rash have been described, but rash usually does not develop. Laboratory abnormalities include a marked shift to the left in the white blood cell differential, with many immature granulocytes; hypocalcemia; hypoalbuminemia; and thrombocytopenia, which usually

TABLE 39-4

PROPOSED CASE DEFINITION FOR THE STREPTOCOCCAL TOXIC SHOCK SYNDROME[a]

I. Isolation of group A streptococci (*Streptococcus pyogenes*)
  A. From a normally sterile site
  B. From a nonsterile site
II. Clinical signs of severity
  A. Hypotension *and*
  B. ≥2 of the following signs
    1. Renal impairment
    2. Coagulopathy
    3. Liver function impairment
    4. Adult respiratory distress syndrome
    5. A generalized erythematous macular rash that may desquamate
    6. Soft tissue necrosis, including necrotizing fasciitis or myositis; *or* gangrene

[a]An illness fulfilling criteria IA, IIA, and IIB is defined as a *definite* case. An illness fulfilling criteria IB, IIA, and IIB is defined as a *probable* case if no other etiology for the illness is identified.
Source: Modified from Working Group on Severe Streptococcal Infections: JAMA 269:390, 1993.

becomes more pronounced on the second or third day of illness. In contrast to patients with staphylococcal TSS, the majority with streptococcal TSS are bacteremic. The most common associated infection is a soft tissue infection—necrotizing fasciitis, myositis, or cellulitis—although a variety of other associated local infections have been described, including pneumonia, peritonitis, osteomyelitis, and myometritis. Streptococcal TSS is associated with a mortality rate of ≥30%, with most deaths secondary to shock and respiratory failure. Because of its rapidly progressive and lethal course, early recognition of the syndrome is essential. Patients should receive aggressive supportive care (fluid resuscitation, pressors, and mechanical ventilation) in addition to antimicrobial therapy and, in cases associated with necrotizing fasciitis, surgical debridement. Exactly why certain patients develop this fulminant syndrome is not known. Early studies of the streptococcal strains isolated from these patients demonstrated a strong association with the production of pyrogenic exotoxin A. This association has been inconsistent in subsequent case series. Pyrogenic exotoxin A and several other streptococcal exotoxins act as superantigens to trigger release of inflammatory cytokines from T lymphocytes. Fever, shock, and organ dysfunction in streptococcal TSS may reflect, in part, the systemic effects of superantigen-mediated cytokine release.

TREATMENT **Streptococcal Toxic Shock Syndrome**

In light of the possible role of pyrogenic exotoxins or other streptococcal toxins in streptococcal TSS, treatment with clindamycin has been advocated by some authorities (Table 39-3), who argue that, through its direct action on protein synthesis, clindamycin is more effective in rapidly terminating toxin production than penicillin—a cell-wall agent. Support for this view comes from studies of an experimental model of streptococcal myositis, in which mice given clindamycin had a higher rate of survival than those given penicillin. Comparable data on the treatment of human infections are not available, although retrospective analysis has suggested a better outcome when patients with invasive soft tissue infection are treated with clindamycin rather than with cell wall–active antibiotics. Although clindamycin resistance in GAS is uncommon (<2% among U.S. isolates), it has been documented. Thus, if clindamycin is used for initial treatment of a critically ill patient, penicillin should be given as well until the antibiotic susceptibility of the streptococcal isolate is known. IV immunoglobulin has been used as adjunctive therapy for streptococcal TSS (Table 39-3). Pooled immunoglobulin preparations contain antibodies capable of neutralizing the effects of streptococcal toxins. Anecdotal reports and case series have suggested favorable clinical responses to IV immunoglobulin, but no adequately powered, prospective, controlled trials have been reported.

PREVENTION

No vaccine against GAS is commercially available. A formulation that consists of recombinant peptides containing epitopes of 26 M-protein types has undergone phase 1 and 2 testing in volunteers. Early results indicate that the vaccine is well tolerated and elicits type-specific antibody responses. Vaccines based on a conserved region of M protein or on a mixture of other conserved GAS protein antigens are in earlier stages of development.

Household contacts of individuals with invasive GAS infection (e.g., bacteremia, necrotizing fasciitis, or streptococcal TSS) are at greater risk of invasive infection than the general population. Asymptomatic pharyngeal colonization with GAS has been detected in up to 25% of persons with >4 h/d of same-room exposure to an index case. However, antibiotic prophylaxis is not routinely recommended for contacts of patients with invasive disease since such an approach (if effective) would require treatment of hundreds of contacts to prevent a single case.

STREPTOCOCCI OF GROUPS C AND G

Group C and group G streptococci are β-hemolytic bacteria that occasionally cause human infections similar to those caused by GAS. Strains that form small colonies on blood agar (<0.5 mm) are generally members of the *S. milleri* (*S. intermedius, S. anginosus*) group (see "Viridans Streptococci," later in the chapter). Large-colony group C and G streptococci of human origin are now considered a single species, *S. dysgalactiae* subsp. *equisimilis*. They have been associated with pharyngitis, cellulitis and soft tissue infections, pneumonia, bacteremia, endocarditis, and septic arthritis. Puerperal sepsis, meningitis, epidural abscess, intraabdominal abscess, urinary tract infection, and neonatal sepsis have also been reported. Group C or G streptococcal bacteremia most often affects elderly or chronically ill patients and, in the absence of obvious local infection, is likely to reflect endocarditis. Septic arthritis, sometimes involving multiple joints, may complicate endocarditis or develop in its absence. Distinct streptococcal species of Lancefield group C cause infections in domesticated animals, especially horses and cattle; some human infections are acquired through contact with animals or consumption of unpasteurized milk. These zoonotic organisms include *S. equi* subsp. *zooepidemicus* and *S. equi* subsp. *equi*.

TREATMENT **Group C or G Streptococcal Infection**

Penicillin is the drug of choice for treatment of group C or G streptococcal infections. Antibiotic treatment is the same as for similar syndromes due to GAS (Table 39-3). Patients with bacteremia or septic arthritis should receive IV penicillin (2–4 mU every 4 h). All group C and G streptococci are sensitive to penicillin; nearly all are inhibited in vitro by concentrations of ≥0.03 μg/mL.

Occasional isolates exhibit tolerance: although inhibited by low concentrations of penicillin, they are killed only by significantly higher concentrations. The clinical significance of tolerance is unknown. Because of the poor clinical response of some patients to penicillin alone, the addition of gentamicin (1 mg/kg every 8 h for patients with normal renal function) is recommended by some authorities for treatment of endocarditis or septic arthritis due to group C or G streptococci; however, combination therapy has not been shown to be superior to penicillin treatment alone. Patients with joint infections often require repeated aspiration or open drainage and debridement for cure; the response to treatment may be slow, particularly in debilitated patients and those with involvement of multiple joints. Infection of prosthetic joints almost always requires prosthesis removal in addition to antibiotic therapy.

GROUP B STREPTOCOCCI

Identified first as a cause of mastitis in cows, streptococci belonging to Lancefield's group B have since been recognized as a major cause of sepsis and meningitis in human neonates. GBS is also a frequent cause of peripartum fever in women and an occasional cause of serious infection in nonpregnant adults. Since the widespread institution of prenatal screening for GBS in the 1990s, the incidence of neonatal infection per 1000 live births has fallen from ~2–3 cases to ~0.8 case. During the same period, GBS infection in adults with underlying chronic illnesses has become more common; adults now account for a larger proportion of invasive GBS infections than do newborns. Lancefield group B consists of a single species, *S. agalactiae*, which is definitively identified with specific antiserum to the group B cell wall–associated carbohydrate antigen. A streptococcal isolate can be classified presumptively as GBS on the basis of biochemical tests, including hydrolysis of sodium hippurate (in which 99% of isolates are positive), hydrolysis of bile esculin (in which 99–100% are negative), bacitracin susceptibility (in which 92% are resistant), and production of CAMP factor (in which 98–100% are positive). CAMP factor is a phospholipase produced by GBS that causes synergistic hemolysis with β lysin produced by certain strains of *S. aureus*. Its presence can be demonstrated by cross-streaking of the test isolate and an appropriate staphylococcal strain on a blood agar plate. GBS organisms causing human infections are encapsulated by one of ten antigenically distinct polysaccharides. The capsular polysaccharide is an important virulence factor. Antibodies to the capsular polysaccharide afford protection against GBS of the same (but not of a different) capsular type.

INFECTION IN NEONATES

Two general types of GBS infection in infants are defined by the age of the patient at presentation. *Early-onset infections* occur within the first week of life, with a median age of 20 h at onset. Approximately half of these infants have signs of GBS disease at birth. The infection is acquired during or shortly before birth from the colonized maternal genital tract. Surveillance studies have shown that 5–40% of women are vaginal or rectal carriers of GBS. Approximately 50% of infants delivered vaginally by carrier mothers become colonized, although only 1–2% of those colonized develop clinically evident infection. Prematurity and maternal risk factors (prolonged labor, obstetric complications, and maternal fever) are often involved. The presentation of early-onset infection is the same as that of other forms of neonatal sepsis. Typical findings include respiratory distress, lethargy, and hypotension. Essentially all infants with early-onset disease are bacteremic, one-third to one-half have pneumonia and/or respiratory distress syndrome, and one-third have meningitis.

Late-onset infections occur in infants 1 week to 3 months old and, in rare instances, in older infants (mean age at onset, 3–4 weeks). The infecting organism may be acquired during delivery (as in early-onset cases) or during later contact with a colonized mother, nursery personnel, or another source. Meningitis is the most common manifestation of late-onset infection and in most cases is associated with a strain of capsular type III. Infants present with fever, lethargy or irritability, poor feeding, and seizures. The various other types of late-onset infection include bacteremia without an identified source, osteomyelitis, septic arthritis, and facial cellulitis associated with submandibular or preauricular adenitis.

TREATMENT Group B Streptococcal Infection in Neonates

Penicillin is the agent of choice for all GBS infections. Empirical broad-spectrum therapy for suspected bacterial sepsis, consisting of ampicillin and gentamicin, is generally administered until culture results become available. If cultures yield GBS, many pediatricians continue to administer gentamicin, along with ampicillin or penicillin, for a few days until clinical improvement becomes evident. Infants with bacteremia or soft tissue infection should receive penicillin at a dosage of 200,000 units/kg per day in divided doses. For meningitis, infants ≥7 days of age should receive 250,000–450,00 units/kg per day in three divided doses; infants >7 days of age should receive 450,000–500,000 units/kg per day in four divided doses. Meningitis should be treated for at least 14 days because of the risk of relapse with shorter courses.

Prevention

The incidence of GBS infection is unusually high among infants of women with risk factors: preterm delivery, early rupture of membranes (>24 h before delivery), prolonged labor, fever, or chorioamnionitis. Because the usual source of the organisms infecting a neonate is the mother's birth canal, efforts have

been made to prevent GBS infections by the identification of high-risk carrier mothers and their treatment with various forms of antibiotic or immunoprophylaxis. Prophylactic administration of ampicillin or penicillin to such patients during delivery reduces the risk of infection in the newborn. This approach has been hampered by logistical difficulties in identifying colonized women before delivery; the results of vaginal cultures early in pregnancy are poor predictors of carrier status at delivery. The CDC recommends screening for anogenital colonization at 35–37 weeks of pregnancy by a swab culture of the lower vagina and anorectum; intrapartum chemoprophylaxis is recommended for culture-positive women and for women who, regardless of culture status, have previously given birth to an infant with GBS infection or have a history of GBS bacteriuria during pregnancy. Women whose culture status is unknown and who develop premature labor (<37 weeks), prolonged rupture of membranes (>18 h), or intrapartum fever should also receive intrapartum chemoprophylaxis. The recommended regimen for chemoprophylaxis is a loading dose of 5 million units of penicillin G followed by 2.5 million units every 4 h until delivery. Cefazolin is an alternative for women with a history of penicillin allergy who are thought not to be at high risk for anaphylaxis. For women with a history of immediate hypersensitivity, clindamycin or erythromycin may be substituted, but only if the colonizing isolate has been demonstrated to be susceptible. If susceptibility testing results are not available or indicate resistance, vancomycin should be used in this situation.

Treatment of all pregnant women who are colonized or have risk factors for neonatal infection will result in exposure of up to one-third of pregnant women and newborns to antibiotics, with the attendant risks of allergic reactions and selection for resistant organisms. Although still in the developmental stages, a GBS vaccine may ultimately offer a better solution to prevention. Because transplacental passage of maternal antibodies produces protective antibody levels in newborns, efforts are under way to develop a vaccine against GBS that can be given to childbearing-age women before or during pregnancy. Results of phase 1 clinical trials of GBS capsular polysaccharide–protein conjugate vaccines suggest that a multivalent conjugate vaccine would be safe and highly immunogenic.

INFECTION IN ADULTS

The majority of GBS infections in otherwise healthy adults are related to pregnancy and parturition. Peripartum fever, the most common manifestation, is sometimes accompanied by symptoms and signs of endometritis or chorioamnionitis (abdominal distention and uterine or adnexal tenderness). Blood and vaginal swab cultures are often positive. Bacteremia is usually transitory but occasionally results in meningitis or endocarditis. Infections in adults that are not associated with the peripartum period generally involve individuals who are elderly or have an underlying chronic illness, such as diabetes mellitus or a malignancy. Among the infections that develop with some frequency in adults are cellulitis and soft tissue infection (including infected diabetic skin ulcers), urinary tract infection, pneumonia, endocarditis, and septic arthritis. Other reported infections include meningitis, osteomyelitis, and intraabdominal or pelvic abscesses. Relapse or recurrence of invasive infection weeks to months after a first episode is documented in ~4% of cases.

TREATMENT **Group B Streptococcal Infection in Adults**

GBS is less sensitive to penicillin than GAS, requiring somewhat higher doses. Adults with serious localized infections (pneumonia, pyelonephritis, abscess) should receive doses of ~12 million units of penicillin G daily; patients with endocarditis or meningitis should receive 18–24 million units per day in divided doses. Vancomycin is an acceptable alternative for penicillin-allergic patients.

NONENTEROCOCCAL GROUP D STREPTOCOCCI

The main nonenterococcal group D streptococci that cause human infections belong to several species previously considered a single species, *S. bovis*. The organisms encompassed by *S. bovis* have recently been subdivided into four species: *S. gallolyticus, S. pasteurianus, S. infantarius,* and *S. lutetiensis*. *S. bovis* endocarditis is often associated with neoplasms of the gastrointestinal tract—most frequently, a colon carcinoma or polyp—but is also reported in association with other bowel lesions. When occult gastrointestinal lesions are carefully sought, abnormalities are found in >60% of patients with *S. bovis* endocarditis. In contrast to the enterococci, nonenterococcal group D streptococci like *S. bovis* are reliably killed by penicillin as a single agent, and penicillin is the agent of choice for *S. bovis* infections.

VIRIDANS AND OTHER STREPTOCOCCI

VIRIDANS STREPTOCOCCI

Consisting of multiple species of α-hemolytic streptococci, the viridans streptococci are a heterogeneous group of organisms that are important agents of bacterial endocarditis (Chap. 20). Several species of viridans streptococci, including *S. salivarius*, *S. mitis*, *S. sanguis*, and *S. mutans*, are part of the normal flora of the mouth, where they live in close association with the teeth and gingiva. Some species contribute to the development of dental caries.

Previously known as *S. morbillorum*, *Gemella morbillorum* has been placed in a separate genus, along with *G. haemolysans*, on the basis of genetic-relatedness studies. These species resemble viridans streptococci with respect to habitat in the human host and associated infections.

The transient viridans streptococcal bacteremia induced by eating, tooth-brushing, flossing, and other sources of minor trauma, together with adherence to biologic

surfaces, is thought to account for the predilection of these organisms to cause endocarditis (see Fig. 20-1). Viridans streptococci are also isolated, often as part of a mixed flora, from sites of sinusitis, brain abscess, and liver abscess.

Viridans streptococcal bacteremia occurs relatively frequently in neutropenic patients, particularly after bone marrow transplantation or high-dose chemotherapy for cancer. Some of these patients develop a sepsis syndrome with high fever and shock. Risk factors for viridans streptococcal bacteremia include chemotherapy with high-dose cytosine arabinoside, prior treatment with trimethoprim-sulfamethoxazole or a fluoroquinolone, treatment with antacids or histamine antagonists, mucositis, and profound neutropenia.

The *S. milleri* group (also referred to as the *S. intermedius* or *S. anginosus* group) includes three species that cause human disease: *S. intermedius*, *S. anginosus*, and *S. constellatus*. These organisms are often considered viridans streptococci, although they differ somewhat from other viridans streptococci in both their hemolytic pattern (they may be α-, β-, or nonhemolytic) and the disease syndromes they cause. This group commonly produces suppurative infections, particularly abscesses of brain and abdominal viscera, and infections related to the oral cavity or respiratory tract, such as peritonsillar abscess, lung abscess, and empyema.

TREATMENT **Infection with Viridans Streptococci**

Isolates from neutropenic patients with bacteremia are often resistant to penicillin; thus, these patients should be treated presumptively with vancomycin until the results of susceptibility testing become available. Viridans streptococci isolated in other clinical settings usually are sensitive to penicillin.

ABIOTROPHIA AND *GRANULICATELLA* SPECIES (NUTRITIONALLY VARIANT STREPTOCOCCI)

Occasional isolates cultured from the blood of patients with endocarditis fail to grow when subcultured on solid media. These *nutritionally variant streptococci* require supplemental thiol compounds or active forms of vitamin B_6 (pyridoxal or pyridoxamine) for growth in the laboratory. The nutritionally variant streptococci are generally grouped with the viridans streptococci because they cause similar types of infections. However, they have been reclassified on the basis of 16S ribosomal RNA sequence comparisons into two separate genera: *Abiotrophia*, with a single species (*A. defectivus*), and *Granulicatella,* with three species associated with human infection (*G. adjacens, G. paraadjacens,* and *G. elegans*).

TREATMENT **Infection with Nutritionally Variant Streptococci**

Treatment failure and relapse appear to be more common in cases of endocarditis due to nutritionally variant streptococci than in those due to the usual viridans streptococci. Thus, the addition of gentamicin (1 mg/kg every 8 h for patients with normal renal function) to the penicillin regimen is recommended for endocarditis due to the nutritionally variant organisms.

OTHER STREPTOCOCCI

S. suis is an important pathogen in swine and has been reported to cause meningitis in humans, usually in individuals with occupational exposure to pigs. Strains of *S. suis* associated with human infections have generally reacted with Lancefield group R typing serum and sometimes with group D typing serum as well. Isolates may be α- or β-hemolytic and are sensitive to penicillin. *S. iniae*, a pathogen of fish, has been associated with infections in humans who have handled live or freshly killed fish. Cellulitis of the hand is the most common form of human infection, although bacteremia and endocarditis have been reported. *Anaerobic streptococci*, or *peptostreptococci*, are part of the normal flora of the oral cavity, bowel, and vagina. Infections caused by the anaerobic streptococci are discussed in Chap. 69.

CHAPTER 40

ENTEROCOCCAL INFECTIONS

Cesar A. Arias ■ Barbara E. Murray

Enterococci have been recognized as potential human pathogens for more than a century, but only in recent years have these organisms acquired prominence as causes of nosocomial infections. The ability of enterococci to survive and/or disseminate in the hospital environment and to acquire antibiotic resistance determinants makes the treatment of some enterococcal infections in critically ill patients a difficult challenge. Enterococci were first mentioned in the French literature in 1899; the "entérocoque" was found in the human gastrointestinal tract and was noted to have the potential to produce significant disease. Indeed, the first pathologic description of an enterococcal infection dates to the same year. A clinical isolate recovered from a patient who died as a consequence of endocarditis was initially designated *Micrococcus zymogenes*, was later named *Streptococcus faecalis* subspecies *zymogenes*, and would now be classified as *Enterococcus faecalis*. The ability of this isolate to cause severe disease in both rabbits and mice illustrated its potential lethality in the appropriate settings.

ETIOLOGY

Enterococci are gram-positive organisms. In clinical specimens, they are usually observed as single cells, diplococci, or short chains **(Fig. 40-1)**, although long chains are noted with some strains. Enterococci were originally classified as streptococci because organisms of the two genera share many morphologic and phenotypic characteristics, including a generally negative catalase reaction. Only DNA hybridization studies and then 16S rRNA sequencing clearly demonstrated that enterococci should be grouped as a genus distinct from the streptococci. Nonetheless, unlike the majority of streptococci, enterococci hydrolyze esculin in the presence of 40% bile salts and grow at high salt concentrations (6.5%) and at high temperatures (46°C). Enterococci are usually reported by the clinical laboratory to be nonhemolytic on the basis of their inability to lyse the ovine or bovine red blood cells (RBCs) commonly used in agar plates; however, some strains of *E. faecalis* do lyse RBCs from humans, horses, and rabbits. The majority of clinically relevant enterococcal species hydrolyze pyrrolidonyl-β-naphthylamide (PYR); this characteristic is helpful in differentiating enterococci from organisms of the *Streptococcus bovis* group (*S. gallolyticus* subsp. *gallolyticus*, *S. gallolyticus* subsp. *pasteurianus*, and *S. infantarius* subsp. *coli*) and from *Leuconostoc* species. Although at least 18 species of enterococci have been isolated from human infections, the overwhelming majority of cases are caused by two species: *E. faecalis* and *E. faecium*. Less frequently isolated species include *E. gallinarum*, *E. durans*, *E. hirae*, and *E. avium*.

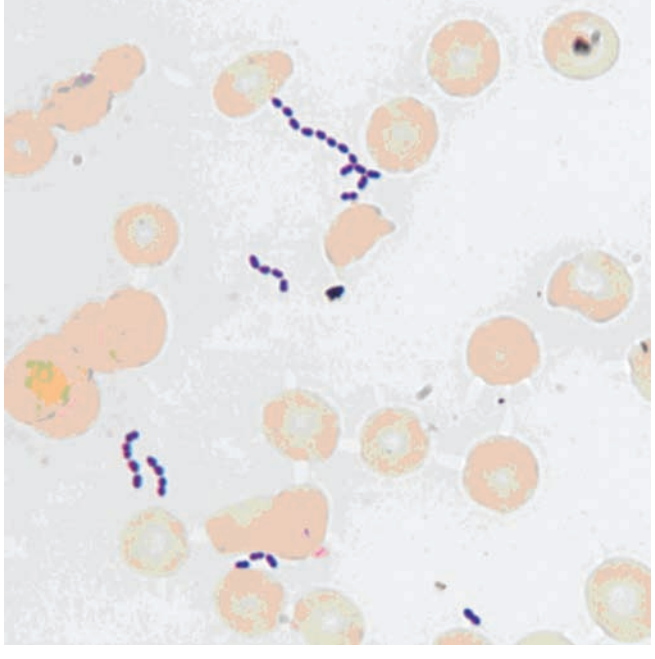


FIGURE 40-1
Gram's stain of cultured blood from a patient with enterococcal bacteremia. Oval gram-positive bacterial cells are arranged as diplococci and short chains. (*Courtesy of Audrey Wanger, PhD.*)

PATHOGENESIS

Enterococci are normal inhabitants of the large bowel of human adults, although they usually make up <1% of the culturable intestinal microflora. In the healthy human gastrointestinal tract, enterococci are typically symbionts that coexist with other bacteria; in fact, the utility of certain enterococcal strains as probiotics in the treatment of diarrhea suggests their possible role in maintaining the homeostatic equilibrium of the human bowel. Enterococci are intrinsically resistant to a variety of commonly used antibiotics; thus one of the most important factors that disrupts this equilibrium and promotes increased gastrointestinal colonization by enterococci is the administration of antimicrobial agents. In particular, antibiotics that are excreted in the bile and have broad-spectrum activity (i.e., certain cephalosporins that target anaerobes and gram-negative bacteria) are associated with the recovery of higher numbers of enterococci from feces. This increased colonization appears to be due not only to simple enterococcal replacement in a given "biological niche" after the eradication of competing components of the flora, but also (at least in mice) to the suppression—upon reduction of the gram-negative microflora by antibiotics—of important immunologic signals (e.g., the lectin RegIIIγ) that help keep enterococcal counts low in the normal human bowel. Several studies have shown that higher levels of gastrointestinal colonization are a critical factor in the pathogenesis of enterococcal infections. However, the mechanisms by which enterococci successfully colonize the bowel and gain access to the lymphatics and/or bloodstream remain incompletely understood.

Several vertebrate, worm, and insect models have been developed to study the role of possible pathogenic determinants of both *E. faecalis* and *E. faecium*. Three main groups of factors may increase the ability of enterococci to colonize the gastrointestinal tract and/or cause disease. The first group, *enterococcal secreted factors*, are molecules released outside the bacterial cell that contribute to the process of infection; the best-studied of these molecules include enterococcal hemolysin/cytolysin and two enterococcal proteases (gelatinase and serine protease). Enterococcal cytolysin is a heterodimeric toxin produced by some strains of *E. faecalis* that is capable of lysing human RBCs as well as polymorphonuclear leukocytes and macrophages. The *E. faecalis* proteases GelE and SprE are thought to mediate virulence by several mechanisms, including the degradation of host tissues and the modification of critical components of the immune system. Mutants lacking the genes corresponding to these proteins are highly attenuated in experimental peritonitis, endocarditis, and endophthalmitis.

The second group of virulence factors, *enterococcal surface components* (e.g., adhesins), are thought to contribute to bacterial attachment to extracellular matrix molecules in the human host. Several molecules on the surface of enterococci have been characterized and shown to play a role in the pathogenesis of enterococcal infections. Among the characterized adhesins is aggregation substance of *E. faecalis*, which mediates the attachment of cells to each other, thereby facilitating conjugative plasmid exchange. Several lines of evidence indicate that aggregation substance and enterococcal cytolysin act synergistically to increase the virulence potential of *E. faecalis* strains in experimental endocarditis. The *E. faecalis* surface protein (adhesin of collagen of *E. faecalis*, or Ace) and its *E. faecium* homologue (Acm) are microbial surface components recognizing adhesive matrix molecules (MSCRAMMs) involved in bacterial attachment to host proteins such as collagen, fibronectin, and fibrinogen; both Ace and Acm are important in the pathogenesis of experimental endocarditis. Pili of gram-positive bacteria have been shown to be important mediators of attachment to and invasion of host tissues and are considered potential targets for immunotherapy. Both *E. faecalis* and *E. faecium* have surface pili. Mutants of *E. faecalis* lacking pili are attenuated in both experimental endocarditis and urinary tract infections (UTIs). Other surface proteins that share structural homology with MSCRAMMs and appear to play a role in enterococcal attachment to the host and in virulence include the *E. faecalis* enterococcal surface protein (Esp) and its *E. faecium* homologue (Esp_{fm}), the second collagen adhesin of *E. faecium* (Scm), the surface proteins of *E. faecium* (Fms), SgrA (which binds to components of the basal lamina), and EcbA (which binds to collagen type V). Additional surface components apparently associated with pathogenicity include polysaccharides, which are thought to interfere with phagocytosis of the organism by host immune cells. Some *E. faecalis* strains appear to harbor at least three distinct classes of capsular polysaccharide; some of these polysaccharides play a role in virulence and are potential targets for immunotherapy.

The third group of virulence factors have not been well characterized: the *E. faecalis* stress protein Gls24, which has been associated with enterococcal resistance to bile salts and appears to be important in the pathogenesis of endocarditis, and the hyl_{Efm}-containing plasmids of *E. faecium*, which are transferable between strains and increase colonization by *E. faecium*. In a mouse model of peritonitis, acquisition of these plasmids augmented the lethality of a commensal strain of *E. faecium*.

The sequencing of bacterial genomes has increased our understanding of bacterial diversity, evolution, pathogenesis, and antibiotic resistance mechanisms. The genome sequences of >80 enterococcal strains are currently available, and some have been entirely closed and annotated. Sequence analysis has shown that the genetic diversity of enterococci is due mainly to the acquisition of mobile DNA (e.g., plasmids, transposons, and phages) and the recombination of "core" genomes. Furthermore, analysis of *E. faecium* indicates that this species harbors a malleable genome

(the *accessory* genome) into which exogenous elements (including DNA from phages) are incorporated at substantial levels. This genomic information has provided new clues about enterococcal evolution from a commensal organism into an important nosocomial pathogen.

EPIDEMIOLOGY

According to the National Healthcare Safety Network of the Centers for Disease Control and Prevention, enterococci are the second most common organisms (after staphylococci) isolated from hospital-associated infections in the United States. Although *E. faecalis* remains the predominant species recovered from nosocomial infections, the isolation of *E. faecium* has increased substantially in the past 10–15 years. In fact, *E. faecium* is now almost as common as *E. faecalis* as an etiologic agent of hospital-associated infections. This point is important, since *E. faecium* is by far the most resistant and challenging enterococcal species to treat; indeed, >80% of *E. faecium* isolates recovered in U.S. hospitals are resistant to vancomycin, and >90% are resistant to ampicillin (historically the most effective β-lactam drug against enterococci). Resistance to vancomycin and ampicillin in *E. faecalis* isolates is much less common (~7% and ~4%, respectively).

The dynamics of enterococcal transmission and dissemination in the hospital environment have been extensively studied, with a focus on vancomycin-resistant enterococci (VRE). These studies have revealed that VRE colonization of the gastrointestinal tract is a critical step in the natural history of enterococcal disease and that a substantial proportion of patients colonized with VRE remain colonized for prolonged periods (sometimes >1 year) and are more likely to develop an *Enterococcus*-related illness (e.g., bacteremia) than are patients colonized with antibiotic-susceptible strains. The most important factors associated with VRE colonization and persistence in the gut include prolonged hospitalization; long courses of antibiotic therapy; hospitalization in long-term-care facilities, surgical units, and/or intensive care units; organ transplantation; renal failure (particularly in patients undergoing hemodialysis) and/or diabetes; high APACHE scores; and physical proximity to patients infected or colonized with VRE or to these patients' rooms. Once a patient becomes colonized with VRE, several key factors are involved in the organisms' dissemination in the hospital environment. VRE can survive exposure to heat and certain disinfectants and have been found on numerous inanimate objects in the hospital, including bed rails, medical equipment, doorknobs, gloves, telephones, and computer keyboards. Thus health care workers play a pivotal role in enterococcal transmission from patient to patient, and infection control measures are crucial in breaking the chain of transmission. Moreover, two meta-analyses have found that VRE infection increases the risk of death, independent of the patient's clinical status, over that among individuals infected with a glycopeptide-susceptible enterococcal strain.

The epidemiology of enterococcal disease and the emergence of VRE have followed somewhat different trends in other parts of the world than in the United States. In Europe, the emergence of VRE in the mid-1980s was seen primarily in isolates recovered from animals and healthy humans rather than from hospitalized patients. The presence of VRE was associated with the use of the glycopeptide avoparcin as a growth promoter in animal feeds; this association prompted the European Union to ban the use of this compound in animal husbandry in 1996. However, after an initial decrease in the isolation of VRE from animals and humans, the prevalence of hospital-associated VRE infections has slowly increased in some European countries, with important regional differences. For example, rates of vancomycin resistance among *E. faecium* clinical isolates in Europe are highest in Greece, the United Kingdom, and Portugal (10–30%), whereas rates in Scandinavian countries and the Netherlands are <1%. These regional differences have been attributed in part to the implementation of aggressive policies of infection control in countries such as the Netherlands; these policies have kept the frequency of nosocomial methicillin-resistant *Staphylococcus aureus* (MRSA) and VRE very low. In spite of regional differences, rates of VRE continue to be much lower in most of Europe than in the United States. The reasons are not totally understood, although it has been postulated that the difference is related to the higher levels of human antibiotic use in the United States. Rates of enterococcal resistance to vancomycin in some Latin American countries are also lower (~4%) than those in the United States. Conversely, in Asia, rates of vancomycin resistance among enterococci appear to be similar to those in U.S. hospitals. Genetic analyses of vancomycin-resistant *E. faecium* in different parts of the world suggest that the nosocomial emergence and dissemination of these organisms globally are related to the success of unique clonal lineages (e.g., clonal cluster 17, or CC17) that were initially characterized by resistance to ampicillin and later acquired the genes responsible for resistance to vancomycin.

CLINICAL SYNDROMES

URINARY TRACT INFECTIONS AND PROSTATITIS

Enterococci are well-known agents of nosocomial UTI, the most common infection caused by these organisms (Chap. 28). Enterococcal UTIs are usually associated with indwelling catheterization, instrumentation, or anatomic abnormalities of the genitourinary tract, and it is often challenging to differentiate between true infection and colonization (particularly in patients with chronic indwelling catheters). The presence of leukocytes

in the urine in conjunction with systemic manifestations (e.g., fever) or local signs and symptoms of infection with no other explanation and a positive urine culture (>10^5 CFU) suggests the diagnosis. Moreover, enterococcal UTIs often occur in critically ill patients whose comorbidities may obscure the diagnosis. In many cases, removal of the indwelling catheter may suffice without specific antimicrobial therapy. In rare circumstances, UTIs caused by enterococci may run a complicated course, with the development of pyelonephritis and perinephric abscesses that may be a portal of entry for bloodstream infections (see below). Enterococci are also known causes of chronic prostatitis, particularly in patients in whom the urinary tract has been manipulated surgically or endoscopically. These infections can be difficult to treat since the agents most potent against enterococci (i.e., aminopenicillins and glycopeptides) penetrate prostatic tissue poorly. Chronic prostatic infection can be a source of recurrent enterococcal bacteremia.

BACTEREMIA AND ENDOCARDITIS

Bacteremia without endocarditis is one of the most common presentations of enterococcal disease. Intravascular catheters and other devices are commonly associated with these bacteremic episodes (Chap. 14). Other well-known sources of enterococcal bacteremia include the gastrointestinal and hepatobiliary tracts; pelvic and intraabdominal foci; and (less frequently) wound infections, UTIs, and bone infections. In the United States, enterococci rank second (after coagulase-negative staphylococci) as etiologic agents of central line–associated bacteremia. Patients with enterococcal bacteremia usually have comorbidities, have been in the hospital for prolonged periods, and/or have received several courses of antibiotics. Several studies indicate that the presence of *E. faecium* (as opposed to other enterococcal species) in the bloodstream may lead to worse outcomes and increased mortality rates; this finding may be related to the higher prevalence of vancomycin and ampicillin resistance in *E. faecium*, with the consequent reduction of therapeutic options. In many cases (usually when the gastrointestinal tract is the source), enterococcal bacteremia may be polymicrobial, with gram-negative organisms isolated at the same time. In addition, several cases have now been documented in which enterococcal bacteremia was associated with *Strongyloides stercoralis* hyperinfection syndrome in immunocompromised patients.

Enterococci are important causes of community- and health care–associated endocarditis, ranking second after staphylococci in the latter infections (Chap. 20). The presumed initial source of bacteremia leading to endocarditis is the gastrointestinal or genitourinary tract—e.g., in patients who have malignant and inflammatory conditions of the gut or have undergone procedures in which these tracts are manipulated. The affected patients tend to be male and elderly and to have other debilitating diseases and heart conditions. Both prosthetic and native valves can be involved; mitral and aortic valves are affected most often. Community-associated endocarditis (usually caused by *E. faecalis*) also occurs in patients with no apparent risk factors or cardiac abnormalities. Endocarditis in women of childbearing age has been well described. The typical presentation of enterococcal endocarditis is a subacute course with fever, weight loss, malaise, and a cardiac murmur; typical stigmata of endocarditis (e.g., petechiae, Osler's nodes, Roth's spots) are found in only a minority of patients. Some atypical manifestations include arthralgias and signs and symptoms of metastatic disease (splenic abscesses, hiccups, pain in the left flank, pleural effusion, and spondylodiscitis). Embolic complications are variable and can affect the brain. Heart failure is a common complication of enterococcal endocarditis, and valve replacement may be critical in curing this infection, particularly when multidrug-resistant organisms or major complications are involved. The duration of therapy is usually 4–6 weeks, with more prolonged courses suggested for multidrug-resistant isolates in the absence of valvular replacement or with prolonged illness prior to treatment.

MENINGITIS

Enterococcal meningitis is an uncommon disease (accounting for only ~4% of meningitis cases) that is often associated with neurosurgical interventions and conditions such as shunts, central nervous system (CNS) trauma, and cerebrospinal fluid (CSF) leakage (Chap. 31). In some instances—usually in patients with a debilitating condition such as cardiovascular or congenital heart disease, chronic renal failure, malignancy, receipt of immunosuppressive therapy, or HIV/AIDS—presumed hematogenous seeding of the meninges is seen in infections such as endocarditis or bacteremia. Fever and changes in mental status are common, whereas overt meningeal signs are less so. CSF findings are consistent with bacterial infection—i.e., pleocytosis with a predominance of polymorphonuclear leukocytes (average, ~500/μL), an elevated protein level (usually >100 mg/dL), and a decreased glucose concentration (average, 28 mg/dL). Gram's staining yields a positive result in about half of cases, with a high rate of organism recovery from CSF cultures; the most common species isolated are *E. faecalis* and *E. faecium*. Complications include hydrocephalus, brain abscesses, and stroke; an association with *Strongyloides* hyperinfection has also been documented.

INTRAABDOMINAL, PELVIC, AND SOFT TISSUE INFECTIONS

As mentioned earlier, enterococci are part of the commensal flora of the gastrointestinal tract and can produce spontaneous peritonitis in cirrhotic individuals and in patients undergoing chronic ambulatory peritoneal dialysis (Chap. 25). These organisms are commonly found (usually along with other bacteria, including enteric gram-negative species and anaerobes) in clinical samples from intraabdominal and pelvic collections. The presence of enterococci in intraabdominal infections is

sometimes considered to be of low clinical relevance. Several studies have shown that the role of enterococci in intraabdominal infections originating in the community and involving previously healthy patients is minor, since surgery and broad-spectrum antimicrobial drugs that do not target enterococci are often sufficient in managing these infections successfully. In the last few decades, however, these organisms have become prominent as a cause of intraabdominal infections in hospitalized patients because of the emergence and spread of vancomycin resistance among enterococci and the increase in rates of nosocomial infections due to multidrug-resistant *E. faecium* isolates. In fact, several studies have now documented treatment failures due to enterococci, with consequently increased rates of postoperative complications and death in intraabdominal infections. Thus, anti-enterococcal therapy is recommended for nosocomial peritonitis in immunocompromised or severely ill patients who have had a prolonged hospital stay, have undergone multiple procedures, have persistent abdominal sepsis and collections, or have risk factors for the development of endocarditis (i.e., prosthetic or damaged heart valves). Conversely, treatment for enterococci in the first episode of intraabdominal infections originating in the community and affecting previously healthy patients with no important cardiac risk factors for endocarditis does not appear to be beneficial.

Enterococci are commonly isolated from soft tissue infections (Chap. 22), particularly those involving surgical wounds (Chap. 14). In fact, these organisms rank third as agents of nosocomial surgical-site infection, with *E. faecalis* the most frequently isolated species. The clinical relevance of enterococci in some of these infections—as in intraabdominal infections—is a matter of debate; differentiating between colonization and true infection can be challenging, although in some cases enterococci have been recovered from lung, liver, and skin abscesses. Diabetic foot and decubitus ulcers are often colonized with enterococci and may be the portal of entry for bone infections.

OTHER INFECTIONS

Enterococci are well-known causes of neonatal infections including sepsis (mostly late-onset), bacteremia, meningitis, pneumonia, and UTI. Outbreaks of enterococcal sepsis in neonatal units have been well documented. Risk factors for enterococcal disease in newborns include prematurity, low birth weight, indwelling devices, and abdominal surgery. Enterococci have also been described as etiologic agents of bone and joint infections including vertebral osteomyelitis, usually in patients with underlying conditions such as diabetes or endocarditis. Similarly, enterococci have been isolated from bone infections in patients who have undergone arthroplasty or reconstruction of fractures with the placement of hardware. Since enterococci can produce a biofilm that is likely to alter the efficacy of otherwise active anti-enterococcal agents, treatment of infections that involve foreign material is challenging, and removal of the hardware may be necessary to eradicate the infection. Rare cases of enterococcal pneumonia, lung abscess, and spontaneous empyema have been reported.

TREATMENT Enterococcal Infections

GENERAL PRINCIPLES Enterococci are intrinsically resistant and/or tolerant to several antimicrobial agents [with *tolerance* defined as lack of killing by drug concentrations 16 times higher than the minimal inhibitory concentration (MIC)]. Monotherapy for endocarditis with a β-lactam antibiotic (to which many enterococci are tolerant) has produced disappointing results, with low cure rates at the end of therapy. However, the addition of an aminoglycoside to a cell wall–active agent (a β-lactam or a glycopeptide) increases cure rates and eradicates the organisms; moreover, this combination is synergistic and bactericidal in vitro. Therefore, combination therapy with a cell wall–active agent and an aminoglycoside is the standard of care for endovascular infections caused by enterococci. This synergistic effect can be explained, at least in part, by the increased penetration of the aminoglycoside into the bacterial cell, presumably as a result of cell wall alterations attributable to the β-lactam or glycopeptide. Nonetheless, attaining synergistic bactericidal activity in the treatment of severe enterococcal infections has become increasingly difficult because of the development of resistance to virtually all antibiotics available for this purpose.

The treatment of *E. faecalis* differs substantially from that of *E. faecium* (Tables 40-1 and 40-2), mainly because of differences in resistance profiles (see below); for example, resistance to ampicillin and vancomycin is rare in *E. faecalis*, whereas these antibiotics are only infrequently useful against current isolates of *E. faecium*. Moreover, as a consequence of the challenges and therapeutic limitations posed by the emergence of drug resistance, valve replacement may need to be considered in the treatment of endocarditis caused by multidrug-resistant enterococci. Less severe infections are often related to indwelling intravascular catheters; removal of the catheter increases the likelihood of enterococcal eradication of the organism by a short course of appropriate antimicrobial therapy.

CHOICE OF ANTIMICROBIAL AGENTS Among the β-lactam agents, the most active are the aminopenicillins (ampicillin, amoxicillin) and ureidopenicillins (i.e., piperacillins); next most active are penicillin G and imipenem. Against *E. faecium*, a combination of high-dose ampicillin (up to 30 g/d) and an aminoglycoside (Table 40-2) has been suggested even for ampicillin-resistant strains if the MIC is <64 μg/mL, since a plasma ampicillin concentration of >100 μg/mL can be achieved at high doses. The only two aminoglycosides recommended for synergistic therapy in severe enterococcal infections are gentamicin and streptomycin. The use of amikacin is discouraged, tobramycin should never be used against *E. faecium*, and aminoglycoside

TABLE 40-1

SUGGESTED REGIMENS FOR THE MANAGEMENT OF INFECTIONS CAUSED BY *ENTEROCOCCUS FAECALIS*

CLINICAL SYNDROME	AMPICILLIN OR PENICILLIN[a]	HIGH-LEVEL RESISTANCE TO AMINOGLYCOSIDES[b]	SUGGESTED THERAPEUTIC OPTIONS[c]
Endovascular infections (includes endocarditis)	Susceptible	No	Ampicillin (12 g/d IV in divided doses q4h or by continuous infusion) *or* penicillin (18–30 million units/d IV in divided doses q4h or by continuous infusion) ***plus*** an aminoglycoside[d] Vancomycin (15–20 mg/kg per dose q8–12h, not to exceed 2 g per dose)[e] ***plus*** an aminoglycoside[d]
	Susceptible	Yes	Ampicillin (12 g/d IV in divided doses q4h) ***plus*** ceftriaxone (2 g q12h) *or* cefotaxime High-dose daptomycin[f] ± another active agent[g] Vancomycin (15–20 mg/kg per dose q8–12h, not to exceed 2 g per dose)[e] Ampicillin ***plus*** imipenem
Nonendovascular bacteremia[h]	Susceptible	No	Ampicillin (12 g/d IV in divided doses q4h) *or* penicillin (18 mU/d IV in divided doses q4h)[i] Vancomycin (15–20 mg/kg per dose q8–12h, not to exceed 2 g per dose)[e,i]
	Susceptible	Yes	Ampicillin[j] (12 g/d IV in divided doses q4h) *or* penicillin Vancomycin (15–20 mg/kg per dose q8–12 h, not to exceed 2 g per dose)[e] High-dose daptomycin[f]
Meningitis	Susceptible	No	Ampicillin (20–24 g/d IV in divided doses q4h) *or* penicillin (24 mU/d IV in divided doses q4h) ***plus*** an aminoglycoside[k] Vancomycin (500–750 mg IV q6h)[e] ***plus*** an aminoglycoside[k] Linezolid
	Susceptible	Yes	Ampicillin (20–24 g/d IV in divided doses q4h) *or* penicillin (24 mU/d IV in divided doses q4h) ***plus*** ceftriaxone (2 g q12h) *or* cefotaxime Vancomycin (500–750 mg IV q6h)[e] Linezolid High-dose daptomycin[f] (***plus*** intrathecal daptomycin) ± another active agent[g]
Urinary tract infections (uncomplicated)	Not applicable	Not applicable	Ampicillin (500 mg IV or PO q6h) Nitrofurantoin (100 mg PO q6h) Fosfomycin (3-g single dose PO)[l]

[a]In rare cases, β-lactamase-producing isolates may be found. Because these isolates are not detected by conventional MIC determination, additional tests (e.g., the nitrocefin disk test) are recommended for isolates from endocarditis. The use of ampicillin/sulbactam (12–24 g/d) is suggested in these cases.

[b]Determined by the clinical microbiology laboratory only for gentamicin or streptomycin as growth of enterococci in brain-heart infusion agar containing gentamicin (500 μg/mL) and streptomycin (2000 μg/mL). Resistance to one compound does not indicate resistance to the other, and the laboratory reports high-level resistance to each compound individually. In this table, *Yes* to high-level resistance to aminoglycosides indicates that the laboratory has reported resistance to synergism with both gentamicin and streptomycin.

[c]Author's first-choice regimen is underlined for each category.

[d]Gentamicin (1–1.5 mg/kg IV q8h) or streptomycin (15 mg/kg per day IV or IM in two divided doses).

[e]Vancomycin is recommended only as an alternative to β-lactam agents in case of allergy, toxicity, or inability to desensitize. Monitoring of vancomycin levels is recommended, although no data for enterococci are available; a regimen that achieves trough serum levels of 15–20 μg/mL is suggested by some experts, although high doses may predispose to renal toxicity. CSF concentrations may also be determined. Vancomycin-resistant strains of *E. faecalis* have been reported.

[f]Consider doses of 8–12 mg/kg per day (off-label use).

[g]Active agents may include ampicillin, a fluoroquinolone (which, if the isolate is susceptible, may be favored in meningitis), and tigecycline.

[h]In selected cases of catheter-associated bacteremia, removal of the catheter and a short course of therapy (~5–7 days) may be sufficient. A single positive blood culture that is likely to be associated with a catheter in a patient who is otherwise doing well may not require therapy after removal of the catheter.

[i]The addition of an aminoglycoside may be considered in severe infections.

[j]The addition of ceftriaxone (or cefotaxime) may be considered in severe infections.

[k]The addition of intrathecal or intraventricular therapy with gentamicin (2–10 mg/d) or vancomycin (10–20 mg/d), when the isolate is susceptible, has been suggested by some authorities for recalcitrant cases.

[l]Approved by the FDA only for uncomplicated urinary tract infections caused by vancomycin-susceptible *E. faecalis*.

TABLE 40-2

SUGGESTED REGIMENS FOR THE MANAGEMENT OF INFECTIONS CAUSED BY VANCOMYCIN-RESISTANT *ENTEROCOCCUS FAECIUM*

CLINICAL SYNDROME	AMPICILLIN MIC (μg/mL)	HIGH-LEVEL RESISTANCE TO AMINOGLYCOSIDES[a]	SUGGESTED THERAPEUTIC OPTIONS[b]
Endovascular infections (includes endocarditis)	≤64	No	High-dose ampicillin[c] ***plus*** an aminoglycoside[d] See regimens for MIC >64 μg/mL
	>64	No	High-dose daptomycin[e] ***plus*** an aminoglycoside[d] ± another active agent[f] Q/D[g] (22.5 mg/kg per day in divided doses q8h) ± another active agent[f] Linezolid[g] (600 mg IV q12h) ± another active agent[f]
	≤64	Yes	High-dose ampicillin[c] ***plus*** high-dose daptomycin[e] Q/D[g] (22.5 mg/kg per day in divided doses q8h) ***plus*** high-dose ampicillin[c] *or* doxycycline (100 mg IV q12h) with rifampin (300 mg PO q12h, if susceptible) High-dose ampicillin[c] ***plus*** imipenem-cilastatin (500 mg IV q6h)[h]
	>64	Yes	High-dose daptomycin[e] ***plus*** another active agent[f] Q/D[g] (22.5 mg/kg per day in divided doses q8h) ***plus*** doxycycline (100 mg IV q12h) with rifampin (300 mg PO q12h, if susceptible) Linezolid[g] (600 mg IV q12h) ± another active agent[f]
Non-endovascular bacteremia[i]	≤64	No	High-dose ampicillin[c] ± an aminoglycoside[d]
	>64	No	Q/D[g] ± another active agent[f] Daptomycin[e] ± an aminoglycoside[d] Linezolid[g] ± another active agent[f]
	≤64	Yes	High-dose ampicillin[c] ± Q/D[g] (22.5 mg/kg per day in divided doses q8h) High-dose ampicillin[c] ± daptomycin[e] Linezolid[g] (600 mg IV q12h) ± another active agent[f]
	>64	Yes	Q/D[g] (22.5 mg/kg per day in divided doses q8h) ± another active agent[f] Daptomycin[e] ± another active agent[f] Linezolid[g] (600 mg IV q12h) ± another active agent[f]
Meningitis[j]	<16	No	High-dose ampicillin[c] ***plus*** gentamicin (5.1–7 mg/kg, single daily dose) *or* streptomycin (15 mg/kg, single daily dose)
	≥16	No	Linezolid ± another CSF-penetrating active agent[k] High-dose daptomycin[e] (plus intrathecal daptomycin[j]) ***plus*** gentamicin (5.1–7 mg/kg, single daily dose)[j] ± another CSF-penetrating active agent[k]
	<16	Yes	High-dose ampicillin[c] ***plus*** high-dose daptomycin[e] (plus intrathecal daptomycin)[j] Linezolid ± another CSF-penetrating active agent[k] Q/D[j] (22.5 mg/kg per day in divided doses q8h) ***plus*** intrathecal Q/D ***plus*** high-dose ampicillin[c]
	≥16	Yes	Linezolid ± another CSF-penetrating active agent[k] High-dose daptomycin[e] ± another CSF-penetrating active agent[k] Q/D[j] (22.5 mg/kg per (plus intrathecal daptomycin) in divided doses q8h) ***plus*** intrathecal Q/D ± another CSF-penetrating active agent[k]

(*continued*)

TABLE 40-2

SUGGESTED REGIMENS FOR THE MANAGEMENT OF INFECTIONS CAUSED BY VANCOMYCIN-RESISTANT *ENTEROCOCCUS FAECIUM* (*CONTINUED*)

CLINICAL SYNDROME	AMPICILLIN MIC (μg/mL)	HIGH-LEVEL RESISTANCE TO AMINOGLYCOSIDES[a]	SUGGESTED THERAPEUTIC OPTIONS[b]
Urinary tract infections	<512	Not applicable	Nitrofurantoin (100 mg PO q6h) Fosfomycin (3 g PO, one dose)[l] Ampicillin or amoxicillin (2 g IV or PO q4–6h)[m]

[a]*Yes* to high-level resistance to aminoglycosides indicates resistance to both gentamicin and streptomycin (the only two aminoglycosides recommended for the treatment of enterococcal infections). Resistance to one compound does not indicate resistance to the other.
[b]Author's first-choice regimen(s) are underlined for each category.
[c]Doses up to 30 g/d IV in divided doses q4h may be considered; clinical data on safety at these high doses are not available.
[d]Gentamicin (1–1.5 mg/kg IV q8h) or streptomycin (15 mg/kg per day IV or IM in two divided doses).
[e]Daptomycin at a dosage of 8–12 mg/kg once daily is suggested (off-label); close monitoring of creatine phosphokinase levels is recommended throughout therapy because of possible rhabdomyolysis.
[f]Agents with potential activity include doxycycline with rifampin or tigecycline (50 mg IV q12h after an initial loading dose of 100 mg IV) or fluoroquinolones (if the isolate is susceptible to each agent).
[g]Quinupristin-dalfopristin (Q/D) and linezolid are listed in the American Heart Association recommendations for the treatment of endocarditis caused by vancomycin- and ampicillin-resistant *E. faecium*.
[h]If the imipenem MIC is <32 μg/mL.
[i]In selected cases of catheter-associated bacteremia, removal of the catheter and a short course of therapy (~5–7 days) may be sufficient. A single positive blood culture that is likely to be associated with a catheter in a patient who is otherwise doing well may not require therapy after removal of the catheter.
[j]Intrathecal gentamicin (if no high-level resistance is detected; 2–10 mg/d) or Q/D (1–5 mg/d) has been used in combination with systemic therapy in refractory cases of postoperative meningitis. If Q/D is chosen, simultaneous systemic and intrathecal therapy is suggested. Intraventricular daptomycin has been used in two cases of meningitis.
[k]Fluoroquinolone antibiotics (e.g., moxifloxacin) and rifampin (if the isolate is susceptible to each agent) reach therapeutic levels in CSF.
[l]Approved by the FDA only for uncomplicated urinary tract infections caused by vancomycin-susceptible *E. faecalis*.
[m]Concentrations of amoxicillin in urine far exceed those in serum and can be potentially effective even against isolates with high MICs. Doses up to 12 g/d are suggested for isolates with MICs of >64 μg/mL.

monotherapy is not effective. Vancomycin is an alternative to β-lactam drugs for the treatment of *E. faecalis* infections but is less useful against *E. faecium* because resistance is common. Cephalosporins (except ceftobiprole for *E. faecalis*) are inactive against enterococci.

Linezolid and quinupristin/dalfopristin (Q/D) are approved by the U.S. Food and Drug Administration (FDA) for the treatment of some VRE infections (Table 40-2). Linezolid is not bactericidal, and its use in severe endovascular infections has produced mixed results; therefore, it is recommended only as an alternative to other agents. In addition, linezolid may cause significant toxicities (thrombocytopenia and peripheral neuropathy) when used in regimens given for >2 weeks. Nonetheless, this drug may play a role in the treatment of enterococcal meningitis and other CNS infections, although clinical data are limited. Q/D is not active against most *E. faecalis* isolates, and its in vivo efficacy against *E. faecium* may be compromised by resistance (see below). Adverse reactions to Q/D (including pain and inflammation at the infusion site and severe arthralgias and myalgias leading to discontinuation of treatment) are common. Therefore, this drug should be used with caution and probably combined with other agents (Table 40-2). The lipopeptide daptomycin is a bactericidal antibiotic with potent in vitro activity against all enterococci. Although daptomycin is not approved by the FDA for the treatment of VRE or *E. faecium* infections, it has been used alone (at high dosage) or in combination with other agents with apparent success against multidrug-resistant enterococcal infections (Tables 40-1 and 40-2). The main adverse reactions to daptomycin are elevated creatinine phosphokinase levels and eosinophilic pneumonitis. Daptomycin is not useful against pulmonary infections because the pulmonary surfactant inhibits its antibacterial activity. Although the glycylcycline tigecycline is active in vitro against all enterococci (regardless of the isolates' vancomycin susceptibility), its use as monotherapy for endovascular or severe enterococcal infections is not recommended because of low attainable blood levels. Telavancin, a lipoglycopeptide approved by the FDA for the treatment of skin and soft tissue infections, is active against vancomycin-susceptible enterococci but less so against VRE. Oritavancin, a compound of the same class that is active against VRE, is in the late stages of clinical development and may offer promise for the treatment of VRE infections in the future.

ANTIMICROBIAL RESISTANCE

As mentioned above, resistance to ampicillin continues to be observed only infrequently in *E. faecalis*, although rare outbreaks caused by β-lactamase-producing isolates have occurred in the United States and Argentina. However, ampicillin resistance is common in *E. faecium*. The mechanism of ampicillin resistance in *E. faecium* is related to a penicillin-binding protein (PBP) designated PBP5, which is the target of β-lactam antibiotics. PBP5 exhibits lower

affinity for ampicillin than other PBPs and can synthesize cell wall in the presence of this antibiotic, even when other PBPs are inhibited. Two common mechanisms of high-level ampicillin resistance (MIC, >64 μg/mL) in clinical strains are (1) mutations in the PBP5-encoding gene that further decrease the affinity of PBP5 for ampicillin and (2) hyperproduction of PBP5. These factors preclude the use of all β-lactam agents in the treatment of *E. faecium* infections.

Vancomycin is a glycopeptide antibiotic that inhibits cell wall peptidoglycan synthesis in susceptible enterococci and has been widely used against enterococcal infections in clinical practice when the use of penicillins is limited by resistance, allergy, or adverse reactions. This effect is mediated by binding of the antibiotic to peptidoglycan precursors (UDP-MurNAc-pentapeptides) upon their exit from the bacterial cytoplasm. The interaction of vancomycin with the peptidoglycan is specific and involves the last two D-alanine residues of the precursor. The first isolates of VRE were documented in 1986, and vancomycin resistance (particularly in *E. faecium*) has since increased considerably around the world. The mechanism involves the replacement of the last D-alanine residue of peptidoglycan precursors with D-lactate or D-serine, with consequent high- and low-level resistance, respectively. There is significant heterogeneity among isolates, but either substitution substantially decreases the affinity of vancomycin for the peptidoglycan; with the D-lactate substitution, the MIC is increased by up to one thousand-fold. Vancomycin-resistant organisms also produce enzymes that destroy the D-alanine–D-alanine-ending precursors, ensuring that additional binding sites for vancomycin are not available.

High-level resistance to aminoglycosides (of which gentamicin and streptomycin are the only two tested in clinical laboratories) abolishes the synergism observed between cell wall–active agents and the aminoglycoside. This important phenotype is routinely sought in isolates from serious infections (Tables 40-1 and 40-2). The laboratory reports high-level resistance as gentamicin and streptomycin MICs of >500 μg/mL and >2000 μg/mL, respectively (agar dilution method), or as "SYN-R" (resistance to synergism). Genes encoding aminoglycoside-modifying enzymes are usually the cause of high-level resistance to these compounds and are widely disseminated among enterococci, decreasing the options for the treatment of severe enterococcal infections. The aforementioned enterococcal resistance to newer antibiotics such as linezolid (usually due to mutations in the 23S rRNA genes), Q/D, daptomycin, and tigecycline further reduces therapeutic alternatives.

CHAPTER 41
ACUTE RHEUMATIC FEVER

Jonathan R. Carapetis

Acute rheumatic fever (ARF) is a multisystem disease resulting from an autoimmune reaction to infection with group A *Streptococcus* (Chap. 39). Although many parts of the body may be affected, almost all of the manifestations resolve completely. The exception is cardiac valvular damage [rheumatic heart disease (RHD)], which may persist after the other features have disappeared.

GLOBAL CONSIDERATIONS

ARF and RHD are diseases of poverty. They were common in all countries until the early twentieth century, when their incidence began to decline in industrialized nations. This decline was largely attributable to improved living conditions—particularly less crowded housing and better hygiene—which resulted in reduced transmission of group A streptococci. The introduction of antibiotics and improved systems of medical care had a supplemental effect. Recurrent outbreaks of ARF began in the 1980s in the Rocky Mountain states of the United States, where elevated rates persist.

The virtual disappearance of ARF and reduction in the incidence of RHD in industrialized countries during the twentieth century unfortunately were not replicated in developing countries, where these diseases continue unabated. RHD is the most common cause of heart disease in children in developing countries and is a major cause of mortality and morbidity in adults as well. It has been estimated that between 15 and 19 million people

worldwide are affected by RHD, with approximately one-quarter of a million deaths occurring each year. Some 95% of ARF cases and RHD deaths now occur in developing countries.

Although ARF and RHD are relatively common in all developing countries, they occur at particularly elevated rates in certain regions. These "hot spots" are sub-Saharan Africa, Pacific nations, Australasia, and the Indian subcontinent **(Fig. 41-1)**. Unfortunately, most developing countries do not currently have coordinated, register-based RHD control programs, which are proven to be cost-effective in reducing the burden of RHD. Enhancing awareness of RHD and mobilizing resources for its control in developing countries are issues requiring international attention.

EPIDEMIOLOGY

ARF is mainly a disease of children aged 5–14 years. Initial episodes become less common in older adolescents and young adults and are rare in persons aged >30 years. By contrast, recurrent episodes of ARF remain relatively common in adolescents and young adults. This pattern contrasts with the prevalence of RHD, which peaks between 25 and 40 years of age. There is no clear gender association for ARF, but RHD more commonly affects females, sometimes up to twice as frequently as males.

PATHOGENESIS

ORGANISM FACTORS

Currently available evidence indicates that ARF is exclusively caused by infection of the upper respiratory tract with group A streptococci (see Chap. 39). Classically, certain M serotypes (particularly types 1, 3, 5, 6, 14, 18, 19, 24, 27, and 29) were associated with ARF in high-incidence regions, but it is now thought that any strain of group A *Streptococcus* has the potential to cause ARF. Potential roles of skin infection and of groups C and G streptococci are currently being investigated.

HOST FACTORS

Approximately 3–6% of any population may be susceptible to ARF, and this proportion does not vary dramatically between populations. Familial clustering of cases and concordance in monozygotic twins—particularly for chorea—confirm that susceptibility to ARF is an inherited characteristic. Particular human leukocyte antigen (HLA) class II alleles appear to be strongly associated with susceptibility. Associations have also been described with high levels of circulating mannose-binding lectin and polymorphisms of the transforming growth factor β_1 gene and immunoglobulin genes. High-level expression of a particular alloantigen present on B cells, D8-17, has been found in patients with a history of ARF in many populations, with intermediate-level expression in first-degree family members, suggesting that this may be a marker of inherited susceptibility.

THE IMMUNE RESPONSE

When a susceptible host encounters a group A *Streptococcus*, an autoimmune reaction results, leading to damage to human tissues as a result of cross-reactivity between epitopes on the organism and the host **(Fig. 41-2)**. Cross-reactive epitopes are present in the

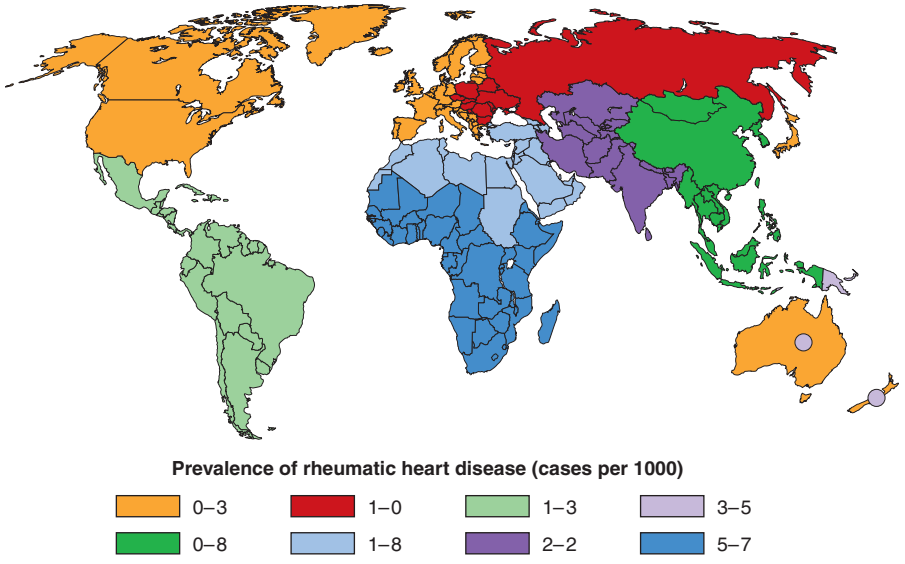


FIGURE 41-1
Prevalence of rheumatic heart disease in children aged 5–14 years. Circles within Australia and New Zealand represent indigenous populations, and also Pacific Islanders in New Zealand. (*From JR Carapetis et al: Lancet Infect Dis. Copyright 2005, with permission from Elsevier.*)

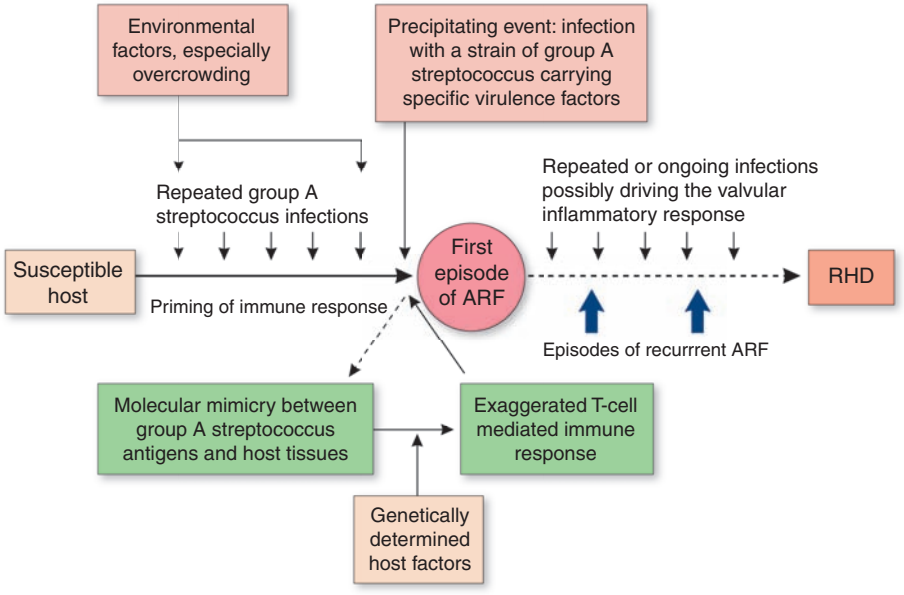


FIGURE 41-2
Pathogenetic pathway for acute rheumatic fever and rheumatic heart disease. (*From JR Carapetis et al: Lancet 366:155, 2005. Copyright 2005, with permission from Elsevier.*)

streptococcal M protein and the *N*-acetylglucosamine of group A streptococcal carbohydrate and are immunologically similar to molecules in human myosin, tropomyosin, keratin, actin, laminin, vimentin, and *N*-acetylglucosamine. It is currently thought that the initial damage is due to cross-reactive antibodies attaching at the cardiac valve endothelium, allowing the entry of primed CD4+ T cells, with subsequent T cell-mediated inflammation.

CLINICAL FEATURES

There is a latent period of ~3 weeks (1–5 weeks) between the precipitating group A streptococcal infection and the appearance of the clinical features of ARF. The exceptions are chorea and indolent carditis, which may follow prolonged latent periods lasting up to 6 months. Although many patients report a prior sore throat, the preceding group A streptococcal infection is commonly subclinical; in these cases it can be confirmed only by streptococcal antibody testing. The most common clinical presentation of ARF is polyarthritis and fever. Polyarthritis is present in 60–75% of cases and carditis in 50–60%. The prevalence of chorea in ARF varies substantially between populations, ranging from <2% to 30%. Erythema marginatum and subcutaneous nodules are now rare, being found in <5% of cases.

HEART INVOLVEMENT

Up to 60% of patients with ARF progress to RHD. The endocardium, pericardium, or myocardium may be affected. Valvular damage is the hallmark of rheumatic carditis. The mitral valve is almost always affected, sometimes together with the aortic valve; isolated aortic valve involvement is rare. Early valvular damage leads to regurgitation. Over ensuing years, usually as a result of recurrent episodes, leaflet thickening, scarring, calcification, and valvular stenosis may develop **(Fig. 41-3)**. Videos 41-1 and 41-2 can be accessed at the following link: http://www.mhprofessional.com/mediacenter/. Therefore, the characteristic manifestation of carditis in previously unaffected individuals is mitral regurgitation, sometimes accompanied by aortic regurgitation. Myocardial inflammation may affect electrical conduction pathways, leading to P-R interval prolongation (first-degree AV block or rarely higher-level block) and softening of the first heart sound.

JOINT INVOLVEMENT

To qualify as a major manifestation, joint involvement in ARF must be arthritic—i.e., objective evidence of inflammation, with hot, swollen, red and/or tender joints, and involvement of more than one joint (i.e., polyarthritis). The typical arthritis is migratory, moving from one joint to another over a period of hours. ARF almost always affects the large joints—most commonly the knees, ankles, hips, and elbows—and is asymmetric. The pain is severe and usually disabling until anti-inflammatory medication is commenced.

Less severe joint involvement is also relatively common but qualifies as only a minor manifestation. Arthralgia without objective joint inflammation usually affects large joints in the same migratory pattern as polyarthritis. In some populations, aseptic monoarthritis may

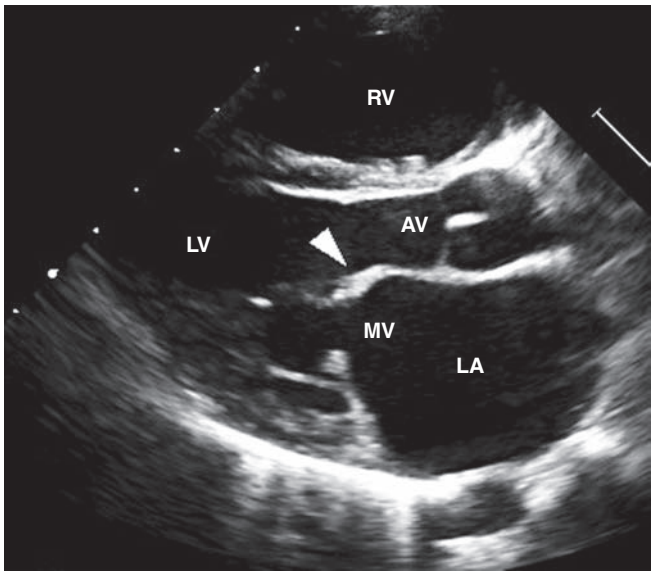


FIGURE 41-3
Transthoracic echocardiographic image from a 5-year-old boy with chronic rheumatic heart disease. This diastolic image demonstrates leaflet thickening, restriction of the anterior mitral valve leaflet tip, and doming of the body of the leaflet toward the interventricular septum. This appearance (marked by the arrowhead) is commonly described as a "hockey stick" or an "elbow" deformity. AV, aortic valve; LA, left atrium; LV, left ventricle; MV, mitral valve; RV, right ventricle. (*Courtesy of Dr. Bo Remenyi, Department of Paediatric and Congential Cardiac Services, Starship Children's Hospital, Auckland, New Zealand.*)

be a presenting feature of ARF, possibly because of early commencement of anti-inflammatory medication before the typical migratory pattern is established.

The joint manifestations of ARF are highly responsive to salicylates and other nonsteroidal anti-inflammatory drugs (NSAIDs). Indeed, joint involvement that persists more than 1 or 2 days after the start of salicylate treatment is unlikely to be due to ARF. Conversely, if salicylates are commenced early in the illness, before fever and migratory polyarthritis have become manifest, it may be difficult to make a diagnosis of ARF. For this reason, salicylates and other NSAIDs should be withheld—and pain managed with acetaminophen or codeine—until the diagnosis is confirmed.

CHOREA

Sydenham's chorea commonly occurs in the absence of other manifestations, follows a prolonged latent period after group A streptococcal infection, and is found mainly in females. The choreiform movements affect particularly the head (causing characteristic darting movements of the tongue) and the upper limbs. They may be generalized or restricted to one side of the body (hemi-chorea). The chorea varies in severity. In mild cases it may be evident only on careful examination, while in the most severe cases the affected individuals are unable to perform activities of daily living and are at risk of injuring themselves. Chorea eventually resolves completely, usually within 6 weeks.

SKIN MANIFESTATIONS

The classic rash of ARF is *erythema marginatum* (Chap. 9), which begins as pink macules that clear centrally, leaving a serpiginous, spreading edge. The rash is evanescent, appearing and disappearing before the examiner's eyes. It occurs usually on the trunk, sometimes on the limbs, but almost never on the face.

Subcutaneous nodules occur as painless, small (0.5–2 cm), mobile lumps beneath the skin overlying bony prominences, particularly of the hands, feet, elbows, occiput, and occasionally the vertebrae. They are a delayed manifestation, appearing 2–3 weeks after the onset of disease, last for just a few days up to 3 weeks, and are commonly associated with carditis.

OTHER FEATURES

Fever occurs in most cases of ARF, although rarely in cases of pure chorea. Although high-grade fever (≥39°C) is the rule, lower-grade temperature elevations are not uncommon. Elevated acute-phase reactants are also present in most cases. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are often dramatically elevated. Occasionally the peripheral leukocyte count is mildly elevated.

EVIDENCE OF A PRECEDING GROUP A STREPTOCOCCAL INFECTION

With the exception of chorea and low-grade carditis, both of which may become manifest many months later, evidence of a preceding group A streptococcal infection is essential in making the diagnosis of ARF. As most cases do not have a positive throat swab culture or rapid antigen test, serologic evidence is usually needed. The most common serologic tests are the antistreptolysin O (ASO) and anti-DNase B (ADB) titers. Where possible, age-specific reference ranges should be determined in a local population of healthy people without a recent group A streptococcal infection.

OTHER POST-STREPTOCOCCAL SYNDROMES THAT MAY BE CONFUSED WITH RHEUMATIC FEVER

Post-streptococcal reactive arthritis (PSRA) is differentiated from ARF on the basis of: (1) small-joint involvement that is often symmetric; (2) a short latent period following streptococcal infection (usually <1 week); (3) occasional causation by nongroup A β-hemolytic streptococcal infection; (4) slower responsiveness to salicylates; and (5) the absence of other features of ARF, particularly carditis.

Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS) is a term that links a range of tic disorders and obsessive-compulsive symptoms with group A streptococcal infections. People with PANDAS are said not to be at risk of carditis, unlike patients with Sydenham's chorea. The diagnoses of PANDAS and PSRA should rarely be made in populations with a high incidence of ARF.

CONFIRMING THE DIAGNOSIS

Because there is no definitive test, the diagnosis of ARF relies on the presence of a combination of typical clinical features together with evidence of the precipitating group A streptococcal infection and the exclusion of other diagnoses. This uncertainty led Dr. T. Duckett Jones in 1944 to develop a set of criteria (subsequently known as the *Jones criteria*) to aid in the diagnosis. An expert panel convened by the World Health Organization (WHO) clarified the use of the Jones criteria in ARF recurrences **(Table 41-1)**. Because each revision of the Jones criteria since 1944 has reduced sensitivity and increased specificity in response to the decline in incidence of ARF in high-income countries, there is now concern that they may be too insensitive for countries where ARF incidence remains high. As a result, some countries (e.g., Australia and New Zealand) have developed their own, more sensitive diagnostic criteria for ARF in their populations (links available at *the RHDnet website www.worldheart.org/rhd*).

TREATMENT Acute Rheumatic Fever

Patients with possible ARF should be followed closely to ensure that the diagnosis is confirmed; treatment of heart failure and other symptoms is undertaken; and preventive measures, including commencement of secondary prophylaxis, inclusion on an ARF registry, and health education, are commenced. Echocardiography should be performed on all possible cases to aid in making the diagnosis and to determi ne the severity at baseline of any carditis. Other tests that should be performed are listed in **Table 41-2**.

There is no treatment for ARF that has been proven to alter the likelihood of developing or the severity of RHD. With the exception of treatment of heart failure, which may be life-saving in cases of severe carditis, the treatment of ARF is symptom-based.

ANTIBIOTICS All patients with ARF should receive antibiotics sufficient to treat the precipitating group A streptococcal infection (Chap. 39). Penicillin is the drug of choice and can be given either (1) orally as phenoxymethyl penicillin, 500 mg (250 mg for children ≤27 kg) PO twice daily, or amoxicillin, 50 mg/kg (max 1 g) daily, for 10 days; or (2) intramuscularly as benzathine penicillin G in a single dose of 1.2 million units (600,000 units for children ≤27 kg).

TABLE 41-1

2002–2003 WORLD HEALTH ORGANIZATION CRITERIA FOR THE DIAGNOSIS OF RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE (BASED ON THE 1992 REVISED JONES CRITERIA)

DIAGNOSTIC CATEGORIES	CRITERIA
Primary episode of rheumatic fever[a]	Two major or one major and two minor manifestations plus evidence of preceding group A streptococcal infection
Recurrent attack of rheumatic fever in a patient without established rheumatic heart disease	Two major or one major and two minor manifestations plus evidence of preceding group A streptococcal infection
Recurrent attack of rheumatic fever in a patient with established rheumatic heart disease[b]	Two minor manifestations plus evidence of preceding group A streptococcal infection[c]
Rheumatic chorea Insidious onset rheumatic carditis[b]	Other major manifestations or evidence of group A streptococcal infection not required
Chronic valve lesions of rheumatic heart disease (patients presenting for the first time with pure mitral stenosis or mixed mitral valve disease and/or aortic valve disease)[d]	Do not require any other criteria to be diagnosed as having rheumatic heart disease
Major manifestations	Carditis Polyarthritis Chorea Erythema marginatum Subcutaneous nodules
Minor manifestations	Clinical: fever, polyarthralgia Laboratory: elevated erythrocyte sedimentation rate or leukocyte count[e] Electrocardiogram: prolonged P-R interval
Supporting evidence of a preceding streptococcal infection within the last 45 days	Elevated or rising antistreptolysin O or other streptococcal antibody, *or* A positive throat culture, *or* Rapid antigen test for group A *Streptococcus*, *or* Recent scarlet fever[e]

[a]Patients may present with polyarthritis (or with only polyarthralgia or monoarthritis) and with several (three or more) other minor manifestations, together with evidence of recent group A streptococcal infection. Some of these cases may later turn out to be rheumatic fever. It is prudent to consider them as cases of "probable rheumatic fever" (once other diagnoses are excluded) and advise regular secondary prophylaxis. Such patients require close follow-up and regular examination of the heart. This cautious approach is particularly suitable for patients in vulnerable age groups in high-incidence settings.
[b]Infective endocarditis should be excluded.
[c]Some patients with recurrent attacks may not fulfill these criteria.
[d]Congenital heart disease should be excluded.
[e]1992 Revised Jones Criteria do not include elevated leukocyte count as a laboratory minor manifestation (but do include elevated C-reactive protein) and do not include recent scarlet fever as supporting evidence of a recent streptococcal infection.
Source: Reprinted with permission from WHO Expert Consultation on Rheumatic Fever and Rheumatic Heart Disease (2001: Geneva, Switzerland): *Rheumatic Fever and Rheumatic Heart Disease: Report of a WHO Expert Consultation* (WHO Tech Rep Ser, 923). Geneva, World Health Organization, 2004.

TABLE 41-2

RECOMMENDED TESTS IN CASES OF POSSIBLE ACUTE RHEUMATIC FEVER

Recommended for all cases
White blood cell count
Erythrocyte sedimentation rate
C-reactive protein
Blood cultures if febrile
Electrocardiogram (repeat in 2 weeks and 2 months if prolonged P-R interval or other rhythm abnormality)
Chest x-ray if clinical or echocardiographic evidence of carditis
Echocardiogram (consider repeating after 1 month if negative)
Throat swab (preferably before giving antibiotics)—culture for group A *Streptococcus*
Anti-streptococcal serology: both anti-streptolysin O and anti-DNase B titers, if available (repeat 10–14 days later if 1st test not confirmatory)
Tests for alternative diagnoses, depending on clinical features
Repeated blood cultures if possible endocarditis
Joint aspirate (microscopy and culture) for possible septic arthritis
Copper, ceruloplasmin, anti-nuclear antibody, drug screen for choreiform movements
Serology and autoimmune markers for arboviral, autoimmune, or reactive arthritis

Source: Reprinted with permission from National Heart Foundation of Australia.

SALICYLATES AND NSAIDS These may be used for the treatment of arthritis, arthralgia, and fever, once the diagnosis is confirmed. They are of no proven value in the treatment of carditis or chorea. Aspirin is the drug of choice. An initial dose of 80–100 mg/kg per day in children (4–8 g/d in adults) in 4–5 divided doses is often needed for the first few days up to 2 weeks. A lower dose should be used if symptoms of salicylate toxicity emerge, such as nausea, vomiting, or tinnitus. When the acute symptoms are substantially resolved, the dose can be reduced to 60–70 mg/kg per day for a further 2–4 weeks. Fever, joint manifestations, and elevated acute-phase reactants sometimes recur up to 3 weeks after the medication is discontinued. This does not indicate a recurrence and can be managed by recommencing salicylates for a brief period. Although less well studied, naproxen at a dose of 10–20 mg/kg per day has been reported to lead to good symptomatic response.

CONGESTIVE HEART FAILURE The use of glucocorticoids in ARF remains controversial. Two meta-analyses have failed to demonstrate a benefit of glucocorticoids over placebo or salicylates in improving the short- or longer term outcome of carditis. However, the studies included in these meta-analyses all took place >40 years ago and did not use medications in common usage today. Many clinicians treat cases of severe carditis (causing heart failure) with glucocorticoids in the belief that they may reduce the acute inflammation and result in more rapid resolution of failure. However, the potential benefits of this treatment should be balanced against the possible adverse effects, including gastrointestinal bleeding and fluid retention. If used, prednisone or prednisolone are recommended at doses of 1–2 mg/kg per day (maximum, 80 mg). Glucocorticoids are often required for only a few days or up to a maximum of 3 weeks.

MANAGEMENT OF HEART FAILURE Traditional recommendations for long-term bed rest, once the cornerstone of management, are no longer widely practiced. Instead, bed rest should be prescribed as needed while arthritis and arthralgia are present and for patients with heart failure. Once symptoms are well controlled, gradual mobilization can commence as tolerated.

CHOREA Medications to control the abnormal movements do not alter the duration or outcome of chorea. Milder cases can usually be managed by providing a calm environment. In patients with severe chorea, carbamazepine or sodium valproate are preferred to haloperidol. A response may not be seen for 1–2 weeks, and a successful response may only be to reduce rather than resolve the abnormal movements. Medication should be continued for 1–2 weeks after symptoms subside.

Small studies have suggested that intravenous immunoglobulia (IVIg) may lead to more rapid resolution of chorea but has shown no benefit on the short- or long-term outcome of carditis in ARF without chorea. In the absence of better data, IVIg is *not* recommended except in cases of severe chorea refractory to other treatments.

PROGNOSIS

Untreated, ARF lasts on average 12 weeks. With treatment, patients are usually discharged from hospital within 1–2 weeks. Inflammatory markers should be monitored every 1–2 weeks until they have normalized (usually within 4–6 weeks), and an echocardiogram should be performed after 1 month to determine if there has been progression of carditis. Cases with more severe carditis need close clinical and echocardiographic monitoring in the longer term.

Once the acute episode has resolved, the priority in management is to ensure long-term clinical follow-up and adherence to a regimen of secondary prophylaxis. Patients should be entered onto the local ARF registry (if one exists) and contact made with primary care practitioners to ensure a plan for follow-up and administration of secondary prophylaxis before the patient is discharged. Patients and their families should also be educated about their disease, emphasizing the

importance of adherence to secondary prophylaxis. If carditis is present, they should also be informed of the need for antibiotic prophylaxis against endocarditis for dental and surgical procedures.

PREVENTION

PRIMARY PREVENTION

Ideally, primary prevention would entail elimination of the major risk factors for streptococcal infection, particularly overcrowded housing. This goal is difficult to achieve in most places where ARF is common.

Therefore, the mainstay of primary prevention for ARF remains primary prophylaxis (i.e., the timely and complete treatment of group A streptococcal sore throat with antibiotics). If commenced within 9 days of sore throat onset, a course of penicillin (as outlined above for treatment of ARF) will prevent almost all cases of ARF that would otherwise have developed. This important strategy relies on individuals presenting for medical care when they have a sore throat, the availability of trained health and microbiology staff along with the materials and infrastructure to take throat swabs, and a reliable supply of penicillin. Unfortunately, many of these elements are not available in developing countries.

SECONDARY PREVENTION

The mainstay of controlling ARF and RHD is secondary prevention. Because patients with ARF are at dramatically higher risk than the general population of developing a further episode of ARF after a group A streptococcal infection, they should receive long-term penicillin prophylaxis to prevent recurrences. The best antibiotic for secondary prophylaxis is benzathine penicillin G (1.2 million units, or 600,000 units if ≤27 kg) delivered every 4 weeks. It can be given every 3 weeks, or even every 2 weeks, to persons considered to be at particularly high risk, although in settings where good compliance with 4-weekly dosing can be achieved, more frequent dosing is rarely needed. Oral penicillin V (250 mg) can be given twice-daily instead but is somewhat less effective than benzathine penicillin G. Penicillin-allergic patients can receive erythromycin (250 mg) twice daily.

The duration of secondary prophylaxis is determined by many factors, in particular the duration since the last episode of ARF (recurrences become less likely with increasing time), age (recurrences are less likely with increasing age), and the severity of RHD (if severe, it may be prudent to avoid even a very small risk of recurrence because of the potentially serious consequences) **(Table 41-3)**. Secondary prophylaxis is best delivered as part of a coordinated RHD control program based around a registry of patients. Registries improve the ability to follow patients, to identify those who default from prophylaxis, and to institute strategies to improve adherence.

TABLE 41-3

AMERICAN HEART ASSOCIATION RECOMMENDATIONS FOR DURATION OF SECONDARY PROPHYLAXIS[a]

CATEGORY OF PATIENT	DURATION OF PROPHYLAXIS
Rheumatic fever without carditis	For 5 years after the last attack or 21 years of age (whichever is longer)
Rheumatic fever with carditis but no residual valvular disease	For 10 years after the last attack, or 21 years of age (whichever is longer)
Rheumatic fever with persistent valvular disease, evident clinically or on echocardiography	For 10 years after the last attack, or 40 years of age (whichever is longer); sometimes lifelong prophylaxis

[a]These are only recommendations and must be modified by individual circumstances as warranted. Note that other organizations have slightly different recommendations (see *www.worldheart.org/rhd for links*).

Source: Adapted from AHA Scientific Statement Prevention of Rheumatic Fever and Diagnosis and Treatment of Acute Streptococcal Pharyngitis. Circulation 119:1541, 2009.

CHAPTER 42

DIPHTHERIA AND OTHER INFECTIONS CAUSED BY CORYNEBACTERIA AND RELATED SPECIES

William R. Bishai ■ John R. Murphy

DIPHTHERIA

Diphtheria is a nasopharyngeal and skin infection caused by *Corynebacterium diphtheriae*. Toxigenic strains of *C. diphtheriae* produce a protein toxin that causes systemic toxicity, myocarditis, and polyneuropathy. The toxin is associated with the formation of pseudomembranes in the pharynx during respiratory diphtheria. While toxigenic strains most frequently cause pharyngeal diphtheria, nontoxigenic strains commonly cause cutaneous disease.

In the United States and Europe, diphtheria has been controlled in recent years with effective vaccination, although sporadic outbreaks have occurred. Diphtheria is still common in the Caribbean, Latin America, and the Indian subcontinent, where mass immunization programs are not enforced. Large epidemics have occurred in the independent states formerly encompassed by the Soviet Union. Additional outbreaks have been reported in Algeria, China, and Ecuador.

ETIOLOGY

C. diphtheriae is a gram-positive, unencapsulated, nonmotile, nonsporulating bacillus. *C. diphtheriae* organisms have a characteristic club-shaped bacillary appearance and typically form clusters of parallel rays (palisades) that are referred to as *Chinese characters*. In the specific laboratory media recommended for the cultivation of *C. diphtheriae*, tellurite, colistin, or nalidixic acid allows selective isolation of the organism in the presence of other autochthonous pharyngeal microbes. Human isolates of *C. diphtheriae* may display nontoxigenic (tox^-) or toxigenic (tox^+) phenotypes. Corynebacteriophage beta carries the structural gene (*tox*) encoding diphtheria toxin, and a family of closely related corynebacteriophages are responsible for toxigenic conversion of tox^- *C. diphtheriae* to the tox^+ phenotype. Moreover, lysogenic conversion from a nontoxigenic to a toxigenic phenotype has been shown to occur in situ. Growth of toxigenic strains of *C. diphtheriae* under iron-limiting conditions leads to the optimal expression of diphtheria toxin, and these conditions are believed to trigger *tox* expression and subsequent pathogenesis during human infection.

EPIDEMIOLOGY

C. diphtheriae is transmitted via the aerosol route, primarily during close contact. There are no significant reservoirs other than humans. The incubation period for respiratory diphtheria is 2–5 days; however, disease can develop as long as 10 days after exposure. Before the vaccine era, most individuals over the age of 10 were immune to *C. diphtheriae*; infants were protected by maternal IgG antibodies, but became susceptible after ~6 months of age. Thus, the disease was seen primarily in children and nonimmune young adults. In temperate regions, respiratory diphtheria occurs year-round but is most common during winter months.

The development of diphtheria antitoxin and diphtheria toxoid vaccine led to the near-elimination of diphtheria in Western countries. The annual peak incidence rate was 191 cases per 100,000 population in the United States in 1921; in contrast, since 1980, the annual figure for the United States as a whole has been <5 cases. Nevertheless, pockets of colonization have persisted in North America, particularly in South Dakota, Ontario, and Washington state. Immunity induced by vaccination during childhood gradually decreases in adulthood. An estimated 30% of men 60–69 years old have antitoxin titers below the protective level. In addition to older age and lack of vaccination, risk factors for diphtheria outbreaks include alcoholism, low socioeconomic status, crowded living conditions, and Native American ethnic background. An outbreak that occurred in Seattle in 1972–1982 included 1100 cases, primarily manifesting as cutaneous disease. During the 1990s in the states of the former Soviet Union, a much larger diphtheria epidemic

caused >150,000 cases and >5000 deaths. Clonally related toxigenic *C. diphtheriae* strains of the ET8 complex were associated with this outbreak. Given that the ET8 complex expressed a toxin against which the prevalent diphtheria toxoid vaccine was effective, the epidemic was attributed to failure of the public health infrastructure to effectively vaccinate the population. Beginning in 1998, the epidemic was controlled by mass vaccination programs. During the epidemic, the incidence rate was high among individuals from >15 years of age up to 50 years of age. Socioeconomic instability, migration, deteriorating public health programs, frequent vaccine shortages, delays in implementation of vaccination and of treatment in response to cases, and lack of public education and awareness were contributing factors in that outbreak.

Significant outbreaks of diphtheria and diphtheria-related mortality continue to be reported from many developing countries, particularly in Africa and Asia. Statistics collected by the World Health Organization indicate the occurrence of ~7000 reported diphtheria cases in 2008 and ~5000 diphtheria deaths in 2004. Although ~82% of the global population has been adequately vaccinated, only 26% of countries have successfully vaccinated >80% of individuals in all districts.

Cutaneous diphtheria is usually a secondary infection that follows a primary skin lesion due to trauma, allergy, or autoimmunity. Most often, isolates from cases of cutaneous disease lack the *tox* gene and, therefore, do not express diphtheria toxin. In tropical regions, cutaneous diphtheria is more common than respiratory diphtheria. In contrast to respiratory disease, cutaneous diphtheria is not a reportable disease in United States.

Nontoxigenic strains of *C. diphtheriae* have also been associated with bacteremia and invasive disease in the urban poor in Vancouver, Canada, and with pharyngitis in Europe. Outbreaks have occurred among homosexual men and IV drug users.

PATHOGENESIS AND IMMUNOLOGY

Diphtheria toxin, produced by toxigenic strains of *C. diphtheriae*, is the primary virulence factor in clinical disease. The toxin is synthesized in precursor form; is released as a 535-amino-acid, single-chain protein; and has an LD_{50} of ~100 ng/kg of body weight. The toxin is produced in the pseudomembranous lesion and is taken up into the bloodstream, through which it is distributed to all organ systems. Once bound to its cell surface receptor (a heparin-binding, epidermal growth factor–like precursor), the toxin is internalized by receptor-mediated endocytosis and enters the cytosol from an acidified early endosomal compartment. In vitro, the toxin may be separated into two chains after digestion with serine proteases: the N-terminal A fragment and the C-terminal B fragment. Delivery of the A fragment into the eukaryotic cell cytosol results in irreversible inhibition of protein synthesis by NAD+-dependent ADP ribosylation of elongation factor 2. The eventual result is the death of the cell.

In 1926, Ramon at the Institut Pasteur found that formalinization of diphtheria toxin resulted in the production of diphtheria toxoid, which was nontoxic but highly immunogenic. Subsequent studies showed that immunization with diphtheria toxoid elicited antibodies that neutralized the toxin and prevented most manifestations of diphtheria. In the 1930s, mass immunization of children and susceptible adults commenced in the United States and Europe.

Individuals with an antitoxin titer of >0.01 unit/mL are at low risk of diphtheria disease. In populations where a majority of individuals have protective antitoxin titers, the carrier rate for toxigenic strains of *C. diphtheriae* decreases and the overall risk of diphtheria among susceptible individuals is reduced. Nevertheless, individuals with nonprotective titers may contract diphtheria through either travel or exposure to individuals who have recently returned from regions where the disease is endemic.

Characteristic pathologic findings of diphtheria include mucosal ulcers with a pseudomembranous coating composed of an inner band of fibrin and a luminal band of neutrophils. Initially white and firmly adherent, in advanced diphtheria the pseudomembranes turn gray and even green or black as necrosis progresses. Mucosal ulcers result from toxin-induced necrosis of the epithelium accompanied by edema, hyperemia, and vascular congestion of the submucosal base. A fibrinosuppurative exudate from the ulcer develops into the pseudomembrane. Ulcers and pseudomembranes in severe respiratory diphtheria may extend from the pharynx into medium-sized bronchial airways. Expanding and sloughing membranes may result in fatal airway obstruction.

APPROACH TO THE PATIENT: Diphtheria

Although diphtheria is rare in the United States and other developed countries, this diagnosis should be considered in patients who have severe pharyngitis, particularly with difficulty swallowing, respiratory compromise, or signs of systemic disease including myocarditis or generalized weakness. In the differential diagnosis, the leading causes of pharyngitis that should be considered are respiratory viruses (rhinoviruses, influenza viruses, parainfluenza viruses, coronaviruses, and adenoviruses; ~25% of cases), group A streptococci (15–30%), group C streptococci (~5%), atypical bacteria such as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* (15–20% in some series), and other viruses such as herpes simplex virus (~4%) and Epstein-Barr virus (EBV; <1% in infectious mononucleosis). Less common causes are acute HIV infection, infection with *Neisseria gonorrhoeae*, fusobacterial infection (e.g., Lemierre syndrome), and thrush due to *Candida albicans* or other *Candida* species. The presence of a pharyngeal pseudomembrane or an extensive exudate should prompt consideration of diphtheria (Fig. 42-1).

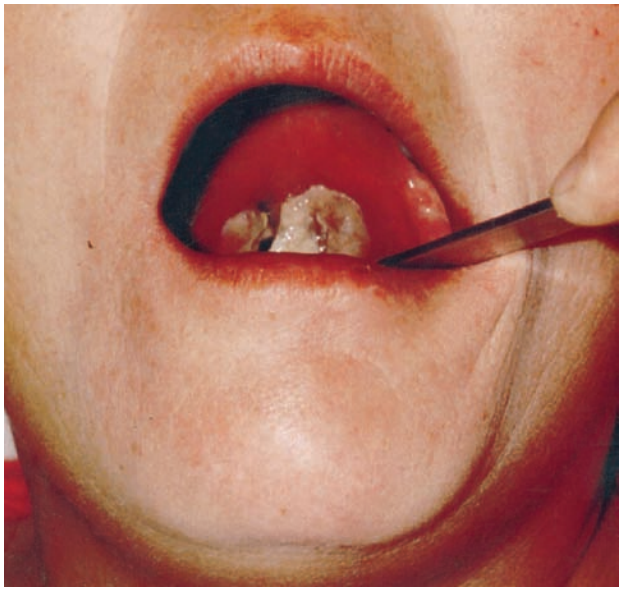


FIGURE 42-1
Respiratory diphtheria due to toxigenic *C. diphtheriae* producing exudative pharyngitis in a 47-year-old woman with neck edema and a pseudomembrane extending from the uvula to the pharyngeal wall. The characteristic white pseudomembrane is caused by diphtheria toxin–mediated necrosis of the respiratory epithelial layer, producing fibrinous coagulative exudate. Submucosal edema adds to airway narrowing. The pharyngitis is acute in onset, and respiratory obstruction from the pseudomembrane may occur in severe cases. Inoculation of pseudomembrane fragments or submembranous swabs onto Löffler's or tellurite selective medium reveals *C. diphtheriae.* (*Photograph by P. Strebel, MD, used by permission. From Kadirova R et al: J Infect Dis 181:S110, 2000.*)

CLINICAL MANIFESTATIONS

Respiratory diphtheria

The clinical diagnosis of diphtheria is based on the constellation of sore throat; adherent tonsillar, pharyngeal, or nasal pseudomembranous lesions; and low-grade fever. In addition, diagnosis requires the isolation of *C. diphtheriae* or the histopathologic isolation of compatible gram-positive organisms. The Centers for Disease Control and Prevention (CDC) recognizes confirmed respiratory diphtheria (laboratory proven or epidemiologically linked to a culture-confirmed case) and probable respiratory diphtheria (clinically compatible but not laboratory proven or epidemiologically linked). Carriers are defined as individuals who have positive cultures for *C. diphtheriae* and either are asymptomatic or have symptoms but lack pseudomembranes. Most patients seek medical care for initial manifestations of sore throat and fever. Occasionally, weakness, dysphagia, headache, and voice change are the initial manifestations. Neck edema and difficulty breathing are seen in more advanced cases and carry a poor prognosis.

The systemic manifestations of diphtheria stem from the effects of diphtheria toxin and include weakness as a result of neurotoxicity and cardiac arrhythmias or congestive heart failure due to myocarditis. The pseudomembranous lesion is most often located in the tonsillopharyngeal region. Less commonly, the lesions are detected in the larynx, nares, and trachea or bronchial passages. Large pseudomembranes are associated with severe disease and a poor prognosis. A few patients develop massive swelling of the tonsils and present with "bull-neck" diphtheria, which results from massive edema of the submandibular and paratracheal region and is further characterized by foul breath, thick speech, and stridorous breathing. The diphtheritic pseudomembrane is gray or whitish and sharply demarcated. Unlike the exudative lesion associated with streptococcal pharyngitis, the pseudomembrane in diphtheria is tightly adherent to the underlying tissues. Attempts to dislodge the membrane may cause bleeding. Hoarseness suggests laryngeal diphtheria, in which laryngoscopy may be diagnostically helpful.

Cutaneous diphtheria

This is a variable dermatosis most often characterized by punched-out ulcerative lesions with necrotic sloughing or pseudomembrane formation **(Fig. 42-2)**. The diagnosis requires cultivation of *C. diphtheriae* from lesions, which most commonly occur on the extremities. Patients usually seek medical attention because of nonhealing or enlarging skin ulcers, which may be associated with a preexisting wound or dermatoses such as eczema, psoriasis, and venous stasis disease. The lesions rarely exceed 5 cm.

Other clinical manifestations

C. diphtheriae causes rare cases of endocarditis and septic arthritis, most often in patients with preexisting risk factors such as cardiac valvular disease, injection drug use, or cirrhosis.

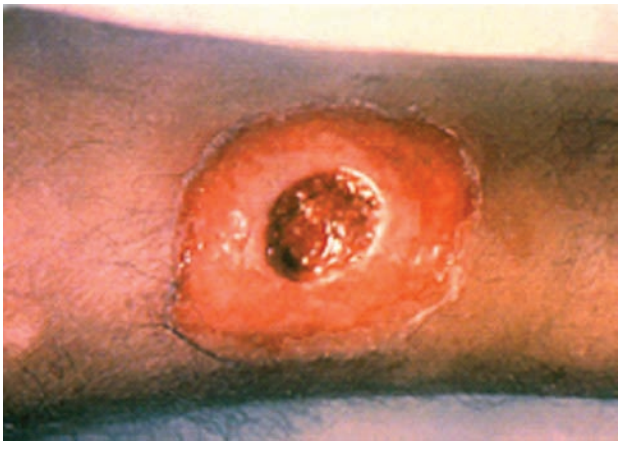


FIGURE 42-2
Cutaneous diphtheria due to nontoxigenic *C. diphtheriae* on the lower extremity. (*From the Centers for Disease Control and Prevention.*)

COMPLICATIONS

Airway obstruction poses a significant early risk in patients presenting with advanced diphtheria. Pseudomembranes may slough and obstruct the airway or may advance to the larynx or into the tracheobronchial tree. Children are particularly prone to obstruction because of their small airways.

Polyneuropathy and myocarditis are late toxic manifestations of diphtheria. During the outbreak in the Kyrgyz Republic in 1995, myocarditis was seen in 22% and neuropathy in 5% of hospitalized patients. The mortality rate was 7% among patients with myocarditis as opposed to 2% among those without myocardial manifestations. The median time to death in hospitalized patients was 4.5 days. Myocarditis is typically associated with dysrhythmia of the conduction tract and dilated cardiomyopathy.

Neurologic manifestations may appear during the first or second week of illness, typically beginning with dysphagia and nasal dysarthria and progressing to other signs of cranial nerve involvement, including weakness of the tongue and facial numbness. Ciliary paralysis, which is typical, manifests as blurred vision due to paralysis of pupillary accommodation, with a preserved light reflex. Cranial neuropathy may be followed by respiratory and abdominal muscle weakness requiring artificial ventilation. Several weeks later—sometimes as cranial neuropathy is improving—a generalized sensorimotor polyneuropathy may appear, with prominent autonomic manifestations (including hypotension) in some cases. The clinical syndrome and the findings on lumbar puncture of raised levels of protein without pleocytosis in cerebrospinal fluid resemble Guillain-Barré syndrome. Pathologically, diphtheria neuropathy is a noninflammatory demyelinating disorder mediated by the exotoxin. Gradual improvement is the rule in patients who survive the acute phase.

Other complications of diphtheria include pneumonia, renal failure, encephalitis, cerebral infarction, and pulmonary embolism. Serum sickness can result from treatment with diphtheria antitoxin (see "Treatment: Diptheria," next).

DIAGNOSIS

The diagnosis of diphtheria is based on clinical signs and symptoms plus laboratory confirmation. Respiratory diphtheria should be considered in patients with sore throat, pharyngeal exudates, and fever. Other symptoms may include hoarseness, stridor, or palatal paralysis. The presence of a pseudomembrane should prompt consideration of diphtheria. Once a clinical diagnosis of diphtheria is made, diphtheria antitoxin should be administered as soon as possible.

Laboratory diagnosis is based either on cultivation of *C. diphtheriae* or toxigenic *C. ulcerans* from the site of infection or on the demonstration of local lesions with characteristic histopathology. *C. pseudodiphtheriticum*, a nontoxigenic organism, is a common component of the normal throat flora and does not pose a significant risk. Throat samples should be submitted to the laboratory for culture with the notation that diphtheria is being considered. This information should prompt cultivation on special selective medium and subsequent biochemical testing to differentiate *C. diphtheriae* from other nasopharyngeal commensal corynebacteria. All laboratory isolates of *C. diphtheriae*, including nontoxigenic strains, should be submitted to the CDC.

A diagnosis of cutaneous diphtheria requires laboratory confirmation since the lesions are not characteristic and are clinically indistinguishable from other dermatoses. Diphtheritic ulcers occasionally—but not consistently—have a punched-out appearance (Fig. 42-2). Patients in whom cutaneous diphtheria is identified should have the nasopharynx cultured for *C. diphtheriae*. The laboratory media for cutaneous diphtheria are the same as those used for respiratory diphtheria: Löffler's or Tinsdale's selective medium in addition to nonselective medium such as blood agar. As has been mentioned, respiratory diphtheria remains a notifiable disease in the United States, whereas cutaneous diphtheria is not.

TREATMENT Diphtheria

DIPHTHERIA ANTITOXIN Prompt administration of diphtheria antitoxin is critical in the management of respiratory diphtheria. The antitoxin—a horse antiserum—is effective in reducing the extent of local disease as well as the risk of complications of myocarditis and neuropathy. Rapid institution of antitoxin therapy is also associated with a significant reduction in mortality risk. Because diphtheria antitoxin cannot neutralize cell-bound toxin, prompt initiation is important. This product, which is no longer made commercially in the United States, is available from the CDC under an investigational new drug protocol and may be obtained by calling the Emergency Operations center at 770-488-7100; the relevant Web site is *www.cdc.gov/vaccines/vpd-vac/diphtheria/dat/dat-main.htm*. The current protocol for the use of antitoxin includes a test dose to rule out immediate-type hypersensitivity. Patients who exhibit hypersensitivity require desensitization before a full therapeutic dose of antitoxin is administered.

ANTIMICROBIAL THERAPY Antibiotics are used in the management of diphtheria primarily to prevent transmission to other susceptible contacts. Recommended options for the treatment of patients with respiratory diphtheria are as follows: (1) procaine penicillin G at a dosage of 600,000 units (for children, 12,500–25,000 U/kg) IM every 12 h until the patient can swallow comfortably, after which oral penicillin V is given at 125–250 mg four times daily to complete a 14-day course; or (2) erythromycin at a dosage of 500 mg IV every 6 h (for children, 40–50 mg/kg per day IV in two or four divided doses) until the patient can

swallow comfortably, after which 500 mg is given by mouth four times daily to complete a 14-day course.

A clinical study in Vietnam found that penicillin was associated with a more rapid resolution of fever and a lower rate of bacterial resistance than erythromycin; however, relapses were more common with penicillin. Erythromycin therapy targets protein synthesis and thus offers the presumed benefit of stopping toxin synthesis more quickly than a cell wall–active β-lactam agent. Alternative agents for patients who are allergic to penicillin or cannot take erythromycin include rifampin and clindamycin. Eradication of *C. diphtheriae* should be documented at least 1 day after antimicrobial therapy is complete. A repeat throat culture 2 weeks later is recommended. For patients in whom the organism is not eradicated after a 14-day course of erythromycin or penicillin, an additional 10-day course followed by repeat culture is recommended.

Cutaneous diphtheria should be treated as described earlier for respiratory disease. Individuals infected with toxigenic strains should receive antitoxin. It is important to treat the underlying cause of the dermatoses in addition to the superinfection with *C. diphtheriae*.

Patients who recover from respiratory or cutaneous diphtheria should have antitoxin levels measured. If diphtheria antitoxin has been administered, this test should be performed 6 months later. Patients who recover from respiratory or cutaneous diphtheria should receive the appropriate vaccine (see "Prevention," next) to ensure the development of protective antibody titers, which does not occur in all cases.

MANAGEMENT Patients in whom diphtheria is suspected should be hospitalized in respiratory isolation rooms, with close monitoring of cardiac and respiratory function. A cardiac workup is recommended to assess the possibility of myocarditis. In patients with extensive pseudomembranes, consultation with an anesthesiologist or an ear, nose, and throat specialist is recommended because of the possibility that tracheostomy or intubation will be required. In some settings, pseudomembranes can be removed surgically. Treatment with glucocorticoids has not been shown to reduce the risk of myocarditis or polyneuropathy.

PROGNOSIS

Fatal pseudomembranous diphtheria typically occurs in patients with nonprotective antibody titers and in unimmunized patients. The pseudomembrane may increase in size from the time it is first noted. Risk factors for death include bull-neck diphtheria; myocarditis with ventricular tachycardia; atrial fibrillation; complete heart block; an age of >60 years or <6 months; alcoholism; extensive pseudomembrane elongation; and laryngeal, tracheal, or bronchial involvement. Another important predictor of fatal outcome is the interval between local disease development and antitoxin administration. Cutaneous diphtheria has a low mortality rate and is rarely associated with myocarditis or peripheral neuropathy.

PREVENTION

Vaccination

Sustained campaigns for vaccination of children and adequate boosting vaccination of adults are responsible for the exceedingly low incidence of diphtheria in most developed nations. At present, diphtheria toxoid vaccine is coadministered with tetanus (with or without acellular pertussis) vaccine. DTaP (full-level diphtheria and tetanus toxoids and acellular pertussis vaccine, adsorbed) is the currently recommended vaccine for children up to the age of 7; DTaP replaced DTP (diphtheria and tetanus toxoids and whole-cell pertussis vaccine) in 1997. Tdap is a tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine formulated for adolescents and adults. Tdap was licensed for use in the United States in 2005 and is the recommended booster vaccine for children 11–12 years old and the recommended catch-up vaccine for children 7–10 and 13–18 years old. As of 2006, it is recommended that (1) adults 19–64 years old receive a single dose of Tdap if their last dose of Td (tetanus and reduced-dose diphtheria toxoids, adsorbed) was >10 years earlier and (2) intervals of <10 years be implemented for Tdap vaccination of health care workers, adults anticipating contact with infants, and adults not previously vaccinated for pertussis. Adults who have received acellular pertussis vaccines should continue to receive decennial Td booster vaccinations. The vaccination schedule is detailed in Chap. 4.

Prophylaxis of contacts

Close contacts of diphtheria patients should undergo throat culture to determine whether they are carriers. After samples for throat culture are obtained, antimicrobial prophylaxis should be considered for all close contacts, even those who are culture-negative. The options are 7–10 days of oral erythromycin or one dose of IM benzathine penicillin G (1.2 million units for persons ≥6 years old or 600,000 units for children <6 years old).

Contacts of diphtheria cases who have an uncertain immunization status should receive the appropriate diphtheria toxoid–containing vaccine. Tdap (rather than Td) is now recommended as the booster vaccine of choice for adults who have not recently received an acellular pertussis–containing vaccine. Carriers of *C. diphtheriae* in the community should be treated and vaccinated when identified.

NONDIPHTHERIAL CORYNEBACTERIA AND RELATED SPECIES

Nondiphtherial corynebacteria, which are also referred to as *diphtheroids* or *coryneforms*, are a widely diverse collection of bacteria that are taxonomically lumped together on the basis of their 16S rDNA signature nucleotides. The diversity of this group is exemplified by the wide range in guanine-plus-cytosine content (45–70%). Although frequently considered colonizers or contaminants, the nondiphtherial corynebacteria have

been associated with invasive disease, particularly in immunocompromised patients. Specifically, for example, these organisms have been implicated in bacteremia, endocarditis, and other serious infections, particularly in association with catheters and prosthetic devices. Patients infected with nondiphtherial corynebacteria usually have significant medical comorbidity or immunosuppression. Several of these organisms, including *C. jeikeium* and *C. urealyticum*, are associated with resistance to multiple antibiotics. The related organism *Rhodococcus equi* is associated with necrotizing pneumonia and granulomatous infection, particularly in immunocompromised individuals. Other related species that can cause infections in humans are *Actinomyces* (formerly *Corynebacterium*) *pyogenes* and *Arcanobacterium* (formerly *Corynebacterium*) *haemolyticum*.

MICROBIOLOGY AND LABORATORY DIAGNOSIS

These organisms are non-acid-fast, catalase-positive, aerobic or facultatively anaerobic bacilli. Their colonial morphologies vary widely; some species are small and α-hemolytic (similar to lactobacilli), whereas others form large white colonies (similar to yeasts). Many nondiphtherial coryneforms require special medium (e.g., Löffler's, Tinsdale's, or telluride medium) for growth.

EPIDEMIOLOGY

Humans are the natural reservoirs for several nondiphtherial coryneforms, including *C. xerosis*, *C. pseudodiphtheriticum*, *C. striatum*, *C. minutissimum*, *C. jeikeium*, *C. urealyticum*, and *A. haemolyticum*. Animal reservoirs are responsible for carriage of *A. pyogenes*, *C. ulcerans*, and *C. pseudotuberculosis*. Soil is the natural reservoir for *R. equi*.

C. pseudodiphtheriticum is part of the normal flora of the human pharynx and skin. *C. xerosis* is found on the skin, nasopharynx, and conjunctiva; *C. auris* in the external auditory canal; and *C. striatum* in the anterior nares and on the skin. *C. jeikeium* and *C. urealyticum* are found in the axilla, groin, and perineum, particularly in hospitalized patients. *C. ulcerans* and *C. pseudotuberculosis* infections have been associated with the consumption of raw milk from infected cattle.

SPECIFIC NONDIPHTHERIAL CORYNEFORMS

C. ulcerans

This organism causes a diphtheria-like illness and produces both diphtheria toxin and a dermonecrotic toxin. *C. ulcerans* is a commensal in horses and cattle and has been isolated from cow's milk. The organism causes exudative pharyngitis, primarily during summer months, in rural areas, and among individuals exposed to cattle. In contrast to diphtheria, *C. ulcerans* infection is considered a zoonosis, and pigs have been identified as a source of human infection; person-to-person transmission has not been established. Nevertheless, treatment with antitoxin and antibiotics should be initiated when respiratory *C. ulcerans* is identified, and a contact investigation (including throat cultures to determine the need for antimicrobial prophylaxis and vaccination with the appropriate diphtheria toxoid–containing vaccine for unimmunized human contacts) should be conducted. The organism grows on Löffler's, Tinsdale's, and telluride media as well as blood agar. In addition to exudative pharyngitis, cutaneous disease due to *C. ulcerans* has been reported. *C. ulcerans* is susceptible to a wide panel of antibiotics. Erythromycin and macrolides appear to be the first-line agents.

C. pseudotuberculosis (ovis)

Infections caused by *C. pseudotuberculosis* are rare and are reported almost exclusively from Australia. *C. pseudotuberculosis* causes suppurative granulomatous lymphadenitis and an eosinophilic pneumonia syndrome among individuals who handle horses, cattle, goats, and deer or who drink unpasteurized milk. The organism is an important veterinary pathogen, causing suppurative lymphadenitis, abscesses, and pneumonia, but is rarely a human pathogen. Successful treatment with erythromycin or tetracycline has been reported, with surgery also performed when indicated.

C. jeikeium (group JK)

After a 1976 survey of diseases caused by nondiphtherial corynebacteria, CDC group JK was recognized as an important opportunistic pathogen among neutropenic patients and later emerged in HIV-infected patients as a cause of AIDS-associated opportunistic infection. Accordingly, the organism was reclassified as a separate species, *C. jeikeium*. The predominant syndrome associated with *C. jeikeium* is sepsis, which can occur in conjunction with pneumonia, endocarditis, meningitis, osteomyelitis, or epidural abscess. Risk factors for *C. jeikeium* infection include hematologic malignancy, neutropenia from comorbid conditions, prolonged hospitalization, exposure to multiple antibiotics, and skin disruption. There is evidence that *C. jeikeium* is part of the normal flora of the inguinal, axillary, genital, and perirectal areas in hospitalized patients.

Broad-spectrum antimicrobial therapy appears to select for colonization. Originally described in the United States, *C. jeikeium* has also been reported in Europe. The gram-positive coccobacilli, which slightly resemble streptococci, grow as small, gray to white, glistening, nonhemolytic colonies on blood agar. *C. jeikeium* lacks urease and nitrate reductase and does not ferment most carbohydrates. It is resistant to most antibiotics tested except for vancomycin. Effective therapy involves removal of the source of infection, be it a catheter, a prosthetic joint, or a prosthetic valve. There have been efforts to prevent *C. jeikeium* infection by use of antibacterial soap in the care of high-risk patients in intensive care settings.

C. urealyticum (group D2)

Identified as a urease-positive nondiphtherial *Corynebacterium* in 1972, *C. urealyticum* is an opportunistic cause of sepsis and urinary tract infection. This organism appears to be the etiologic agent of a severe urinary tract syndrome known as *alkaline-encrusted cystitis*: a chronic inflammatory bladder infection associated with deposition of ammonium magnesium phosphate on the surface and walls of ulcerating lesions in the bladder. Obstructive uropathy due to this organism has been reported in renal transplant recipients. In addition, *C. urealyticum* has been associated with pneumonia, peritonitis, endocarditis, osteomyelitis, and wound infection. It is similar to *C. jeikeium* in its resistance to most antibiotics except vancomycin, which has been used successfully in the treatment of severe infections.

C. minutissimum

Erythrasma is a cutaneous infection producing reddish-brown, macular, scaly, pruritic intertriginous patches. The dermatologic presentation under the Wood's lamp is of coral-red fluorescence. *C. minutissimum* appears to be a common cause of erythrasma, although there is evidence for a polymicrobial etiology in certain settings. In addition, this fluorescent microbe has been associated with bacteremia in patients with hematologic malignancy. Erythrasma responds to topical erythromycin, clarithromycin, clindamycin, or fusidic acid, although more severe infections may require oral macrolide therapy.

OTHER NONDIPHTHERIAL CORYNEBACTERIA

C. xerosis is a human commensal found in the conjunctiva, nasopharynx, and skin. This nontoxigenic organism is occasionally identified as a source of invasive infection in immunocompromised or postoperative patients and prosthetic joint recipients. *C. striatum* is found in the anterior nares and on the skin, face, and upper torso of normal individuals. Also nontoxigenic, this organism has been associated with invasive opportunistic infections in severely ill or immunocompromised patients. *C. amycolatum* is a species isolated from human skin and is identified on the basis of a unique 16S ribosomal RNA sequence associated with opportunistic infection. *C. glucuronolyticum* is a nonlipophilic species that causes male genitourinary tract infections such as prostatitis and urethritis. These infections may be successfully treated with a wide variety of antibacterial agents, including β-lactams, rifampin, aminoglycosides, or vancomycin; however, the organism appears to be resistant to fluoroquinolones, macrolides, and tetracyclines. *C. imitans* has been identified in Eastern Europe as a nontoxigenic cause of pharyngitis. *C. auris* has been isolated from children with otitis media and is susceptible to fluoroquinolones, rifampin, tetracycline, and vancomycin, but resistant to penicillin G and variably susceptible to macrolides. *C. pseudodiphtheriticum* (*C. hofmannii*) is a nontoxigenic component of the normal human flora. Human infections—particularly endocarditis of either prosthetic or native valves and invasive pneumonia—have been identified only rarely. Although *C. pseudodiphtheriticum* may be isolated from the nasopharynx of patients with suspected diphtheria, it is part of the normal flora and does not produce diphtheria toxin. *C. propinquum*, a close relative of *C. pseudodiphtheriticum*, is part of CDC group ANF-3 and is isolated from human respiratory tract specimens and blood. *C. afermentans* subspecies *lipophilum* belongs to CDC group ANF-1 and has been isolated from human blood and abscess infections. *C. accolens* has been isolated from wound drainage, throat swabs, and sputum and is typically identified as a satellite of staphylococcal organisms; it has been associated with endocarditis. *C. bovis* is a veterinary commensal that has not been clearly identified as a cause of human disease. *C. aquaticum* is a water-associated organism that is occasionally isolated from patients using medical devices (e.g., for chronic ambulatory peritoneal dialysis or venous access).

RHODOCOCCUS

Rhodococcus species are phylogenetically related to the corynebacteria. These gram-positive coccobacilli have been associated with tuberculosis-like infections in humans with granulomatous pathology. Although *R. equi* is best known, other species have been identified, including *R.* (also *Gordonia*) *bronchialis*, *R.* (also *Tsukamurella*) *aurantiacus*, *R. luteus*, *R. erythropolis*, *R. rhodochrous*, and *R. rubropertinctus*. *R. equi* has been recognized as a cause of pneumonia in horses since the 1920s; it causes related infections in cattle, sheep, and swine. *R. equi* is found in soil as an environmental microbe. The organisms vary in length; appear as spherical to long, curved, clubbed rods; and produce large, irregular mucoid colonies. *R. equi* does not ferment carbohydrates or liquefy gelatin and is often acid-fast. An intracellular pathogen of macrophages, *R. equi* can cause granulomatous necrosis and caseation. The organism has been identified most commonly in pulmonary infections, but infections of brain, bone, and skin have also been reported. Most commonly, *R. equi* disease manifests as nodular cavitary pneumonia of the upper lobe—a picture similar to that seen in tuberculosis or nocardiosis. Most patients are immunocompromised, often with HIV infection. Subcutaneous nodular lesions have also been identified. The involvement of *R. equi* should be considered in any patient presenting with a tuberculosis-like syndrome.

Infection due to *R. equi* has been treated successfully with antibiotics that penetrate intracellularly, including macrolides, clindamycin, rifampin, trimethoprim-sulfamethoxazole, tigecycline, and linezolid. β-Lactam antibiotics have not been useful. The organism is routinely susceptible to vancomycin, which is considered the drug of choice although there may be a role for oral therapies with bactericidal agents such as linezolid.

ACTINOMYCES PYOGENES

A cause of seasonal leg ulcers in humans in rural Thailand, *A. pyogenes* is a well-known pathogen of cattle, sheep, goats, and pigs. A few human cases of sepsis,

endocarditis, septic arthritis, pneumonia, meningitis, and empyema have been reported. The agent is susceptible to β-lactams, tetracycline, aminoglycosides, and fluoroquinolones.

ARCANOBACTERIUM HAEMOLYTICUM

A. haemolyticum was identified as an agent of wound infections in U.S. soldiers in the South Pacific during World War II. This organism appears to be a commensal of the human nasopharynx and skin, but has been implicated as a cause of pharyngitis and chronic skin ulcers. In contrast to the much more common pharyngitis caused by *Streptococcus pyogenes*, *A. haemolyticum* pharyngitis is associated with a scarlatiniform rash on the trunk and proximal extremities in about half of cases; this illness is occasionally confused with toxic shock syndrome. Because *A. haemolyticum* pharyngitis primarily affects teenagers, it has been postulated that the rash-pharyngitis syndrome may represent copathogenicity or synergy with EBV or opportunistic secondary infection complicating EBV infection. *A. haemolyticum* has also been reported as a cause of bacteremia, soft tissue infection, osteomyelitis, and cavitary pneumonia, predominantly in the setting of underlying diabetes mellitus. The organism is susceptible to β-lactams, macrolides, fluoroquinolones, clindamycin, vancomycin, and doxycycline. Penicillin resistance has been reported.

CHAPTER 43

LISTERIA MONOCYTOGENES INFECTIONS

Elizabeth L. Hohmann ■ Daniel A. Portnoy

Listeria monocytogenes is a food-borne pathogen that can cause serious infections, particularly in pregnant women and immunocompromised individuals. A ubiquitous saprophytic environmental bacterium, *L. monocytogenes* is also a facultative intracellular pathogen with a broad host range. Humans are probably accidental hosts for this microorganism. *L. monocytogenes* is of interest not only to clinicians but also to basic scientists as a model intracellular pathogen that is used to study basic mechanisms of microbial pathogenesis and host immunity.

MICROBIOLOGY

L. monocytogenes is a facultatively anaerobic, nonsporulating, gram-positive rod that grows over a broad temperature range, including refrigeration temperatures. This organism is motile during growth at low temperatures but much less so at 37°C. The vast majority of cases of human listerial disease can be traced to serotypes 1/2a, 1/2b, and 4. *L. monocytogenes* is weakly β-hemolytic on blood agar, and (as detailed later) its β-hemolysin is an essential determinant of its pathogenicity.

PATHOGENESIS

Infections with *L. monocytogenes* follow ingestion of contaminated food that contains the bacteria at high concentrations. The conversion from environmental saprophyte to pathogen involves the coordinate regulation of bacterial determinants of pathogenesis that mediate entry into cells, intracellular growth, and cell-to-cell spread. Many of the organism's pathogenic strategies can be examined experimentally in tissue culture models of infection; such a model is presented in Fig. 43–1. Like other enteric pathogens, *L. monocytogenes* induces its own internalization by cells that are not normally phagocytic. Its entry into cells is mediated by host surface proteins classified as internalins. Internalin-mediated entry is important in the crossing of intestinal, blood-brain, and fetoplacental barriers, although how *L. monocytogenes* traffics from the intestine to the brain or fetus is only beginning to be investigated. In a pregnant guinea pig model of infection, *L. monocytogenes* was shown to traffic from maternal organs to the placenta; surprisingly, however, it also trafficked from the placenta back to maternal organs. These data are consistent with a model in which miscarriage can be viewed as a host defense strategy to eliminate a nidus of infection.

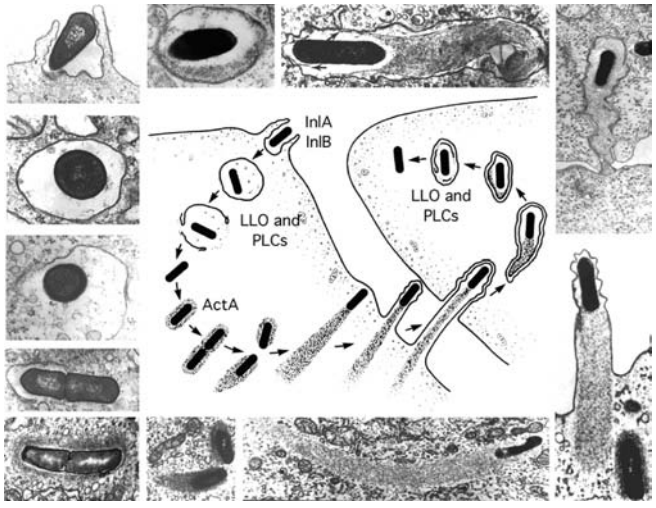


FIGURE 43-1
Stages in the intracellular life cycle of *Listeria monocytogenes.* The central diagram depicts cell entry, escape from a vacuole, actin nucleation, actin-based motility, and cell-to-cell spread. Surrounding the diagram are representative electron micrographs from which it was derived. ActA, surface protein mediating nucleation of host actin filaments to propel bacteria intra- and intercellularly; LLO, listeriolysin O; PLCs, phospholipases C; Inl, internalin. See text for further details. (*Adapted with permission from LG Tilney and DA Portnoy: J Cell Biol 109:1597, 1989. © Rockefeller University Press.*)

An essential determinant of the pathogenesis of *L. monocytogenes* is its β-hemolysin, listeriolysin O (LLO). LLO is a pore-forming, cholesterol-dependent cytolysin. (Related cytolysins include streptolysin O, pneumolysin, and perfringolysin O, all of which are produced by extracellular pathogens.) LLO is largely responsible for mediating the rupture of the phagosomal membrane that forms after phagocytosis of *L. monocytogenes*. LLO probably acts by inserting itself into an acidifying phagosome, thereby preventing the vesicle's maturation. In addition, LLO acts as a translocation pore for one or both of the *L. monocytogenes* phospholipases that also contribute to vacuolar lysis. LLO synthesis and activity are controlled at multiple levels to ensure that its lytic activity is limited to acidic vacuoles and does not affect the cytosol. Mutations in LLO that influence its synthesis, cytosolic half-life, or pH optimum cause premature toxicity to infected cells. There is an inverse relationship between toxicity and virulence—i.e., the more cytotoxic the strain, the less virulent it is in animals. This relationship may seem paradoxical, but, as an intracellular pathogen, *L. monocytogenes* benefits from leaving its host cell unharmed.

Shortly after exposure to the mammalian-cell cytosol, *L. monocytogenes* expresses a surface protein, ActA, that mediates the nucleation of host actin filaments to propel the bacteria intra- and intercellularly. ActA mimics host proteins of the Wiskott-Aldrich syndrome protein (WASP) family by promoting the actin nucleation properties of the Arp2/3 complex. Thus, *L. monocytogenes* can enter the cytosol of almost any eukaryotic cell or cell extract and can exploit a conserved and essential actin-based motility system. Other pathogens as diverse as certain *Shigella*, *Mycobacterium*, *Rickettsia*, and *Burkholderia* spp. use a related pathogenic strategy that allows cell-to-cell spread without exposure to the extracellular milieu.

IMMUNE RESPONSE

The innate and acquired immune responses to *L. monocytogenes* have been studied extensively in mice. Shortly after IV injection, most bacteria are found in Kupffer cells in the liver, with some organisms in splenic dendritic cells and macrophages. Listeriae that survive the bactericidal activity of initially infected macrophages grow in the cytosol and spread from cell to cell. In the liver, the result is infection of hepatocytes. Neutrophils are crucial to host defense during the first 24 h of infection, while influx of activated macrophages from the bone marrow is critical subsequently. Mice that survive sublethal infection clear the infection within a week, with consequent sterile immunity. Studies with knockout mice have been instrumental in dissecting the roles played by chemokines and cytokines during infection. For example, interferon γ and tumor necrosis factor (TNF) are essential in controlling infection. While innate immunity is sufficient to control infection, the acquired immune response is required for sterile immunity. Immunity is cell-mediated; antibody plays no measurable role. The critical effector cells are cytotoxic (CD8+) T cells that recognize and lyse infected cells, and the resulting extracellular bacteria are killed by circulating activated phagocytes. Animals that survive challenge with sublethal doses of bacteria become immune to subsequent infection. A hallmark of the *L. monocytogenes* model is that killed vaccines do not provide protective immunity. The explanation for this fundamental observation is multifactorial, involving the generation of appropriate cytokines and the compartmentalization of bacterial proteins for antigen processing and presentation. Because the organism has the capacity to induce a robust cell-mediated immune response, attenuated strains have been engineered to express foreign antigens and are undergoing clinical studies as therapeutic vaccines for cancer and infectious disease applications.

EPIDEMIOLOGY

L. monocytogenes usually enters the body via the gastrointestinal tract in foods. Listeriosis is most often sporadic, although outbreaks do occur. Recent annual incidences in the United States range from 2 to 9 cases per 1 million population. No epidemiologic or clinical evidence supports human-to-human transmission (other than vertical transmission from mother to fetus) or waterborne infection. In line with its survival and multiplication at refrigeration temperatures, *L. monocytogenes* is commonly found in processed and unprocessed foods of animal and plant origin, especially soft cheeses, delicatessen meats, hot dogs, milk, and cold salads. Because

food supplies are increasingly centralized and normal hosts tolerate the organism well, outbreaks may not be immediately apparent; pulsed-field gel electrophoresis has proved useful in linking cases to specific foods. FoodNet, an active U.S. surveillance program, documented no significant change in the estimated incidence of listeriosis from 2005 through 2008. The U.S. Food and Drug Administration has a zero-tolerance policy for *L. monocytogenes* in ready-to-eat foods.

DIAGNOSIS

Symptoms of listerial infection overlap greatly with those of other infectious diseases. Timely diagnosis requires that the illness be considered in groups at risk: pregnant women; elderly persons; neonates; individuals immunocompromised by organ transplants, cancer, or treatment with TNF antagonists or glucocorticoids; and patients with a variety of chronic medical conditions, including alcoholism, diabetes, renal disease, rheumatologic illness, and iron overload. Meningitis in older adults (especially with parenchymal brain involvement or subcortical brain abscess) should trigger consideration of *L. monocytogenes* infection. Listeriosis occasionally affects healthy, young, nonpregnant individuals. HIV-infected patients are at risk; however, listeriosis seems to be prevented by trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis targeting other AIDS-related infections. The diagnosis is typically made by culture of blood, cerebrospinal fluid (CSF), or amniotic fluid. *L. monocytogenes* may be confused with "diphtheroids" or pneumococci in gram-stained CSF or may be gram-variable and confused with *Haemophilus* spp. Serologic tests and polymerase chain reaction assays are not clinically useful diagnostic tools at present.

CLINICAL MANIFESTATIONS

Listerial infections present as several clinical syndromes, of which meningitis and septicemia are most common. Monocytosis is seen in infected rabbits, but is not a hallmark of human infection.

Gastroenteritis

Appreciated only since the outbreaks of the late 1980s, listerial gastroenteritis typically develops within 48 h of ingestion of a large inoculum of bacteria in contaminated foods such as milk, deli meats, and salads. Attack rates are high (50–100%). *L. monocytogenes* is neither sought nor found in routine fecal cultures, but its involvement should be considered in outbreaks when cultures for other likely pathogens are negative. Sporadic intestinal illness appears to be uncommon. Manifestations include fever, diarrhea, headache, and constitutional symptoms. The largest reported outbreak occurred in an Italian school system and included 1566 individuals; ~20% of patients were hospitalized, but only one person had a positive blood culture. Isolated gastrointestinal illness does not require antibiotic treatment. Surveillance studies show that 0.1–5% of healthy asymptomatic adults may have stool cultures positive for the organism.

Bacteremia

L. monocytogenes septicemia presents with fever, chills, and myalgias/arthralgias and cannot be differentiated from septicemia involving other organisms. Meningeal symptoms, focal neurologic findings, or mental status changes may suggest the diagnosis. Bacteremia is documented in 70–90% of cancer patients with listeriosis. A nonspecific flulike illness with fever is a common presentation in pregnant women. Endocarditis of prosthetic and native valves is an uncommon complication, with reported fatality rates of 35–50% in case series. A lumbar puncture is often prudent, although not necessary, in pregnant women without central nervous system (CNS) symptoms.

Meningitis

L. monocytogenes causes ~5–10% of all cases of community-acquired bacterial meningitis in adults in the United States. Case-fatality rates are reported to be 15–26% and do not appear to have changed over time. This diagnosis should be considered in all older or chronically ill adults with "aseptic" meningitis. The presentation is more frequently subacute (with illness developing over several days) than in meningitis of other bacterial etiologies, and nuchal rigidity and meningeal signs are less common. Photophobia is infrequent. Focal findings and seizures are common in some but not all series. The CSF profile in listerial meningitis most often shows white blood cell (WBC) counts in the range of 100–5000/μL (rarely higher); 75% of patients have WBC counts below 1000/μL, usually with a neutrophil predominance more modest than that in other bacterial meningitides. Low glucose levels and positive results on Gram's staining are found ~30–40% of the time. Hydrocephalus can occur.

Meningoencephalitis and focal CNS infection

L. monocytogenes can directly invade the brain parenchyma, producing either cerebritis or focal abscess. Approximately 10% of cases of CNS infection are macroscopic abscesses resulting from bacteremic seeding; the affected patients often have positive blood cultures. Concurrent meningitis can exist, but the CSF may appear normal. Abscesses can be misdiagnosed as metastatic or primary tumors and, in rare instances, occur in the cerebellum and the spinal cord. Invasion of the brainstem results in a characteristic severe rhombencephalitis, usually in otherwise healthy older adults. The presentation may be biphasic, with a prodrome of fever and headache followed by asymmetric cranial nerve deficits, cerebellar signs, and hemiparetic and hemisensory deficits. Respiratory failure can occur. The subacute course and the often minimally abnormal CSF findings may delay the diagnosis, which may be suggested

by MRI images showing ring-enhancing lesions after gadolinium contrast and hyperintense lesions on diffusion-weighted imaging. MRI is superior to CT for the diagnosis of these infections.

Infection in pregnant women and neonates

Listeriosis in pregnancy is a severe and important infection. The usual presentation is a nonspecific acute or subacute febrile illness with myalgias, arthralgias, backache, and headache. Pregnant women with listeriosis are usually bacteremic. This syndrome should prompt blood cultures, especially in the absence of another reasonable explanation. Involvement of the CNS is rare in the absence of other risk factors. Preterm delivery is a common complication, and the diagnosis may be made only postpartum. As many as 70–90% of fetuses from infected women can become infected. Prepartum treatment of bacteremic women enhances the chances of delivery of a healthy infant. Women usually do well after delivery: maternal deaths are very rare, even when the diagnosis is made late in pregnancy or postpartum. Overall mortality rates for fetuses infected in utero approach 50% in some series; among live-born neonates treated with antibiotics, mortality rates are much lower (~20%). *Granulomatosis infantiseptica* is an overwhelming listerial fetal infection with miliary microabscesses and granulomas, most often in the skin, liver, and spleen. Less severe neonatal infection acquired in utero presents at birth. "Late-onset" neonatal illness typically develops ~10–30 days postpartum. Mothers of infants with late-onset disease are not ill.

TREATMENT **Infections Caused by *Listeria monocytogenes***

No clinical trials have compared antimicrobial agents for the treatment of *L. monocytogenes* infections. Data obtained in studies conducted in vitro and in animals as well as observational clinical data indicate that ampicillin is the drug of choice, although penicillin is also highly active. Adults should receive IV ampicillin at high doses (2 g every 4 h), and many experts recommend the addition of gentamicin for synergy (1.0–1.7 mg/kg every 8 h); retrospective uncontrolled trials are not conclusive, but one study suggests that gentamicin may not help. TMP-SMX, given IV, is the best alternative for the penicillin-allergic patient (15–20 mg of TMP/kg per day in divided doses every 6–8 h). The dosages recommended cover CNS infection and bacteremia (see next for duration); dosages must be reduced for patients with renal insufficiency. One small nonrandomized study supports a combination of ampicillin and TMP-SMX. Case reports document success with vancomycin, imipenem, meropenem, linezolid, tetracycline, and macrolides, although there are also reports of clinical failure or disease development with some of these agents. Cephalosporins are *not* effective and should not be used. Neonates should receive ampicillin and gentamicin at doses based on weight.

The duration of therapy depends on the syndrome: 2 weeks for bacteremia, 3 weeks for meningitis, 6–8 weeks for brain abscess/encephalitis, and 4–6 weeks for endocarditis in both neonates and adults. Early-onset neonatal disease may be more severe and should be treated for >2 weeks.

COMPLICATIONS AND PROGNOSIS

Many individuals who are promptly diagnosed and treated recover fully, but permanent neurologic sequelae are common in patients with brain abscess or rhombencephalitis. Focal infections of visceral organs; the eye; the pleural, peritoneal, and pericardial spaces; and the bones and joints have all been reported. Of 100 live-born treated neonates in one series, 60% recovered fully, 24% died, and 13% had long-term neurologic or other complications.

PREVENTION

Healthy persons should take standard precautions to prevent food-borne illness: fully cooking meats, washing fresh vegetables, carefully cleaning utensils, and avoiding unpasteurized dairy products. In addition, persons at risk for listeriosis, including pregnant women, should avoid soft cheeses (although hard cheeses and yogurt are not problematic) and should avoid or thoroughly reheat ready-to-eat and delicatessen foods, even though the absolute risk they pose is relatively low.

CHAPTER 44

TETANUS

C. Louise Thwaites ■ Lam Minh Yen

Tetanus is an acute disease manifested by skeletal muscle spasm and autonomic nervous system disturbance. It is caused by a powerful neurotoxin produced by the bacterium *Clostridium tetani* and is completely preventable by vaccination. *C. tetani* is found throughout the world, and tetanus commonly occurs where the vaccination coverage rate is low. In developed countries, the disease is seen occasionally in individuals who are incompletely vaccinated. In any setting, established tetanus is a severe disease with a high mortality rate.

DEFINITION

Tetanus is diagnosed on clinical grounds (sometimes with supportive laboratory confirmation of the presence of *C. tetani*; see "Diagnosis," later in chapter), and case definitions are often used to facilitate clinical and epidemiologic assessments. The Centers for Disease Control and Prevention (CDC) defines tetanus as "the acute onset of hypertonia or. . .painful muscular contractions (usually of the muscles of the jaw and neck) and generalized muscle spasms without other apparent medical cause." Neonatal tetanus is defined by the World Health Organization (WHO) as "an illness occurring in a child who has the normal ability to suck and cry in the first 2 days of life, but who loses this ability between days 3 and 28 of life and becomes rigid and has spasms." Given the unique presentation of neonatal tetanus, the history generally permits accurate classification of the illness with a high degree of probability. Maternal tetanus is defined by the WHO as tetanus occurring during pregnancy or within 6 weeks after the conclusion of pregnancy (whether with birth, miscarriage, or abortion).

ETIOLOGY

C. tetani is an anaerobic, gram-positive, spore-forming rod whose spores are highly resilient and can survive readily in the environment throughout the world. Spores resist boiling and many disinfectants. In addition, *C. tetani* spores and bacilli survive in the intestinal systems of many animals, and fecal carriage is common. The spores or bacteria enter the body through abrasions, wounds, or (in the case of neonates) the umbilical stump. Once in a suitable anaerobic environment, the organisms grow, multiply, and release tetanus toxin, an exotoxin that enters the nervous system and causes disease. Very low concentrations of this highly potent toxin can result in tetanus (minimum lethal human dose, 2.5 ng/kg).

In ~20% of cases of tetanus, no puncture entry wound is found. Superficial abrasions to the limbs are the commonest infection sites in adults. Deeper infections (e.g., attributable to open fracture, abortion, or drug injection) are associated with more severe disease and worse outcomes. In neonates, infection of the umbilical stump can result from inadequate umbilical cord care; in some cultures, for example, the cord is cut with grass or animal dung is applied to the stump. Circumcision or ear-piercing can also result in neonatal tetanus.

EPIDEMIOLOGY

Reliable epidemiologic data on worldwide incidence are difficult to obtain, and tetanus is notoriously underreported. Studies have shown that in much of the world only 2–10% of tetanus cases are recorded. Estimates from the early 1980s suggested that tetanus caused >1 million deaths annually. As worldwide vaccination coverage has improved, the number of cases has fallen, particularly among children and neonates, who have been predominantly targeted in recent vaccination programs. In 2006, an estimated 290,000 people died of tetanus, mostly in Southeast Asia and Africa.

The elimination of maternal and neonatal tetanus is one goal of the WHO and its Expanded Programme on Immunization (EPI). An estimated 5% of maternal mortality in the 1990s was attributed to maternal tetanus. Tetanus in pregnant women and neonates is prevented by maternal immunization during pregnancy (see "Prevention," later in the chapter), which is an integral component of the EPI. Although immunization coverage continues to increase, maternal and neonatal tetanus still represents an important global health burden, causing ~180,000 deaths per year.

Tetanus is a rare disease in the developed world. In 2007, a total of 28 cases were reported to the U.S. national surveillance system. Most cases occur in incompletely vaccinated or unvaccinated individuals. Persons >60 years of age are at greater risk of tetanus because antibody levels decrease over time. Injection drug users—particularly those injecting heroin subcutaneously ("skin-popping")—are increasingly recognized as a high-risk group. Between 1995 and 2000, 15–18% of U.S. tetanus infections occurred in injection drug users. In 2004, an outbreak of tetanus occurred in the United Kingdom, which had previously reported low rates among drug users. The reasons for this outbreak remain unclear but are thought to involve a combination of heroin contamination, skin-popping, and incomplete vaccination.

PATHOGENESIS

C. tetani produces two exotoxins: tetanolysin and tetanospasmin. Tetanolysin, which is related to the clostridial toxins and streptolysin, plays no role in the pathogenesis of the disease. Tetanospasmin, generally referred to as "tetanus toxin," is the neurotoxin that causes the manifestations of disease.

Toxin is transported by intra-axonal transport to motor nuclei of the cranial nerves or ventral horns of the spinal cord. Tetanus toxin is produced as a single 150-kDa protein that is cleaved to produce heavy (100-kDa) and light (50-kDa) chains linked by a disulfide bond and noncovalent forces. The carboxy terminal of the heavy chain binds to specific membrane components in presynaptic α-motor nerve terminals; evidence suggests binding to both polysialogangliosides and membrane proteins. This binding results in toxin internalization and uptake into the nerves. (Botulinum toxins enter the nervous system by a similar method but remain mostly at the neuromuscular junction and thus produce different clinical features.)

Once inside the neuron, the toxin enters a retrograde transport pathway, whereby it is transported proximally to the motor neuron body in what appears to be a highly specific process. Unlike other components of the endosomal contents, which undergo acidification following internalization, tetanus toxin is transported in a carefully regulated pH-neutral environment that prevents an acid-induced conformational change that would result in light-chain expulsion into the surrounding cytosol.

The next stage in toxin trafficking is less clearly understood but involves tetanus toxin's escaping normal lysosomal degradation processes and undergoing translocation across the synapse to the GABA-ergic presynaptic inhibitory interneuron terminals. Here the light chain, which is a zinc-dependent endopeptidase, cleaves vesicle-associated membrane protein 2 (VAMP2, also known as synaptobrevin). This molecule is necessary for presynaptic binding and release of neurotransmitter; thus tetanus toxin prevents transmitter release and effectively blocks inhibitory interneuron discharge. The result is unregulated activity in the motor nervous system. Similar activity in the autonomic system accounts for the characteristic features of skeletal muscle spasm and autonomic system disturbance. The increased circulating catecholamine levels in severe tetanus are associated with cardiovascular complications.

Relatively little is known about the processes of recovery from tetanus. Recovery can take several weeks. Peripheral nerve sprouting is involved in recovery from botulism, and similar central nervous system sprouting may occur in tetanus. Other evidence suggests toxin degradation as a mechanism of recovery.

APPROACH TO THE PATIENT **Tetanus**

The clinical manifestations of tetanus occur only after tetanus toxin has reached presynaptic inhibitory nerves. Once these effects become apparent, there may be little that can be done to affect disease progression. Management strategies aim to support vital functions until the effects of the toxin have worn off. Recent interest has focused on intrathecal methods of antitoxin administration to neutralize toxin within the central nervous system and limit disease progression (see "Treatment," later in the chapter).

CLINICAL MANIFESTATIONS

Tetanus produces a wide spectrum of clinical features that are broadly divided into generalized (including neonatal) and local. In the usually mild form of local tetanus, only isolated areas of the body are affected and only small areas of local muscle spasm may be apparent. If the cranial nerves are involved in localized cephalic tetanus, the phargyngeal or laryngeal muscles may spasm, with consequent aspiration or airway obstruction, and the prognosis may be poor. In the typical progression of generalized tetanus **(Fig. 44-1)**, muscles of the face and jaw often are affected first, presumably because of the shorter distances toxin must travel up motor nerves to reach presynaptic terminals.

In assessing prognosis, the speed at which tetanus develops is important. The incubation period (time from wound to first symptom) and the period of onset (time from first symptom to first generalized spasm) are of particular significance; shorter times are associated with worse outcome. In neonatal tetanus, the younger the infant is when symptoms occur, the worse the prognosis.

The commonest initial symptoms are trismus (lockjaw), muscle pain and stiffness, back pain, and difficulty swallowing. In neonates, difficulty in feeding is the usual presentation. As the disease progresses, muscle spasm develops. Generalized muscle spasm can be very painful. Commonly, the laryngeal muscles are involved early or even in isolation. This is a life-threatening event as complete airway obstruction may ensue. Spasm of the respiratory muscles results in respiratory failure. Without ventilatory support, respiratory failure is the commonest cause of death in tetanus. Spasms strong enough to produce tendon avulsions and crush fractures have been reported, but this outcome is rare.

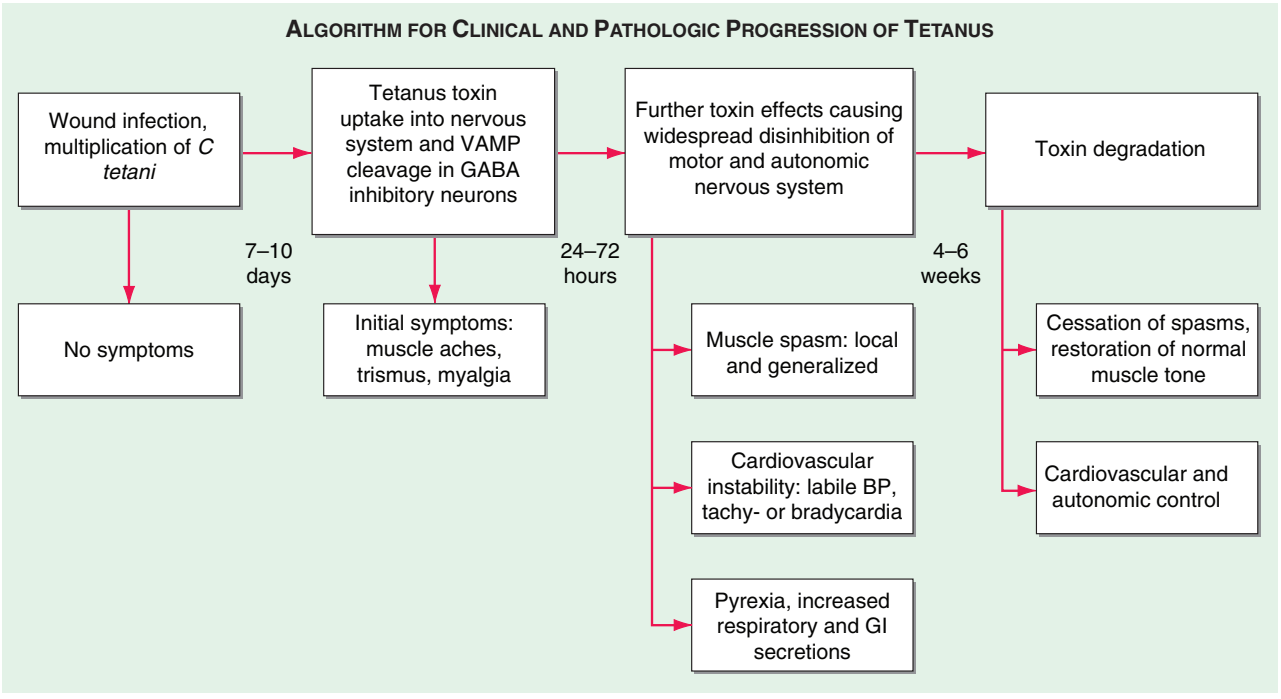


FIGURE 44-1
Clinical and pathologic progression of tetanus. BP, blood pressure; GABA, γ-aminobutyric acid; GI, gastrointestinal; VAMP, vesicle-associated monophosphate (synaptobrevin).

Autonomic disturbance is maximal during the second week of severe tetanus, and death due to cardiovascular events becomes the major risk. Blood pressure is usually labile, with rapid fluctuations from high to low accompanied by tachycardia. Episodes of bradycardia and heart block can also occur. Autonomic involvement is evidenced by gastrointestinal stasis, sweating, increased tracheal secretions, and acute (often high-output) renal failure.

DIAGNOSIS

The diagnosis of tetanus is clinical; culture of *C. tetani* from a wound provides supportive evidence. The few conditions that mimic generalized tetanus include strychnine poisoning and dystonic reactions to antidopaminergic drugs. Abdominal muscle rigidity is characteristically continuous in tetanus but is episodic in the latter two conditions. Cephalic tetanus can be confused with other causes of trismus, such as oropharyngeal infection. Hypocalcemia and meningoencephalitis are included in the differential diagnosis of neonatal tetanus.

TREATMENT Tetanus

If possible, the entry wound should be identified, cleaned, and debrided of necrotic material in order to remove anaerobic foci of infection and prevent further toxin production. Metronidazole (400 mg rectally or 500 mg IV every 6 h for 7 days) is the preferred antibiotic. An alternative is penicillin (100,000–200,000 IU/kg per day), although this drug theoretically may exacerbate spasms. Failure to remove pockets of ongoing infection may result in recurrent or prolonged tetanus.

Antitoxin should be given early in an attempt to deactivate any circulating tetanus toxin and prevent its uptake into the nervous system. Two preparations are available: human tetanus immune globulin (TIG) and equine antitoxin. TIG is the preparation of choice as it is less likely to be associated with anaphylactoid reactions. Standard therapy is 3000–6000 IU of TIG or 10,000–20,000 U of equine antitoxin as a single IM dose. However, there is evidence that intrathecal administration of TIG inhibits disease progression and leads to a better outcome. The results of a randomized controlled trial have been supported by a meta-analysis of trials involving both adults and neonates, with TIG doses of 50–1500 IU administered intrathecally.

Spasms are controlled with heavy sedation using benzodiazepines. Chlorpromazine or phenobarbital are commonly used worldwide, and IV magnesium sulfate has been used as a muscle relaxant. A significant problem with all these treatments is that the doses necessary to control spasms also cause respiratory depression; thus, in resource-limited settings without mechanical ventilators, controlling spasms while maintaining adequate ventilation is problematic, and respiratory failure is a common cause of death. In locations with ventilation equipment, severe spasms are best controlled with a combination of sedatives or magnesium and relatively short-acting, cardiovascularly inert, nondepolarizing neuromuscular blocking agents that

allow titration against spasm intensity. Infusions of propofol have also been used successfully to control spasms and provide sedation.

It is important to establish a secure airway early in severe tetanus. Ideally, patients should be nursed in calm, quiet environments because light and noise can trigger spasms. Tracheal secretions are increased in tetanus, and dysphagia due to pharyngeal involvement combined with hyperactivity of laryngeal muscles makes endotracheal intubation difficult. Thus tracheostomy is the usual method of securing the airway in severe tetanus.

Cardiovascular instability in severe tetanus is notoriously difficult to treat. Rapid fluctuations in blood pressure and heart rate can occur. Cardiovascular stability is improved by increasing sedation with IV magnesium sulfate (plasma concentration, 2–4 mmol/L), morphine, or other sedatives. In addition, drugs acting specifically on the cardiovascular system (e.g., esmolol, calcium antagonists, and inotropes) may be required. Short-acting drugs that allow rapid titration are preferred; particular care should be taken when longer-acting β antagonists are administered, as their use has been associated with hypotensive cardiac arrest.

Complications arising from treatment are common and include thrombophlebitis associated with diazepam injection, ventilator-associated pneumonia, central-line infections, and septicemia. In some centers, prophylaxis against deep-vein thrombosis and thromboembolism is routine.

Recovery from tetanus may take 4–6 weeks. Patients must be given a full primary course of immunization as tetanus toxin is poorly immunogenic and the immune response following natural infection is inadequate.

PROGNOSIS

Rapid development of tetanus is associated with more severe disease and poorer outcome; it is important to note time of onset and length of incubation period. More sophisticated modeling based on data from adults has revealed other important predictors of prognosis (Table 44-1). Few studies have formally addressed long-term outcomes of tetanus. However, it is generally accepted that recovery is typically complete unless periods of hypoventilation have been prolonged or other complications have ensued. Studies of children and neonates have suggested that neonates who have experienced prolonged periods of hypoxia may be at increased risk of learning disabilities, behavioral problems, and cerebral palsy.

TABLE 44-1

FACTORS ASSOCIATED WITH A POOR PROGNOSIS IN TETANUS

ADULT TETANUS	NEONATAL TETANUS
Age >70 years	Younger age, premature birth
Incubation period <7 days	Incubation period <6 days
Short time from first symptom to admission	Delay in hospital admission
Puerperal, IV, postsurgery, burn entry site	Grass used to cut cord
Period of onset[a] <48 h	
Heart rate >140 bpm[b]	
Systolic blood pressure >140 mmHg[b]	
Severe disease or spasms[b]	
Temperature >38.5°C[b]	

[a]Time from first symptom to first generalized spasm.
[b]At hospital admission.

PREVENTION

Tetanus is prevented by good wound care and immunization (Chap. 4). In neonates, use of safe, clean delivery and cord-care practices as well as maternal vaccination are essential. Tetanus toxoid (TT) for vaccination is available in various preparations: single-dose TT, TT with high- or low-dose diphtheria toxoid, or TT with diphtheria toxoid in combination with whole-cell/acellular pertussis, *Haemophilus influenzae* type b, hepatitis B, or polio vaccine.

The WHO guidelines for tetanus vaccination consist of a primary course of three doses in infancy, boosters at 4–7 and 12–15 years of age, and one booster in adulthood. In the United States, the CDC suggests an additional dose at 14–16 months and boosters every 10 years. "Catch-up" schedules recommend a three-dose primary course for unimmunized adolescents followed by two further doses. For persons who have received a complete primary course in childhood but no further boosters, two doses at least 4 weeks apart are recommended.

Standard WHO recommendations for prevention of maternal and neonatal tetanus call for administration of two doses of TT at least 4 weeks apart to the previously unimmunized pregnant woman. However, in high-risk areas, a more intensive approach has been successful, with all women of childbearing age receiving a primary course along with education on safe delivery and postnatal practices.

Individuals sustaining tetanus-prone wounds should be immunized if their vaccination status is incomplete or unknown or if their last booster was given >10 years earlier. Patients sustaining wounds not classified as clean or minor should also undergo passive immunization with TIG.

CHAPTER 45

BOTULISM

Jeremy Sobel ■ Susan Maslanka

Botulinum toxin is the most toxic substance known. Botulism, a rare disease, occurs naturally as four syndromes: (1) food-borne illness due to ingestion of toxin in contaminated food; (2) wound infection due to wound colonization by toxigenic clostridia with in situ toxin production; (3) infant botulism due to colonization of the infant intestine by toxigenic clostridia with in situ toxin production; and (4) adult intestinal toxemia, a rare form of colonization with similarities to infant botulism. In addition to these recognized natural forms, botulism has been reported in association with injections of botulinum toxin for cosmetic or therapeutic purposes and after inhalation of aerosolized botulinum toxin. Botulism is caused by the toxin's inhibition of acetylcholine release at the neuromuscular junction through an enzymatic mechanism. All forms of botulism manifest as a distinct clinical syndrome of symmetric cranial nerve palsies followed by descending symmetric flaccid paralysis of voluntary muscles, which may progress to respiratory compromise and death. The mainstays of therapy are meticulous intensive care and timely treatment with antitoxin, which may limit the extent of paralysis. Rapid clinical diagnosis is critical for decisions about treatment.

ETIOLOGY AND PATHOGENESIS

Botulinum toxin–producing clostridia are anaerobic gram-positive organisms that form subterminal spores and are ubiquitous in the environment. The hardy spores survive environmental conditions and ordinary cooking procedures. Toxin production, however, requires spore germination, which occurs only with a rare confluence of circumstances: an anaerobic atmosphere, a pH of >4.5, low salt and sugar concentrations, and temperatures of 4–120°C. Although commonly ingested, spores do not normally germinate in the intestine.

The various species of toxigenic clostridia—*C. botulinum* groups I, II, and III; *C. argentinense* (toxin type G); *C. baratii* (toxin type F); and *C. butyricum* (toxin type E)—can be differentiated on the basis of phenotypic characteristics, including specific biochemical properties and morphologic appearance on egg yolk agar. Strains of a given species can be distinguished by the antigenic specificity of the botulinum neurotoxin they produce; certain strains may produce more than one toxin serotype.

The seven identified toxin serotypes (A, B, C, D, E, F, and G) are antigenically distinct but structurally similar (~150-kDa zinc-endopeptidase proteins consisting of a 100-kDa heavy chain and a 50-kDa light chain). Whether ingested, inhaled, or produced in the intestine or a wound, botulinum neurotoxin enters the vascular system and is transported to peripheral cholinergic nerve terminals, including neuromuscular junctions, postganglionic parasympathetic nerve endings, and peripheral ganglia. The central nervous system probably is not involved. Steps in neurotoxin activity include (1) heavy-chain binding to nerve terminals, (2) internalization in endocytic vesicles, (3) translocation to cytosol, and (4) light-chain serotype-specific cleavage of one of several proteins involved in the release of the neurotransmitter acetylcholine. Inhibition of acetylcholine release by any of the seven toxin serotypes results in characteristic flaccid paralysis. Recovery follows sprouting of new nerve terminals.

Toxin serotypes A, B, E, and (rarely) F cause human disease. Toxin type A produces the most severe syndrome, with the greatest proportion of patients requiring mechanical ventilation. Toxin type B appears to cause milder disease than type A. Two cases of human illness due to toxin type C and one outbreak caused by toxin type D were reported more than 50 years ago. The reasons for the rarity of cases due to types C and D are not known; all four serotypes that affect humans produce botulism in experimental models. Toxin type E, most often associated with foods of aquatic origin, produces a syndrome of variable severity. The rare cases of illness caused by toxin type F are characterized by rapid progression to quadriplegia and respiratory failure but also by relatively rapid recovery.

EPIDEMIOLOGY

Person-to-person transmission of botulism has not been described.

Food-borne botulism is caused by consumption of foods contaminated with botulinum toxin. Most botulism cases are sporadic; outbreaks are typically small, involving two or three cases. The wide variation in reported rates of botulism by region and continent probably reflects differences both in true incidence and in diagnostic and reporting capacity. Worldwide, the highest incidence rate is reported from the Republic of Georgia and Armenia in the southern Caucasus region, where illness is associated with risky home-canning practices. In the United States during 1990–2000, the median number of food-borne cases per year was 23 (range, 17–43). The incidence rate was highest and the number of cases greatest in Alaska, with contaminated traditional Alaskan Native dishes implicated in every instance. Outside Alaska, food was implicated in 75 of 101 botulinum intoxication events. Of the 68 events caused by homemade foods, 47 (69%) involved home-canned items. Of the 7 events caused by non-homemade foods, five (affecting 10 people) were caused by commercial foods, and two (affecting 25 people) were caused by restaurant-prepared foods. Severe outbreaks traced to commercially prepared foods have occurred in more recent years. In 2006, patients in the U.S. states of Georgia and Florida as well as in the Canadian province of Ontario developed severe botulism after consuming commercially produced carrot juice contaminated with a high level of toxin type A. Very high toxin levels were recorded in some of the patients' serum samples, with toxemia persisting for a record 25 days after illness onset in one patient. Outbreaks caused by contaminated commercial chili occurred in 2001 (15 cases in Texas) and 2007 (8 cases in Ohio, Indiana, and Texas).

Wound botulism is caused by contamination of wounds with *C. botulinum* spores, subsequent spore germination, and toxin production in the anaerobic milieu of an abscess. Since the early 1990s, cases in the United States have occurred almost exclusively in injection drug users. The typical patient is a 30- to 50-year-old resident of the western United States with a long history of black-tar heroin injection.

Infant botulism results from absorption of toxin produced in situ by toxigenic clostridia colonizing the intestine of children ≥1 year of age. Colonization is believed to occur because the normal bowel flora is not yet fully established; this theory is supported by studies in animals. Infant botulism is the most common form of the disease in the United States, with ~80–100 cases reported annually. Geographic "hot spots" are located in areas around Pennsylvania and California.

Adult intestinal toxemia botulism results from absorption of toxin produced in situ after rarely occurring intestinal colonization with toxigenic clostridia. Typically, patients have some anatomic or functional bowel abnormality or have recently used antibiotics that may protect normally fastidious *Clostridium* species from competing components of the bowel flora. Despite antitoxin treatment, protracted symptoms or relapse due to ongoing intraluminal production of toxin may be observed.

Iatrogenic botulism results from injection of toxin. Paralysis of variable severity has followed injection of licensed botulinum toxin products for treatment of conditions involving hypertonicity of large muscle groups. Injection of approved doses of licensed products for cosmetic purposes has not been associated with botulism. Botulism requiring ventilator support has also resulted from illegal injection of research-grade toxin.

BOTULISM AS A POTENTIAL WEAPON OF BIOTERRORISM

Botulinum toxin has been "weaponized" by governments and terrorist organizations. An attack might employ aerosolization of toxin or contamination of foods or beverages ranging in scope from small-scale tampering to contamination of a widely distributed food item. Initially, it might be difficult to differentiate a naturally occurring outbreak from an intentional attack. An unnatural event may be suggested by unusual relationships between patients and atypical exposure vehicles and toxin types. Epidemiologic features consistent with aerosol dissemination may include the victims' being in a common location (e.g., a building or public area) or being exposed to a common ventilation system, along with lack of a common food exposure. Unusual epidemiologic features of an outbreak of food-borne botulism might include implication of an unlikely commercial food product. Nevertheless, an unintentional food-borne botulism outbreak can likewise have unusual features, and an intentional event may have conventional features.

CLINICAL MANIFESTATIONS

The distinctive clinical syndrome of botulism consists of symmetric cranial nerve palsies followed by symmetric descending flaccid paralysis that may progress to respiratory arrest and death. In *food-borne botulism*, the incubation period from ingestion of food containing botulinum toxin to onset of symptoms is usually 18–36 h but, depending on the toxin dose, can range from a few hours to several days. The extent of paralysis (from a few cranial nerves only to quadriplegia) also depends on the toxin dose. The illness ranges from a mild condition for which no medical advice is sought to severe disease that can result in death within 24 h. In *wound botulism* in injection drug users, the incubation period is difficult to establish because most patients inject drug several times daily. The clinical syndrome is indistinguishable from that of food-borne botulism except that gastrointestinal symptoms are typically absent. Often the abscess is a minor lesion, a furuncle, or cellulitic in appearance. The clinical presentation of *infant botulism* resembles that of adult forms of botulism, including inability to suck and swallow, weakened voice, ptosis, and floppy neck, sometimes with progression to generalized flaccidity and respiratory compromise.

Cranial nerve involvement, which almost always marks the onset of symptoms of botulism, usually produces diplopia, dysarthria, dysphonia, and/or dysphagia. Cranial nerve palsies are the presenting manifestations that typically cause patients to seek medical care; their absence or their onset after the appearance of other true neurologic symptoms makes botulism highly unlikely. Weakness progresses, often rapidly, from the head to involve the neck, arms, thorax, and legs; occasionally, weakness is asymmetric.

Cranial nerve palsies are characteristically followed by flaccid, descending, completely symmetric paralysis of voluntary muscles. Paresthesias have been reported and may represent secondary nerve compression from immobility due to paralysis. Paralysis of the diaphragm and accessory breathing muscles may result in respiratory compromise or arrest and death. Pharyngeal collapse secondary to cranial nerve paralysis may compromise the airway and require intubation in the absence of respiratory muscle compromise. Autonomic symptoms may include anhidrosis, with pronounced mucosal erythema and pain mimicking pharyngitis, and postural hypotension. In food-borne botulism, nausea, vomiting, and abdominal pain may precede or follow the onset of paralysis. Constipation due to paralytic ileus is nearly universal, and urinary retention is also common. Extraocular muscle paralysis manifests as blurred vision or diplopia and an inability to accommodate near vision. Ptosis and facial paralysis are frequent; the pupillary reflexes may be depressed, and fixed or dilated pupils are noted in half of patients. Dizziness, dry mouth, and very dry, occasionally sore throat are common. Vital signs are usually normal, but in some cases hypotension occurs. Patients are usually afebrile. The gag reflex may be suppressed, and deep tendon reflexes may be normal or may progressively disappear.

Patients usually exhibit no sensory or cognitive deficits. They are generally alert and oriented, but they may be drowsy, agitated, and anxious. Even when intubated, patients can respond to questions by moving their fingers or toes unless paralysis has affected the digits. Unfortunately, in some instances the severe ptosis, expressionless facies, and weak phonation of patients with botulism have been interpreted as signs of mental status changes from alcohol intoxication, drug overdose, encephalitis, or meningitis; in such cases, the consequences can be delayed diagnosis, prolonged paralysis, and complications. Because of skeletal muscle paralysis, patients experiencing respiratory distress may appear placid and detached even as they near respiratory arrest. Death in untreated botulism is usually due to airway obstruction from pharyngeal muscle paralysis and inadequate tidal volume resulting from paralysis of diaphragmatic and accessory respiratory muscles. Death can also result from nosocomial infections and other sequelae of long-term paralysis, hospitalization, and mechanical ventilatory support.

Toxin binding is irreversible, but nerve terminals do regenerate. In the United States, 95% of patients recover fully, but this process may take many months and often requires extended outpatient rehabilitation therapy.

DIAGNOSIS

Differential diagnosis

In the setting of an outbreak with multiple cases, the diagnosis readily suggests itself; that is, a cluster of two or more cases with compatible symptoms is essentially pathognomonic since other illnesses that resemble botulism do not cause outbreaks. In lone (sporadic) cases, however, the diagnosis is often missed. The differential diagnosis includes Guillain-Barré syndrome (GBS), myasthenia gravis, stroke syndromes, Eaton-Lambert syndrome, and tick paralysis. Less likely are poisoning by tetrodotoxin, shellfish, or a host of rarer agents and antimicrobial drug–associated paralysis. A thorough history and meticulous physical examination can effectively eliminate most alternative diagnoses. Brain imaging may help rule out rare nonlateralizing stroke syndromes.

GBS, a rare autoimmune demyelinating polyneuropathy that often follows an acute infection, presents most often as an ascending paralysis and never causes outbreaks. Occasional GBS cases present as the Miller Fisher variant, whose characteristic triad of ophthalmoplegia, ataxia, and areflexia is easily mistaken for the early descending paralysis of botulism. Protein levels in cerebrospinal fluid (CSF) are elevated in all forms of GBS; because this increase may be delayed until several days after symptom onset, an early lumbar puncture with a negative result may need to be repeated. In contrast, CSF findings are generally normal in botulism, although marginally elevated CSF protein concentrations have been reported in some patients with wound botulism. In experienced hands, electromyography may demonstrate findings consistent with GBS but not with botulism.

The edrophonium (Tensilon) test is sometimes of value in distinguishing botulism (usually a negative result; sometimes borderline positive) from myasthenia gravis (a positive result). A strongly positive edrophonium test, in either the presence or the absence of anti–acetylcholine receptor autoantibodies, confirms the diagnosis of myasthenia gravis.

In most cerebrovascular accidents, physical examination reveals asymmetry of paralysis and upper motor neuron signs. Brain imaging can reveal the rare basilar stroke that produces symmetric bulbar palsies. Eaton-Lambert syndrome usually manifests as proximal limb weakness in a patient already debilitated by cancer. Tick paralysis is a rare flaccid condition closely resembling botulism and caused by neurotoxins of certain ticks.

History and laboratory confirmation

In suspected food-borne botulism, a 3- to 5-day food history should be obtained, with specific questions about home-canned, exotic, and unusual foods. A history of recent consumption of home-canned food substantially enhances the probability of food-borne botulism. The names of contacts who may have shared foods should be obtained early in case the patient's illness progresses to respiratory failure. In wound botulism, material from abscesses should be collected in anaerobic

culture tubes for testing at public health laboratories, and serum samples should be collected. Standard blood work and radiologic studies are not useful in diagnosing botulism.

Botulism in a symptomatic patient can be confirmed in the laboratory by demonstration of toxin in clinical specimens (serum, stool, sterile water or saline enema, gastric aspirates, wound material) or in samples of ingested foods. Isolation of toxigenic clostridia from stool also constitutes evidence of botulism; the organism is rarely isolated from the stools of asymptomatic persons. Wound cultures yielding the organism are highly suggestive in symptomatic cases. In the United States, testing is conducted only in public health laboratories staffed by experienced personnel. The universally accepted method for confirmation of botulism is the mouse bioassay. Neutralization of the paralytic effects in mice by a specific antitoxin provides evidence of that toxin serotype in the clinical sample. Mouse bioassay results may not be available for up to 48 h; accordingly, all decisions about clinical management, including the administration of botulinum antitoxin, must be based on the clinical presentation, with bioassay results serving as confirmation. The sensitivity of the bioassay varies inversely with the time elapsed between symptom onset and sample collection. A test may be negative even when a patient has botulism; however, if the clinical presentation is questionable and test results are negative, additional tests may be necessary to rule out other conditions. New tests for botulism are being developed but remain experimental. At this time, no alternative to the mouse bioassay exists for laboratory confirmation of botulism. In affected muscles, findings consistent with botulism include reduced amplitude of motor potentials and potentiation with rapid repetitive stimulation.

The earliest available serum sample (e.g., that obtained at admission) should be preserved for testing. Vomit or nasogastric tube secretions should be collected immediately. A stool sample should be collected by means of a sterile water enema if the patient is constipated or otherwise unable to produce a sample. All samples, including suspect foods, should be kept refrigerated—not frozen—pending shipment directions from public health officials. In general, ingested toxin is not demonstrable in serum later than 1 week after exposure, although detection 25 days after ingestion has been documented. Toxin and toxigenic clostridia can be detected in stool later in the course of illness, and the toxin is stable indefinitely in many food matrices. Diagnosis of adult intestinal toxemia botulism requires the demonstration of protracted excretion of organisms and toxin in the stool.

TREATMENT **Botulism**

The cornerstones of treatment for botulism are meticulous intensive care and immediate administration of botulinum antitoxin. Persons of all ages (including infants) in whom botulism is suspected should be hospitalized immediately in an intensive care setting, with frequent monitoring of vital capacity and mechanical ventilation if required. Paralysis may last for weeks or months, and meticulous intensive care is required throughout this period of debilitation. The decision to administer botulinum antitoxin—the only specific treatment—must be based on a clinical diagnosis and cannot be postponed while laboratory confirmation is awaited. Botulinum antitoxin neutralizes only toxin molecules that have not yet bound to nerve endings; it cannot reverse existing paralysis. Thus, antitoxin should be given early in the course of illness, ideally <24 h after symptom onset. Infant botulism is treated with a licensed human-origin antitoxin; although the survival rate in infant botulism is nearly 100% with or without antitoxin therapy, this treatment halves the median hospitalization period (from 6 to 3 weeks). Other forms of botulism are treated with equine-source antitoxin. Treatment with the licensed, non-despeciated, equine-origin antitoxins long used in the United States is associated with anaphylaxis, other hypersensitivity reactions, and serum sickness. A new heptavalent despeciated equine antitoxin has replaced the previously used non-despeciated equine antitoxin in this country.

In wound botulism, suspect wounds and abscesses should be cleaned, debrided, and drained promptly. *C. botulinum* is susceptible to penicillins and various other antimicrobial agents. The effectiveness of antimicrobial therapy for wound botulism has not been established, and such treatment should be guided by clinical judgment.

Although no case of person-to-person transmission of botulism has been reported and although levels of toxin in bodily fluids (including serum and stool) are insufficient to cause serious illness, absorption of botulinum toxin through mucosal surfaces, the eye, or nonintact skin sometimes causes local paralysis. Standard precautions should be exercised when evaluating and treating patients. As a precaution, persons exposed to bodily fluids or stool of botulism patients should be advised of the early signs of botulism and instructed to report for evaluation if these signs are noted. Standard hospital decontamination procedures should be used to clean medical equipment and supplies that have come into contact with a botulism patient.

NOTIFICATION, EXPERT CONSULTATION, AND ANTITOXIN PROVISION

Every botulism case is a public health emergency. The clinician must report a suspected case on an emergency basis to the state health department, which will initiate an epidemiologic investigation and put the physician in contact with the Centers for Disease Control and Prevention (CDC) 24-h botulism consultancy service (Emergency Operations Center: 770-488-7100) or a locally available service. The CDC consultant will

(1) review the case by telephone; (2) help arrange laboratory confirmation at appropriate testing facilities; and (3) arrange emergency shipment of antitoxin (adult cases only), which in the United States is available exclusively from the CDC. In addition, the Infant Botulism Treatment and Prevention Program of the California Department of Public Health (510-231-7600) provides 24-h consultation and distributes antitoxin (licensed BabyBIG®) for the treatment of infant botulism cases. Except in cases involving infants who reside in California, laboratory testing requests must still be authorized by the state health department where the infant is located or by the CDC.

PREVENTION

No prophylaxis or licensed vaccine for botulism is available. An experimental vaccine for administration to laboratory workers is available from the CDC. Persons exposed to botulinum toxin should be evaluated by a physician and carefully observed for the development of symptoms. If symptoms do appear, the patient should be treated immediately with botulinum antitoxin as described above. If antitoxin supplies are limited, treatment will most likely benefit patients with symptoms that are progressive but have not yet progressed to respiratory failure.

CHAPTER 46

GAS GANGRENE AND OTHER CLOSTRIDIAL INFECTIONS

Amy E. Bryant ■ Dennis L. Stevens

The genus *Clostridium* encompasses more than 60 species that may be commensals of the gut microflora or may cause a variety of infections in humans and animals through the production of a plethora of proteinaceous exotoxins. *C. tetani* and *C. botulinum*, for example, cause specific clinical disease by elaborating single but highly potent toxins. In contrast, *C. perfringens* and *C. septicum* cause aggressive necrotizing infections that are attributable to multiple toxins, including bacterial proteases, phospholipases, and cytotoxins.

ETIOLOGIC AGENT

Vegetative cells of *Clostridium* species are pleomorphic, rod-shaped, and arranged singly or in short chains (Fig. 46-1); the cells have rounded or sometimes pointed ends. Although clostridia stain gram-positive in the early stages of growth, they may appear to be gram-negative or gram-variable later in the growth cycle or in infected tissue specimens. Most strains are motile by means of peritrichous flagella; *C. septicum* swarms on solid media. Nonmotile species include *C. perfringens*, *C. ramosum*, and *C. innocuum*. Most species are obligately anaerobic, although clostridial tolerance to oxygen varies widely; some species (e.g., *C. septicum*, *C. tertium*) will grow but will not sporulate in air.

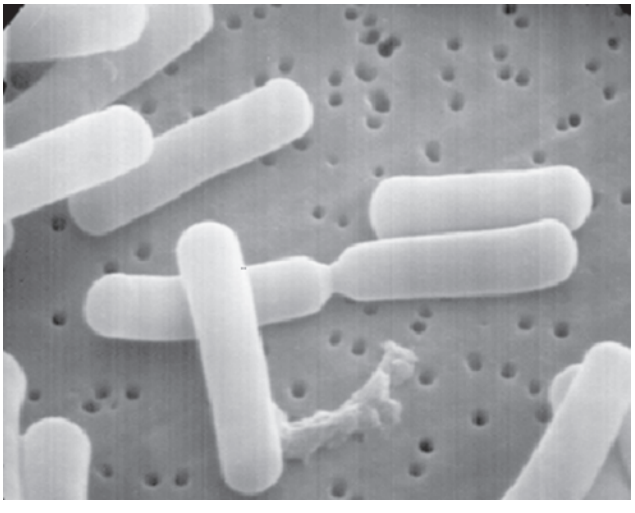


FIGURE 46-1
Scanning electron micrograph of *C. perfringens*.

Clostridia produce more protein toxins than any other bacterial genus, and more than 25 clostridial toxins lethal to mice have been identified. These proteins include neurotoxins, enterotoxins, cytotoxins, collagenases, permeases, necrotizing toxins, lipases, lecithinases, hemolysins, proteinases, hyaluronidases, DNases, ADP-ribosyltransferases, and neuraminidases. Botulinum and tetanus neurotoxins are the most potent toxins known, with lethal doses of 0.2–10 ng/kg for humans. Epsilon toxin, a 33-kDa protein produced by *C. perfringens* types B and D, causes edema and hemorrhage in the brain, heart, spinal cord, and kidneys of animals. It is among the most lethal of the clostridial toxins and is considered a potential agent of bioterrorism (Chap. 7). The genomic sequences of some pathogenic clostridia are now available and are likely to facilitate a comprehensive approach to understanding the virulence factors involved in clostridial pathogenesis.

EPIDEMIOLOGY AND TRANSMISSION

Clostridium species are widespread in nature, forming endospores that are commonly found in soil, feces, sewage, and marine sediments. The ecology of *C. perfringens* in soil is greatly influenced by the degree and duration of animal husbandry in a given location and is relevant to the incidence of gas gangrene caused by contamination of war wounds with soil. For example, the incidence of clostridial gas gangrene is higher in agricultural regions of Europe than in the Sahara Desert of Africa. Similarly, the incidences of tetanus and food-borne botulism are clearly related to the presence of clostridial spores in soil, water, and many foods. Clostridia are present in large numbers in the indigenous microbiota of the intestinal tract of humans and animals, in the female genital tract, and on the oral mucosa. It should be noted that not all commensal clostridia are toxigenic.

Clostridial infections remain a serious public health concern worldwide. In developing nations, food poisoning, necrotizing enterocolitis, and gas gangrene are common because large portions of the population are poor and have little or no immediate access to health care. These infections remain prevalent in developed countries as well. Gas gangrene commonly follows knife or gunshot wounds or vehicular accidents or develops as a complication of surgery or gastrointestinal carcinoma. Severe clostridial infections have emerged as a health threat to injection drug users and to women undergoing childbirth or abortion. Historically, clostridial gas gangrene has been the scourge of the battlefield. The global political situation portends another possible scenario involving mass casualties of war or terrorism, with extensive injuries conducive to gas gangrene. Thus, there is an ongoing need to develop novel strategies to prevent or attenuate the course of clostridial infections in both civilians and military personnel. Vaccination against exotoxins important in pathogenesis would be of great benefit in developing nations and could also be used safely in at-risk populations such as the elderly, patients with diabetes who may require lower-limb surgery due to trauma or poor circulation, and those undergoing intestinal surgery. Moreover, a hyperimmune globulin would be a valuable tool for prophylaxis in victims of acute traumatic injury or for attenuation of the spread of infection in patients with established gas gangrene.

CLINICAL SYNDROMES

Life-threatening clostridial infections range from intoxications (e.g., food poisoning, tetanus) to necrotizing enteritis/colitis, bacteremia, myonecrosis, and toxic shock syndrome (TSS). Tetanus and botulism are discussed in Chaps. 44 and 45, respectively. Colitis due to *C. difficile* is discussed in Chap. 47.

CLOSTRIDIAL WOUND CONTAMINATION

Of open traumatic wounds, 30–80% are reportedly contaminated with clostridial species. In the absence of devitalized tissue, the presence of clostridia does not necessarily lead to infection. In traumatic injuries, clostridia are isolated with equal frequency from both suppurative and well-healing wounds. Thus, diagnosis and treatment of clostridial infection should be based on clinical signs and symptoms and not solely on bacteriologic findings.

POLYMICROBIAL INFECTIONS INVOLVING CLOSTRIDIA

Clostridial species may be found in polymicrobial infections also involving microbial components of the indigenous flora. In these infections, clostridia often appear in association with non-spore-forming anaerobes and facultative or aerobic organisms. Head and neck infections, conjunctivitis, brain abscess, sinusitis, otitis, aspiration pneumonia, lung abscess, pleural empyema, cholecystitis, septic arthritis, and bone infections all may involve clostridia. These conditions are often associated with severe local inflammation but may lack the characteristic systemic signs of toxicity and rapid progression seen in other clostridial infections. In addition, clostridia are isolated from ~66% of intraabdominal infections in which the mucosal integrity of the bowel or respiratory system has been compromised. In this setting, *C. ramosum*, *C. perfringens*, and *C. bifermentans* are the most commonly isolated species. Their presence does not invariably lead to a poor outcome. Clostridia have been isolated from suppurative infections of the female genital tract (e.g., ovarian or pelvic abscess) and from diseased gallbladders. Although the most frequently isolated species is *C. perfringens*, gangrene is not typically observed; however, gas formation in the biliary system can lead to emphysematous cholecystitis, especially in diabetic patients. *C. perfringens* in association with mixed aerobic and anaerobic microbes can cause aggressive life-threatening type I necrotizing fasciitis or Fournier's gangrene.

The treatment of mixed aerobic/anaerobic infection of the abdomen, perineum, or gynecologic organs should be based on Gram's staining, culture, and antibiotic sensitivity information. Reasonable empirical treatment consists of ampicillin or ampicillin/sulbactam combined with either clindamycin or metronidazole **(Table 46-1)**. Broader gram-negative coverage may be necessary if the patient has recently been hospitalized or treated with antibiotics. Such coverage can be obtained by substituting ticarcillin/clavulanic acid, piperacillin/sulbactam, or a penem antibiotic for ampicillin or by adding a fluoroquinolone or an aminoglycoside to the regimen.

ENTERIC CLOSTRIDIAL INFECTIONS

C. perfringens type A is one of the most common bacterial causes of food-borne illness in the United States and Canada. The foods typically implicated include improperly cooked meat and meat products (e.g., gravy) in which residual spores germinate and proliferate during slow cooling or insufficient reheating. Illness results from the ingestion of food containing at least ~10^8 viable vegetative cells, which sporulate in the alkaline environment of the small intestine, producing *C. perfringens* enterotoxin in the process. The diarrhea that develops within 7–30 h of ingestion of contaminated food is generally mild and self-limiting; however, in the very young, the elderly, and the immunocompromised, symptoms are more severe and occasionally fatal. Enterotoxin-producing *C. perfringens* has been implicated as an etiologic agent of persistent diarrhea in elderly patients in nursing homes and tertiary-care institutions and has been considered to play a role in antibiotic-associated diarrhea without pseudomembranous colitis.

C. perfringens strains associated with food poisoning possess the gene (*cpe*) coding for enterotoxin, which acts by forming pores in host cell membranes. *C. perfringens* strains isolated from non-food-borne diseases, such as antibiotic-associated and sporadic diarrhea, carry *cpe* on a plasmid that may be transmitted to other strains. Several methods have been described for the detection of *C. perfringens* enterotoxin in feces, including cell culture assay (Vero cells), enzyme-linked immunosorbent assay, reversed-phase latex agglutination, and polymerase chain reaction (PCR) amplification of *cpe*. Each method has its advantages and limitations.

Enteritis necroticans (gas gangrene of the bowel) is a fulminating clinical illness characterized by extensive necrosis of the intestinal mucosa and wall. Cases can occur sporadically in adults or as epidemics in people of all ages. Enteritis necroticans is caused by α toxin– and β toxin–producing strains of *C. perfringens* type C; β toxin is located on a plasmid and is mainly responsible for pathogenesis. This life-threatening infection causes ischemic necrosis of the jejunum. In Papua New Guinea during the 1960s, enteritis necroticans (known in that locale as *pigbel*) was found to be the most common cause of death in children; it has been associated with pig feasts and occurs both sporadically and in outbreaks. Intramuscular immunization against the β toxin resulted in a decreased incidence of the disease in Papua New Guinea.

TABLE 46-1

TREATMENT OF CLOSTRIDIAL INFECTIONS

CONDITION	ANTIBIOTIC TREATMENT	PENICILLIN ALLERGY	ADJUNCTIVE TREATMENT/ NOTE
Wound contamination	None	—	—
Polymicrobial anaerobic infections involving clostridia (e.g., abdominal wall, gynecologic)	Ampicillin (2 g IV q4h) *plus* Clindamycin (600–900 mg IV q6–8h) *plus* Ciprofloxacin (400 mg IV q6–8 h)	Vancomycin (1 g IV q12h) *plus* Metronidazole (500 mg IV q6h) *plus* Ciprofloxacin (400 mg IV q6–8h)	Empirical therapy should be initiated. Therapy should be based on Gram's stain and culture results and on sensitivity data when available. Add gram-negative coverage if indicated (see text).
Clostridial sepsis	Penicillin, 3–4 mU IV q4–6h *plus* Clindamycin (600–900 mg IV q6–8h)	Clindamycin alone *or* Metronidazole *or* Vancomycin as for polymicrobial anaerobic infections (see above)	Transient bacteremia without signs of systemic toxicity may be clinically insignificant.
Gas gangrene	Penicillin G (4 mU IV q4–6 h) *plus* Clindamycin (600–900 mg IV q6–8h)	Cefoxitin (2 g IV q6h) *plus* Clindamycin (600–900 mg IV q6–8h)	Emergent surgical exploration and thorough debridement are extremely important. Hyperbaric oxygen therapy may be considered after surgery and antibiotics have been initiated.

Enteritis necroticans has also been recognized in the United States, the United Kingdom, Germany ("*darmbrand*"), and other developed nations; especially affected are adults who are malnourished or who have diabetes, alcoholic liver disease, or neutropenia.

Necrotizing enterocolitis, a disease resembling enteritis necroticans but associated with *C. perfringens* type A, has been found in North America in previously healthy adults. It is also a serious gastrointestinal disease of low-birth-weight (premature) infants hospitalized in neonatal intensive care units. The etiology and pathogenesis of this disease have remained enigmatic for more than four decades. Pathologic similarities between necrotizing enterocolitis and enteritis necroticans include the pattern of small-bowel necrosis involving the submucosa, mucosa, and muscularis; the presence of gas dissecting the tissue planes; and the degree of inflammation. Enteritis necroticans most commonly involves the jejunum, whereas necrotizing enterocolitis affects the ileum and frequently the ileocecal valve. Both diseases may manifest as intestinal gas cysts, although this feature is more common in necrotizing enterocolitis. The sources of the gas, which contains hydrogen, methane, and carbon dioxide, are probably the fermentative activities of intestinal bacteria, including clostridia. Epidemiologic data support an important role for *C. perfringens* or other gas-producing microorganisms (e.g., *C. neonatale*, certain other clostridia, or *Klebsiella* species) in the pathogenesis of necrotizing enterocolitis.

Patients with suspected clostridial enteric infection should undergo nasogastric suction and receive IV fluids. Pyrantel is given by mouth, and the bowel is rested by fasting. Benzylpenicillin (1 mU) is given intravenously every 4 h, and the patient is observed for complications requiring surgery. Patients with mild cases recover without surgical intervention. If surgical indications are present (gas in the peritoneal cavity, absent bowel sounds, rebound tenderness, abdominal rigidity), however, the mortality rate ranges from 35% to 100%; fatal outcome is due in part to perforation of the intestine. As pigbel continues to be a common disease in Papua New Guinea, consideration should be given to the use of a *C. perfringens* type C toxoid vaccine in local areas. Two doses given 3–4 months apart are preventive.

CLOSTRIDIAL BACTEREMIA

Clostridium species are important causes of bloodstream infections. Molecular epidemiologic studies of anaerobic bacteremia have identified *C. perfringens* and *C. tertium* as the two most frequently isolated species; these organisms cause up to 79% and 5%, respectively, of clostridial bacteremias. Occasionally, *C. perfringens* bacteremia occurs in the absence of an identifiable infection at another site. When associated with myonecrosis, bacteremia has a grave prognosis.

C. septicum is also commonly associated with bacteremia. This species is isolated only rarely from the feces of healthy individuals but may be found in the normal appendix. More than 50% of patients whose blood cultures are positive for this organism have some gastrointestinal anomaly (e.g., diverticular disease) or underlying malignancy (e.g., carcinoma of the colon). In addition, a clinically important association of *C. septicum* bacteremia with neutropenia of any origin—and, more specifically, with neutropenic enterocolitis involving the terminal ileum or cecum—has been observed. Patients with diabetes mellitus, severe atherosclerotic cardiovascular disease, or anaerobic myonecrosis (gas gangrene) may also develop *C. septicum* bacteremia. *C. septicum* has been recovered from the bloodstream of cirrhotic patients, as have *C. perfringens*, *C. bifermentans*, and other clostridia. Infections of the bloodstream by *C. sordellii* and *C. perfringens* have been associated with TSS.

Bloodstream infection by *C. tertium*, either alone or in combination with *C. septicum* or *C. perfringens*, can be found in patients with serious underlying disease such as malignancy or acute pancreatitis, with or without neutropenic enterocolitis; the frequency has not been systematically studied. *C. tertium* may present special problems in terms of both identification and treatment. This organism may stain gram-negative; is aerotolerant; and is resistant to metronidazole, clindamycin, and cephalosporins.

Other clostridia from the *C. clostridioforme* group (including *C. clostridioforme*, *C. hathewayi*, and *C. bolteae*) can cause bacteremia.

The clinical importance of recognizing clostridial bacteremia—especially that due to *C. septicum*—and starting appropriate treatment immediately cannot be overemphasized. Patients with this condition usually are gravely ill, and infection may metastasize to distant anatomic sites, resulting in spontaneous myonecrosis (see next section). Alternative methods to identify these strains, such as PCR or other rapid diagnostic tests, are not currently available. Anaerobic blood cultures and Gram's stain interpretation remain the best diagnostic tests at this point.

CLOSTRIDIAL SKIN AND SOFT-TISSUE INFECTIONS

Histotoxic clostridial species such as *C. perfringens*, *C. histolyticum*, *C. septicum*, C. *novyi*, and *C. sordellii* cause aggressive necrotizing infections of the skin and soft tissues. These infections are attributable in part to the elaboration of bacterial proteases, phospholipases, and cytotoxins. Necrotizing clostridial soft-tissue infections are rapidly progressive and are characterized by marked tissue destruction, gas in the tissues, and shock; they frequently end in death. Severe pain, crepitus, brawny induration with rapid progression to skin sloughing, violaceous bullae, and marked tachycardia are characteristics found in the majority of patients.

Clostridial myonecrosis (gas gangrene)

Traumatic gas gangrene

C. perfringens myonecrosis (gas gangrene) is one of the most fulminant gram-positive bacterial infections of humans. Even with appropriate antibiotic therapy and management in an intensive care unit, tissue destruction

can progress rapidly. Gas gangrene is accompanied by bacteremia, hypotension, and multiorgan failure and is invariably fatal if untreated. Gas gangrene is a true emergency and requires immediate surgical debridement.

The development of gas gangrene requires an anaerobic environment and contamination of a wound with spores or vegetative organisms. Devitalized tissue, foreign bodies, and ischemia reduce locally available oxygen levels and favor outgrowth of vegetative cells and spores. Thus conditions predisposing to traumatic gas gangrene include crush-type injury, laceration of large or medium-sized arteries, and open fractures of long bones that are contaminated with soil or bits of clothing containing the bacterial spores. Gas gangrene of the abdominal wall and flanks follows penetrating injuries such as knife or gunshot wounds that are sufficient to compromise intestinal integrity, with resultant leakage of the bowel contents into the soft tissues. Proximity to fecal sources of bacteria is a risk factor for cases following hip surgery, adrenaline injections into the buttocks, or amputation of the leg for ischemic vascular disease. In the last decade, cutaneous gas gangrene caused by *C. perfringens*, *C. novyi*, and *C. sordellii* has been described in the United States and northern Europe among persons injecting black-tar heroin subcutaneously.

The incubation period for traumatic gas gangrene can be as short as 6 h and is usually <4 days. The infection is characterized by the sudden onset of excruciating pain at the affected site and the rapid development of a foul-smelling wound containing a thin serosanguineous discharge and gas bubbles. Brawny edema and induration develop and give way to cutaneous blisters containing bluish to maroon-colored fluid. Such tissue later may become liquefied and slough. The margin between healthy and necrotic tissue often advances several inches per hour despite appropriate antibiotic therapy, and radical amputation remains the single best life-saving intervention. Shock and organ failure frequently accompany gas gangrene; when patients become bacteremic, the mortality rate exceeds 50%.

Diagnosis of traumatic gas gangrene is not difficult because the infection always begins at the site of significant trauma, is associated with gas in the tissue, and is rapidly progressive. Gram's staining of drainage or tissue biopsy is usually definitive, demonstrating large gram-positive (or gram-variable) rods, an absence of inflammatory cells, and widespread soft-tissue necrosis.

Spontaneous (nontraumatic) gas gangrene

Spontaneous gas gangrene generally occurs via hematogenous seeding of normal muscle with histotoxic clostridia—principally *C. perfringens*, *C. septicum*, and *C. novyi* and occasionally *C. tertium*—from a gastrointestinal tract portal of entry (as in colonic malignancy, inflammatory bowel disease, diverticulitis, necrotizing enterocolitis, cecitis, or distal ileitis or after gastrointestinal surgery). These gastrointestinal pathologies permit bacterial access to the bloodstream; consequently, aerotolerant *C. septicum* can proliferate in normal tissues. Patients surviving bacteremia or spontaneous gangrene due to *C. septicum* should undergo aggressive diagnostic studies to rule out gastrointestinal pathology.

Additional predisposing host factors include leukemia, lympho proliferative disorders, cancer chemotherapy, radiation therapy, and AIDS. Cyclic, congenital, or acquired neutropenia is also strongly associated with an increased incidence of spontaneous gas gangrene due to *C. septicum*; in such cases, necrotizing enterocolitis, cecitis, or distal ileitis is common, particularly among children.

The first symptom of spontaneous gas gangrene may be confusion followed by the abrupt onset of excruciating pain in the absence of trauma. These findings, along with fever, should heighten suspicion of spontaneous gas gangrene. However, because of the lack of an obvious portal of entry, the correct diagnosis is frequently delayed or missed. The infection is characterized by rapid progression of tissue destruction with demonstrable gas in the tissue **(Fig. 46-2)**. Swelling increases and bullae filled with clear, cloudy, hemorrhagic, or purplish fluid appear. The surrounding skin has a purple hue, which may reflect vascular compromise resulting from the diffusion of bacterial toxins into surrounding tissues. Invasion of healthy tissue rapidly ensues, with quick progression to shock and multiple-organ failure. Mortality rates in this setting range from 67% to 100% among adults; among children, the mortality rate is 59%, with the majority of deaths occurring within 24 h of onset.

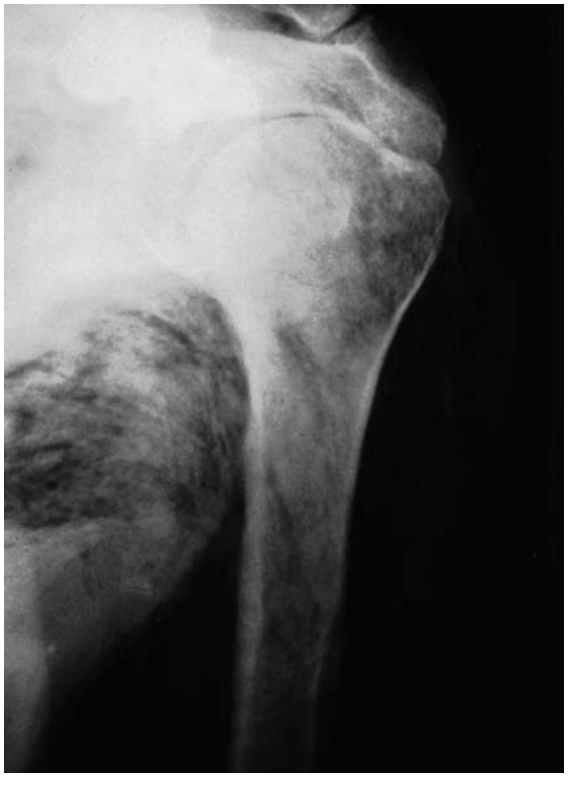


FIGURE 46-2
Radiograph of patient with spontaneous gas gangrene due to *C. septicum*, demonstrating gas in the affected arm and shoulder.

Pathogenesis of gas gangrene

In traumatic gas gangrene, organisms are introduced into devitalized tissue. It is important to recognize that for *C. perfringens* and *C. novyi*, trauma must be sufficient to interrupt the blood supply and thereby to establish an optimal anaerobic environment for growth of these species. These conditions are not strictly required for the more aerotolerant species such as *C. septicum* and *C. tertium*, which can seed normal tissues from gastrointestinal lesions. Once introduced into an appropriate niche, the organisms proliferate locally and elaborate exotoxins.

The major *C. perfringens* extracellular toxins implicated in gas gangrene are α toxin and θ toxin. A lethal hemolysin that has both phospholipase C and sphingomyelinase activities, α toxin has been implicated as the major virulence factor of *C. perfringens*: immunization of mice with the C-terminal domain of α toxin provides protection against lethal challenge with *C. perfringens*, and isogenic α toxin–deficient mutant strains of *C. perfringens* are not lethal in a murine model of gas gangrene. It has been shown in experimental models that the severe pain, rapid progression, marked tissue destruction, and absence of neutrophils in *C. perfringens* gas gangrene are attributable in large part to α toxin–induced occlusion of blood vessels by heterotypic aggregates of platelets and neutrophils. The formation of these aggregates, which occurs within minutes, is largely mediated by α toxin's ability to activate the platelet adhesion molecule gpIIbIIIa **(Fig. 46-3)**; the implication is that platelet glycoprotein inhibitors (e.g., eptifibatide, abciximab) may be therapeutic for maintaining tissue blood flow.

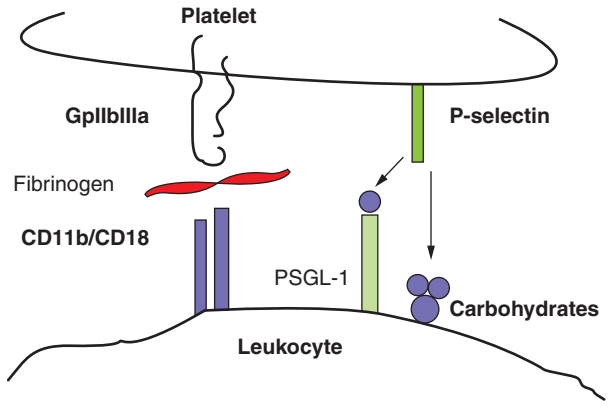


FIGURE 46-3
Schematic illustration of the molecular mechanisms of *C. perfringens* α toxin–induced platelet/neutrophil aggregates. Homotypic aggregates of platelets (not shown) and heterotypic aggregates of platelets and leukocytes are due to α toxin–induced activation of the platelet fibrinogen receptor gpIIbIIIa and upregulation of leukocyte CD11b/CD18. Binding of fibrinogen (*red*) bridges the connection between these adhesion molecules on adjacent cells. An auxiliary role for α toxin–induced upregulation of platelet P-selectin and its binding to leukocyte P-selectin glycoprotein ligand 1 (PSGL-1) or other leukocyte surface carbohydrates has also been demonstrated.

C. perfringens θ toxin (*perfringolysin*) is a member of the thiol-activated cytolysin family known as cholesterol-dependent cytolysins, which includes streptolysin O from group A *Streptococcus*, pneumolysin from *Streptococcus pneumoniae*, and several other toxins. Cholesterol-dependent cytolysins bind as oligomers to cholesterol in host cell membranes. At high concentrations, these toxins form ring-like pores resulting in cell lysis. At sublytic concentrations, θ toxin hyperactivates phagocytes and vascular endothelial cells.

Cardiovascular collapse and end-organ failure occur late in the course of *C. perfringens* gas gangrene and are largely attributable to both direct and indirect effects of α and θ toxins. In experimental models, θ toxin causes markedly reduced systemic vascular resistance but increased cardiac output (e.g., "warm shock"), probably via induction of endogenous mediators (e.g., prostacyclin, platelet-activating factor) that cause vasodilation. This effect is similar to that observed in gram-negative sepsis. In sharp contrast, α toxin directly suppresses myocardial contractility; the consequence is profound hypotension due to a sudden reduction in cardiac output. The roles of other endogenous mediators, such as cytokines (e.g., tumor necrosis factor, interleukin 1, interleukin 6) and vasodilators (e.g., bradykinin) have not been fully elucidated.

C. septicum produces four main toxins—α toxin (lethal, hemolytic, necrotizing activity), β toxin (DNase), γ toxin (hyaluronidase), and Δ" toxin (septicolysin, an oxygen-labile hemolysin)—as well as a protease and a neuraminidase. Unlike the α toxin of *C. perfringens*, that of *C. septicum* does not possess phospholipase activity. The mechanisms remain to be fully elucidated, but it is likely that each of these toxins contributes uniquely to *C. septicum* gas gangrene.

TREATMENT Gas Gangrene

Patients with suspected gas gangrene (either traumatic or spontaneous) should undergo prompt surgical inspection of the infected site. Direct examination of a gram-stained smear of the involved tissues is of major importance. Characteristic histologic findings in clostridial gas gangrene include widespread tissue destruction, a paucity of leukocytes in infected tissues in conjunction with an accumulation of leukocytes in adjacent vessels **(Fig. 46-4)**, and the presence of gram-positive rods (with or without spores). CT and MRI are invaluable for determining whether the infection is localized or is spreading along fascial planes, and needle aspiration or punch biopsy may provide an etiologic diagnosis in at least 20% of cases. However, these techniques should not replace surgical exploration, Gram's staining, and histopathologic examination. When spontaneous gas gangrene is suspected, blood should be cultured since bacteremia usually precedes cutaneous manifestations by several hours.

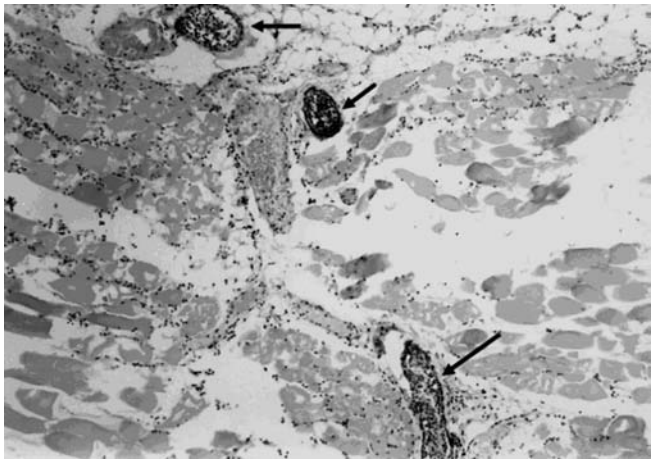


FIGURE 46-4
Histopathology of experimental gas gangrene due to *C. perfringens*, demonstrating widespread muscle necrosis, a paucity of leukocytes in infected tissues, and accumulation of leukocytes in adjacent vessels (*arrows*). These features are due to the effects of α and θ toxins on muscle cells, platelets, leukocytes, and endothelial cells.

For patients with evidence of clostridial gas gangrene, thorough emergent surgical debridement is of extreme importance. All devitalized tissue should be widely resected back to healthy viable muscle and skin so as to remove conditions that allow anaerobic organisms to continue proliferating. Closure of traumatic wounds or compound fractures should be delayed for 5–6 days until it is certain that these sites are free of infection.

Antibiotic treatment of traumatic or spontaneous gas gangrene (Table 46-1) consists of the administration of penicillin and clindamycin for 10–14 days. Penicillin is recommended on the basis of in vitro sensitivity data; clindamycin is recommended because of its superior efficacy over penicillin in animal models of *C. perfringens* gas gangrene and in some clinical reports. Controlled clinical trials comparing the efficacy of these agents in humans have not been performed. In the penicillin-allergic patient, clindamycin may be used alone. The superior efficacy of clindamycin is probably due to its ability to inhibit bacterial protein toxin production, its insensitivity to the size of the bacterial load or the stage of bacterial growth, and its ability to modulate the host's immune response.

C. tertium is resistant to penicillin, cephalosporins, and clindamycin. Appropriate antibiotic therapy for *C. tertium* infection is vancomycin (1 g every 12 h IV) or metronidazole (500 mg every 8 h IV).

The value of adjunctive treatment with hyperbaric oxygen (HBO) for gas gangrene remains controversial. Basic science studies suggest that HBO can inhibit the growth of *C. perfringens*, but not that of the more aerotolerant *C. septicum*. In vitro, blood and macerated muscle inhibit the bactericidal potential of HBO. Numerous studies in animals demonstrate little efficacy of HBO alone, whereas antibiotics alone—especially those that inhibit bacterial protein synthesis—confer marked benefits. Addition of HBO to the therapeutic regimen provides some additional benefit, but only if surgery and antibiotic administration precede HBO treatment.

In conclusion, gas gangrene is a rapidly progressive infection whose outcome depends on prompt recognition, emergent surgery, and timely administration of antibiotics that inhibit toxin production. Gas gangrene associated with bacteremia probably represents a later stage of illness and is associated with the worst outcomes. Emergent surgical debridement is crucial to ensure survival, and ancillary procedures (e.g., CT or MRI) or transport to HBO units should not delay this intervention. Some trauma centers associated with HBO units may have special expertise in managing these aggressive infections, but proximity and speed of transfer must be carefully weighed against the need for haste.

Prognosis of gas gangrene

The prognosis for patients with gas gangrene is more favorable when the infection involves an extremity rather than the trunk or visceral organs, since debridement of the latter sites is more difficult. Gas gangrene is most likely to progress to shock and death in patients with associated bacteremia and intravascular hemolysis. Mortality rates are highest for patients in shock at the time of diagnosis. Mortality rates are relatively high among patients with spontaneous gas gangrene, especially that due to *C. septicum*. Survivors of gas gangrene may undergo multiple debridements and face long periods of hospitalization and rehabilitation.

Prevention of gas gangrene

Initial aggressive debridement of devitalized tissue can reduce the risk of gas gangrene in contaminated deep wounds. Interventions to be avoided include prolonged application of tourniquets and surgical closure of traumatic wounds; patients with compound fractures are at significant risk for gas gangrene if the wound is closed surgically. Vaccination against α toxin is protective in experimental animal models of *C. perfringens* gas gangrene, but has not been investigated in humans. In addition, as mentioned earlier, a hyperimmune globulin would represent a significant advance for prophylaxis in victims of acute traumatic injury or for attenuation of the spread of infection in patients with established gas gangrene.

Toxic shock syndrome

Clostridial infection of the endometrium, particularly that due to *C. sordellii*, can develop after gynecologic procedures, childbirth, or abortion (spontaneous or elective, surgical or medical) and, once established, proceeds rapidly to TSS and death. Systemic manifestations including edema, effusions, profound leukocytosis,

and hemoconcentration are followed by the rapid onset of hypotension and multiple-organ failure. Elevation of the hematocrit to 75–80% and leukocytosis of 50,000–200,000 cells per microliter, with a left shift, are characteristic of *C. sordellii* infection. Pain may not be a prominent feature, and fever is typically absent. In one series, 18% of 45 cases of *C. sordellii* infection were associated with normal childbirth, 11% with medically induced abortion, and 0.4% with spontaneous abortion; the case-fatality rate was 100% in these groups. Of the infections in this series that were not related to gynecologic procedures or childbirth, 22% occurred in injection drug users, and 50% of these patients died. Other infections followed trauma or surgery (42%), mostly in healthy persons, and 53% of these patients died. Overall, the mortality rate was 69% (31 of 45 cases). Of patients who succumbed, 85% died within 2–6 days of initial infection or following procedures.

Early diagnosis of *C. sordellii* infections often proves difficult for several reasons. First, the prevalence of these infections is low. Second, the initial symptoms are nonspecific and frankly misleading. Early in the course, the illness resembles any number of infectious diseases, including viral syndromes. Given these vague symptoms and an absence of fever, physicians usually do not aggressively pursue additional diagnostic tests. The absence of local evidence of infection and the lack of fever make early diagnosis of *C. sordellii* infection particularly problematic in patients who develop deep-seated infection following childbirth, therapeutic abortion, gastrointestinal surgery, or trauma. Such patients are frequently evaluated for pulmonary embolization, gastrointestinal bleeding, pyelonephritis, or cholecystitis. Unfortunately, such delays in diagnosis increase the risk of death, and, as in most necrotizing soft-tissue infections, patients are hypotensive with evidence of organ dysfunction by the time local signs and symptoms become apparent. In contrast, infection is more readily suspected in injection drug users presenting with local swelling, pain, and redness at injection sites; early recognition probably contributes to the lower mortality rates in this group.

Physicians should suspect *C. sordellii* infection in patients who present within 2–7 days after injury, surgery, drug injection, childbirth, or abortion and who complain of pain, nausea, vomiting, and diarrhea but are afebrile. There is little information regarding appropriate treatment for *C. sordellii* infections. In fact, the interval between onset of symptoms and death is often so short that there is little time to initiate empirical antimicrobial therapy. Indeed, anaerobic cultures of blood and wound aspirates are time-consuming, and many hospital laboratories do not routinely perform antimicrobial sensitivity testing on anaerobes. Antibiotic susceptibility data from older studies suggest that *C. sordellii*, like most clostridia, is susceptible to β-lactam antibiotics, clindamycin, tetracycline, and chloramphenicol but is resistant to aminoglycosides and sulfonamides. Antibiotics that suppress toxin synthesis (e.g., clindamycin) may possibly prove useful as therapeutic adjuncts since they are effective in necrotizing infections due to other toxin-producing gram-positive organisms.

Other clostridial skin and soft-tissue infections

Crepitant cellulitis (also called anaerobic cellulitis) occurs principally in diabetic patients and characteristically involves subcutaneous tissues or retroperitoneal tissues, whereas the muscle and fascia are not involved. This infection can progress to fulminant systemic disease.

Cases of *C. histolyticum* infection with cellulitis, abscess formation, or endocarditis have also been documented in injection drug users. Endophthalmitis due to *C. sordellii* or *C. perfringens* has been described. *C. ramosum* is also isolated frequently from clinical specimens, including blood and intraabdominal and soft tissues. This species may be resistant to clindamycin and multiple cephalosporins.

CHAPTER 47

CLOSTRIDIUM DIFFICILE INFECTION, INCLUDING PSEUDOMEMBRANOUS COLITIS

Dale N. Gerding ■ Stuart Johnson

DEFINITION

Clostridium difficile infection (CDI) is a unique colonic disease that is acquired almost exclusively in association with antimicrobial use and the consequent disruption of the normal colonic flora. The most commonly diagnosed diarrheal illness acquired in the hospital, CDI results from the ingestion of spores of *C. difficile* that vegetate, multiply, and secrete toxins, causing diarrhea and pseudomembranous colitis (PMC).

ETIOLOGY AND EPIDEMIOLOGY

C. difficile is an obligately anaerobic, gram-positive, spore-forming bacillus whose spores are found widely in nature, particularly in the environment of hospitals and chronic-care facilities. CDI occurs most frequently in hospitals and nursing homes where the level of antimicrobial use is high and the environment is contaminated by *C. difficile* spores.

Clindamycin, ampicillin, and cephalosporins were the first antibiotics associated with CDI. The second- and third-generation cephalosporins, particularly cefotaxime, ceftriaxone, cefuroxime, and ceftazidime, are agents frequently responsible for this condition, and the fluoroquinolones (ciprofloxacin, levofloxacin, and moxifloxacin) are the most recent drug class to be implicated in hospital outbreaks. Penicillin/β-lactamase-inhibitor combinations such as ticarcillin/clavulanate and piperacillin/tazobactam pose significantly less risk. However, all antibiotics, including vancomycin and metronidazole (the agents most commonly used to treat CDI), have been found to carry a risk of subsequent CDI. Rare cases are reported in patients without prior antibiotic exposure.

C. difficile is acquired exogenously, most frequently in the hospital or nursing home, and is carried in the stool of symptomatic and asymptomatic patients. The rate of fecal colonization is often ≥20% among adult patients hospitalized for >1 week; in contrast, the rate is 1–3% among community residents. Community-onset CDI without recent hospitalization probably accounts for ≤10% of all cases. The risk of *C. difficile* acquisition increases in proportion to length of hospital stay. Asymptomatic fecal carriage of *C. difficile* in healthy neonates is very common, with rates often exceeding 50% during the first 6 months of life, but associated disease in this population is rare. Spores of *C. difficile* are found on environmental surfaces (where the organism can persist for months) and on the hands of hospital personnel who fail to practice good hand hygiene. Hospital epidemics of CDI have been attributed to a single *C. difficile* strain and to multiple strains present simultaneously. Other identified risk factors for CDI include older age, greater severity of underlying illness, gastrointestinal surgery, use of electronic rectal thermometers, enteral tube feeding, and antacid treatment. Use of proton pump inhibitors may be a risk factor, but this risk is probably modest, and no firm data have implicated these agents in patients who are not already receiving antibiotics.

PATHOLOGY AND PATHOGENESIS

Spores of toxigenic *C. difficile* are ingested, survive gastric acidity, germinate in the small bowel, and colonize the lower intestinal tract, where they elaborate two large toxins: toxin A (an enterotoxin) and toxin B (a cytotoxin). These toxins initiate processes resulting in the disruption of epithelial-cell barrier function, diarrhea, and pseudomembrane formation. Toxin A is a potent neutrophil chemoattractant, and both toxins glucosylate the GTP-binding proteins of the Rho subfamily that regulate the actin cell cytoskeleton. Data from studies using molecular disruption of toxin genes in isogenic mutants suggest that toxin B is the essential virulence factor; this possibility, if confirmed, might account for the occurrence of clinical disease caused by toxin A–negative strains. Disruption of the cytoskeleton results in loss of cell shape, adherence, and tight junctions, with

consequent fluid leakage. A third toxin, binary toxin CDT, was previously found in only ~6% of strains but is present in all isolates of the newly recognized epidemic strain (see "Global Considerations," next); this toxin is related to *C. perfringens* iota toxin. Its role in the pathogenesis of CDI has not yet been defined.

The pseudomembranes of PMC are confined to the colonic mucosa and initially appear as 1- to 2-mm whitish-yellow plaques. The intervening mucosa appears unremarkable, but, as the disease progresses, the pseudomembranes coalesce to form larger plaques and become confluent over the entire colon wall **(Fig. 47-1)**. The whole colon is usually involved, but 10% of patients have rectal sparing. Viewed microscopically, the pseudomembranes have a mucosal attachment point and contain necrotic leukocytes, fibrin, mucus, and cellular debris. The epithelium is eroded and necrotic in focal areas, with neutrophil infiltration of the mucosa.

Patients colonized with *C. difficile* were initially thought to be at high risk for CDI. However, four prospective studies have shown that colonized patients actually have a decreased risk of subsequent CDI. At least three events are proposed as essential for the development of CDI **(Fig. 47-2)**. Exposure to antimicrobial agents is the first event and establishes susceptibility to *C. difficile* infection. The second event is exposure to toxigenic *C. difficile*. Given that the majority of patients do not develop CDI after the first two events, a third event is clearly essential for its occurrence. Candidate third events include exposure to a *C. difficile* strain of particular virulence, exposure to antimicrobial agents

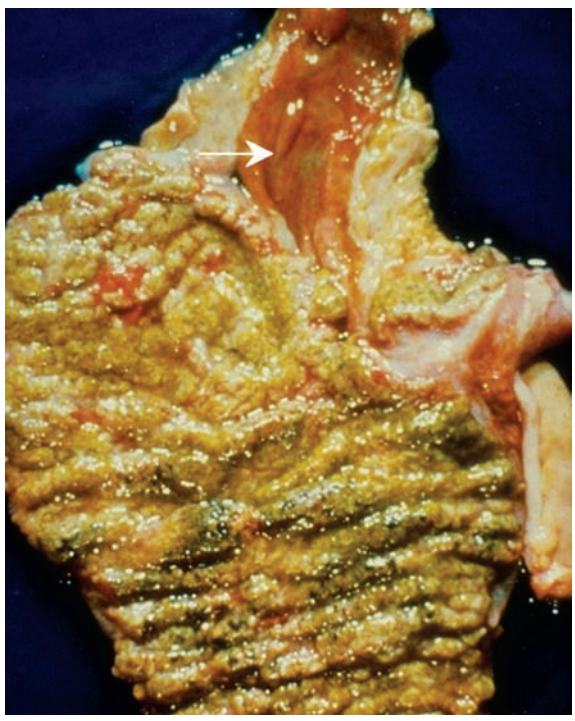


FIGURE 47-1
Autopsy specimen showing confluent pseudomembranes covering the cecum of a patient with pseudomembranous colitis. Note the sparing of the terminal ileum (*arrow*).

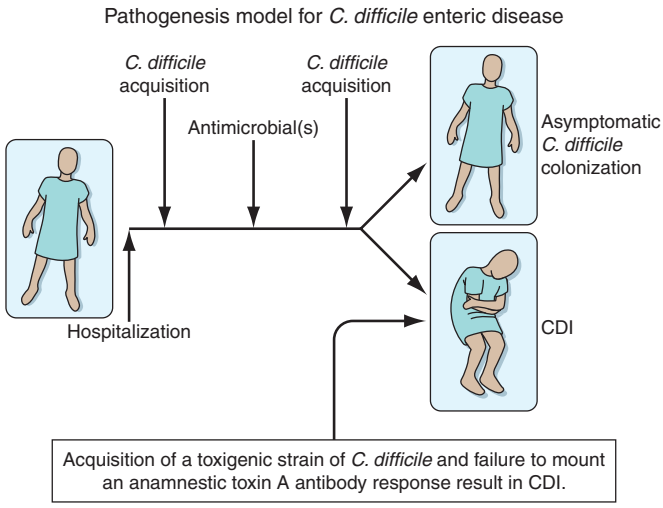


FIGURE 47-2
Pathogenesis model for hospital-acquired *Clostridium difficile* infection (CDI). At least three events are integral to *C. difficile* pathogenesis. Exposure to antibiotics establishes susceptibility to infection. Once susceptible, the patient may acquire nontoxigenic (nonpathogenic) or toxigenic strains of *C. difficile* as a second event. Acquisition of toxigenic *C. difficile* may be followed by asymptomatic colonization or CDI, depending on one or more additional events, including an inadequate host anamnestic IgG response to *C. difficile* toxin A.

especially likely to cause CDI, and an inadequate host immune response. The host anamnestic serum IgG antibody response to toxin A of *C. difficile* is the most likely third event that determines which patients develop diarrhea and which patients remain asymptomatic. The majority of humans first develop antibody to *C. difficile* toxins when colonized asymptomatically during the first year of life. Infants are thought not to develop symptomatic CDI because they lack suitable mucosal toxin receptors that develop later in life. In adulthood, serum levels of IgG antibody to toxin A increase more in response to infection in individuals who become asymptomatic carriers than in those who develop CDI. For persons who develop CDI, increasing levels of antitoxin A during treatment correlate with a lower risk of recurrence of CDI. A clinical trial using monoclonal antibodies to both toxin A and toxin B in addition to standard therapy showed rates of recurrence lower than those obtained with placebo plus standard therapy.

GLOBAL CONSIDERATIONS

Rates and severity of CDI in the United States, Canada, and Europe have increased markedly since the year 2000. Rates in U.S. hospitals tripled between 2000 and 2005. Hospitals in Montreal, Quebec, have reported rates four times higher than the 1997 baseline, with directly attributable mortality of 6.9% (increased from 1.5%). An epidemic strain, variously known as toxinotype III, REA type BI, PCR

ribotype 027, and pulsed-field type NAP1, is thought to account for much of the increase in incidence and has been found in North America, Europe, and Asia. The epidemic organism is characterized by (1) an ability to produce 16–23 times as much toxin A and toxin B as control strains in vitro; (2) the presence of a third toxin (binary toxin CDT); and (3) high-level resistance to all fluoroquinolones. New strains have been and will probably continue to be implicated in outbreaks; their emergence may be explained in part by patterns of antibiotic use, particularly in hospitals.

CLINICAL MANIFESTATIONS

Diarrhea is the most common manifestation caused by *C. difficile*. Stools are almost never grossly bloody and range from soft and unformed to watery or mucoid in consistency, with a characteristic odor. Patients may have as many as 20 bowel movements per day. Clinical and laboratory findings include fever in 28% of cases, abdominal pain in 22%, and leukocytosis in 50%. When adynamic ileus (which is seen on x-ray in ~20% of cases) results in cessation of stool passage, the diagnosis of CDI is frequently overlooked. A clue to the presence of unsuspected CDI in these patients is unexplained leukocytosis, with ≥15,000 white blood cells (WBCs)/μL. Such patients are at high risk for complications of *C. difficile* infection, particularly toxic megacolon and sepsis.

C. difficile diarrhea recurs after treatment in ~15–30% of cases, and this figure may be increasing. Recurrences may represent either relapses due to the same strain or reinfections with a new strain. Susceptibility to recurrence of clinical CDI is likely a result of continued disruption of the normal fecal flora caused by the antibiotic used to treat CDI.

DIAGNOSIS

The diagnosis of CDI is based on a combination of clinical criteria: (1) diarrhea (≥3 unformed stools per 24 h for ≥2 days) with no other recognized cause plus (2) toxin A or B detected in the stool, toxin-producing *C. difficile* detected in the stool by polymerase chain reaction (PCR) or culture, or pseudomembranes seen in the colon. PMC is a more advanced form of CDI and is visualized at endoscopy in only ~50% of patients with diarrhea who have a positive stool culture and toxin assay for *C. difficile* **(Table 47-1)**. Endoscopy is a rapid diagnostic tool in seriously ill patients with suspected PMC and an acute abdomen, but a negative result in this examination does not rule out CDI.

Despite the array of tests available for *C. difficile* and its toxins (Table 47-1), no single test has high sensitivity, high specificity, and rapid turnaround. Most laboratory tests for toxins, including enzyme immunoassays (EIAs), lack sensitivity. However, testing of multiple additional stool specimens is not recommended. PCR assays have now been approved for diagnostic testing and appear to be both rapid and sensitive while retaining high specificity. Empirical treatment is appropriate if CDI is strongly suspected on clinical grounds. Testing of asymptomatic patients is not recommended except for epidemiologic study purposes. In particular, so-called tests of cure following treatment are not recommended because many patients continue to harbor the organism and toxin after

TABLE 47-1

RELATIVE SENSITIVITY AND SPECIFICITY OF DIAGNOSTIC TESTS FOR *CLOSTRIDIUM DIFFICILE* INFECTION (CDI)

TYPE OF TEST	RELATIVE SENSITIVITY[a]	RELATIVE SPECIFICITY[a]	COMMENT
Stool culture for *C. difficile*	++++	+++	Most sensitive test; specificity of ++++ if the *C. difficile* isolate tests positive for toxin; with clinical data, is diagnostic of CDI; turnaround time too slow for practical use
Cell culture cytotoxin test on stool	+++	++++	With clinical data, is diagnostic of CDI; highly specific but not as sensitive as stool culture; slow turnaround time
Enzyme immunoassay for toxin A or toxins A and B in stool	++ to +++	+++	With clinical data, is diagnostic of CDI; rapid results, but not as sensitive as stool culture or cell culture cytotoxin test
Enzyme immunoassay for *C. difficile* common antigen in stool	+++ to ++++	+++	Detects glutamate dehydrogenase found in toxigenic and nontoxigenic strains of *C. difficile* and other stool organisms; more sensitive and less specific than enzyme immunoassay for toxins; rapid results
PCR for *C. difficile* toxin B gene in stool	++++	++++	Detects toxigenic *C. difficile* in stool; newly approved for clinical testing, but appears to be more sensitive than enzyme immunoassay toxin testing and at least as specific
Colonoscopy or sigmoidoscopy	+	++++	Highly specific if pseudomembranes are seen; insensitive compared with other tests

[a]According to both clinical and test-based criteria.
Note: ++++, >90%; +++, 71–90%; ++, 51–70%; +, ~50%.

diarrhea has ceased and test results do not always predict recurrence of CDI. Thus, these results should not be used to restrict placement of patients in long-term-care or nursing home facilities.

TREATMENT *Clostridium difficile* Infection

PRIMARY CDI When possible, discontinuation of any ongoing antimicrobial administration is recommended as the first step in treatment of CDI. Earlier studies indicated that 15–23% of patients respond to this simple measure. However, with the advent of the current epidemic strain and the associated rapid clinical deterioration of some patients, prompt initiation of specific CDI treatment has become the standard. General treatment guidelines include hydration and the avoidance of antiperistaltic agents and opiates, which may mask symptoms and possibly worsen disease. Nevertheless, antiperistaltic agents have been used safely with vancomycin or metronidazole for mild to moderate CDI.

All drugs, particularly vancomycin, should be given orally if possible. When IV metronidazole is administered, fecal bactericidal drug concentrations are achieved during acute diarrhea, and CDI treatment has been successful; however, in the presence of adynamic ileus, IV metronidazole treatment of PMC has failed. In previous randomized trials, diarrhea response rates to oral therapy with vancomycin or metronidazole were ≥94%, but four recent observational studies found that response rates for metronidazole had declined to 62–78%. Although the mean time to resolution of diarrhea is 2–4 days, the response to metronidazole may be much slower. Treatment should not be deemed a failure until a drug has been given for at least 6 days. On the basis of data for shorter courses of vancomycin, it is recommended that metronidazole and vancomycin be given for at least 10 days, although no controlled comparisons are available. Metronidazole is not approved for this indication by the U.S. Food and Drug Administration (FDA), but most patients with mild to moderate illness respond to 500 mg given by mouth three times a day for 10 days; extension of the treatment period may be needed for slow responders. In addition to the reports of increases in metronidazole failures, a prospective, randomized, double-blind, placebo-controlled study has demonstrated the superiority of vancomycin over metronidazole for treatment of severe CDI. The severity assessment score in that study included age as well as laboratory parameters (elevated temperature, low albumin level, or elevated WBC count), documentation of PMC by endoscopy, or treatment of CDI in the intensive care unit. Although a validated severity score is not yet available, it is important to initiate treatment with oral vancomycin for patients who appear seriously ill, particularly if they have a high WBC count (>15,000/μL) or a creatinine level that is ≥1.5 times higher than the premorbid value (Table 47-2). Small randomized trials of nitazoxanide, bacitracin, rifaximin, and fusidic acid for treatment of CDI have been conducted. While these drugs have not yet been extensively studied, shown to be superior, or approved by the FDA for this indication, they provide potential alternatives to vancomycin and metronidazole.

RECURRENT CDI Overall, ~15–30% of patients experience recurrences of CDI, either as relapses caused by the original organism or as reinfections following treatment. Recurrence rates are higher among patients ≥65 years old, those who continue to take antibiotics while being treated for CDI, and those who remain in the hospital after the initial episode of CDI. Patients who have a first recurrence of CDI have a high rate of second recurrence (33–65%). In the first recurrence, retreatment with metronidazole is comparable to treatment with vancomycin (Table 47-2). Recurrent disease, once thought to be relatively mild, has now been documented to pose a significant (11%) risk of serious complications (shock, megacolon, perforation, colectomy, or death within 30 days). There is no standard treatment for multiple recurrences, but long or repeated metronidazole courses should be avoided because of potential neurotoxicity. Approaches include the administration of vancomycin followed by the yeast *Saccharomyces boulardii*; the administration of vancomycin followed by a synthetic fecal bacterial enema; and the intentional colonization of the patient with a nontoxigenic strain of *C. difficile*. None of these biotherapeutic approaches has been approved by the FDA for use in the United States. Other strategies include (1) the use of vancomycin in tapering doses or with pulse dosing every other day for 2–8 weeks and (2) sequential treatment with vancomycin (125 mg four times daily for 10–14 days) followed by rifaximin (400 mg twice daily for 14 days). IV immunoglobulin, which has also been used with some success, presumably provides antibodies to *C. difficile* toxins.

SEVERE COMPLICATED OR FULMINANT CDI Fulminant (rapidly progressive and severe) CDI presents the most difficult treatment challenge. Patients with fulminant disease often do not have diarrhea, and their illness mimics an acute surgical abdomen. Sepsis (hypotension, fever, tachycardia, leukocytosis) may result from severe CDI. An acute abdomen (with or without toxic megacolon) may include signs of obstruction, ileus, colon-wall thickening, and ascites on abdominal CT, often with peripheral-blood leukocytosis (≥20,000 WBCs/μL). With or without diarrhea, the differential diagnosis of an acute abdomen, sepsis, or toxic megacolon should include CDI if the patient has received antibiotics in the past 2 months. Cautious sigmoidoscopy or colonoscopy to visualize PMC and an abdominal CT examination are the best diagnostic tests in patients without diarrhea.

Medical management of fulminant CDI is suboptimal because of the difficulty of delivering metronidazole or vancomycin to the colon by the oral route in the presence of ileus (Table 47-2). The combination of vancomycin

TABLE 47-2

RECOMMENDATIONS FOR THE TREATMENT OF *CLOSTRIDIUM DIFFICILE* INFECTION (CDI)

CLINICAL SETTING	TREATMENT(S)	COMMENTS
Initial episode, mild to moderate	Oral metronidazole (500 mg tid × 10–14 d)	
Initial episode, severe	Oral vancomycin (125 mg qid × 10–14 d)	Indicators of severe disease may include leukocytosis (≥15,000 white blood cells/μL) and a creatinine level ≥ 1.5 times the premorbid value.
Initial episode, severe complicated or fulminant	Vancomycin (500 mg PO or via nasogastric tube) plus metronidazole (500 mg IV q8h) *plus consider* Rectal instillation of vancomycin (500 mg in 100 mL of normal saline as a retention enema q6–8h)	Severe complicated or fulminant CDI is defined as severe CDI with the addition of hypotension, shock, ileus, or toxic megacolon. The duration of treatment may need to be >2 weeks and is dictated by response. Consider using IV tigecycline (50 mg q12h after a 100-mg loading dose) in place of metronidazole.
First recurrence	Same as for initial episode	
Second recurrence	Vancomycin in tapered/pulsed regimen	Typical taper/pulse regimen: 125 mg qid × 10–14 d, then bid × 1 week, then daily × 1 week, then q2–3d for 2–8 weeks
Multiple recurrences	Consider the following options: • Repeat vancomycin taper/pulse • Vancomycin (500 mg qid × 10 d) plus *Saccharomyces boulardii* (500 mg bid × 28 d) • Vancomycin (125 mg qid × 10–14 d); then stop vancomycin and start rifaximin (400 mg bid × 2 weeks) • Nitazoxanide (500 mg bid × 10 d) • Fecal transplantation • IV immunoglobulin (400 mg/kg)	The only controlled study of treatment for recurrent CDI used *S. boulardii* and showed borderline significance compared with placebo.

(given via nasogastric tube and by retention enema) plus IV metronidazole has been used with some success in uncontrolled studies, as has IV tigecycline in small-scale uncontrolled studies. Surgical colectomy may be life-saving if there is no response to medical management. If possible, colectomy should be performed before the serum lactate level reaches 5 mmol/L. The incidence of fulminant CDI requiring colectomy appears to be increasing in the evolving epidemic.

PROGNOSIS

The mortality rate attributed to CDI, previously found to be 0.6–3.5%, has reached 6.9% in recent outbreaks and is progressively higher with increasing age. Most patients recover, but recurrences are common.

PREVENTION AND CONTROL

Strategies for the prevention of CDI are of two types: those aimed at preventing transmission of the organism to the patient and those aimed at reducing the risk of CDI if the organism is transmitted. Transmission of *C. difficile* in clinical practice has been prevented by gloving of personnel, elimination of the use of contaminated electronic thermometers, and use of hypochlorite (bleach) solution for environmental decontamination of patients' rooms. Hand hygiene is critical; hand washing is recommended in CDI outbreaks because alcohol hand gels are not sporicidal. CDI outbreaks have been best controlled by restricting the use of specific antibiotics, such as clindamycin and second- and third-generation cephalosporins. Outbreaks of CDI due to clindamycin-resistant strains have resolved promptly when clindamycin use is restricted.

CHAPTER 48

MENINGOCOCCAL INFECTIONS

Andrew J. Pollard

DEFINITION

Infection with *Neisseria meningitidis* most commonly manifests as asymptomatic colonization in the nasopharynx of healthy adolescents and adults. Invasive disease occurs rarely, usually presenting as either bacterial meningitis or meningococcal septicemia. Patients may also present with occult bacteremia, pneumonia, septic arthritis, conjunctivitis, and chronic meningococcemia.

ETIOLOGY AND MICROBIOLOGY

N. meningitidis is a gram-negative aerobic diplococcus that colonizes humans only and that causes disease after transmission to a susceptible individual. Several related organisms have been recognized, including the pathogen *N. gonorrhoeae* and the commensals *N. lactamica*, *N. flavescens*, *N. mucosa*, *N. sicca*, and *N. subflava*. *N. meningitidis* is a catalase- and oxidase-positive organism that utilizes glucose and maltose to produce acid.

Meningococci associated with invasive disease are usually encapsulated with polysaccharide, and the antigenic nature of the capsule determines an organism's serogroup **(Table 48-1)**. In total, 13 serogroups have been identified (A–D, X–Z, 29E, W135, H–J, and L), but just 5 serogroups—A, B, C, Y, and W135—account for the majority of cases of invasive disease. Acapsular meningococci are commonly isolated from the nasopharynx in studies of carriage; the lack of capsule often is a result of phase variation of capsule expression, but as many as 16% of isolates lack the genes for capsule synthesis and assembly. These "capsule-null" meningococci and those that express capsules other than A, B, C, Y, and W135 are only rarely associated with invasive disease and are most commonly identified in the nasopharynx of asymptomatic carriers.

Beneath the capsule, meningococci are surrounded by an outer phospholipid membrane containing lipopolysaccharide (LPS, endotoxin) and multiple outer-membrane proteins **(Figs. 48-1 and 48-2)**. Antigenic variability in porins expressed in the outer membrane defines the serotype (PorB) and serosubtype (PorA) of the organism, and structural differences in LPS determine the immunotype. Serologic methods for typing of meningococci are restricted by the limited availability of serologic reagents that can distinguish among the organisms' highly variable surface proteins. Where available, high-throughput antigen gene sequencing has superseded serology for meningococcal typing. A large database of antigen gene sequences for the

TABLE 48-1

STRUCTURE OF THE POLYSACCHARIDE CAPSULE OF COMMON DISEASE-CAUSING MENINGOCOCCI

MENINGOCOCCAL SEROGROUP	CHEMICAL STRUCTURE OF OLIGOSACCHARIDE	CURRENT DISEASE EPIDEMIOLOGY
A	2-Acetamido-2-deoxy-D-mannopyranosyl phosphate	Epidemic disease mainly in sub-Saharan Africa; sporadic cases worldwide
B	α-2,8-*N*-acetylneuraminic acid	Sporadic cases worldwide; propensity to cause hyperendemic disease
C	α-2,9-O-acetylneuraminic acid	Small outbreaks and sporadic disease
Y	4-*O*-α-D-glucopyranosyl-*N*-acetylneuraminic acid	Sporadic disease and occasional small institutional outbreaks
W135	4-*O*-α-D-galactopyranosyl-*N*-acetylneuraminic acid	Sporadic disease; outbreaks of disease associated with mass gatherings; epidemics in sub-Saharan Africa

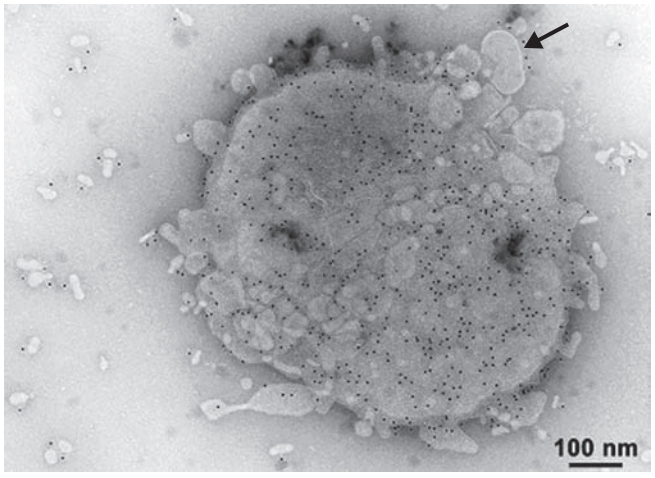


FIGURE 48-1
Electron micrograph of *Neisseria meningitidis*. Black dots are gold-labeled polyclonal antibodies binding surface opacity proteins. Blebs of outer membrane can be seen being released from the bacterial surface (see arrow). (*Photo courtesy of D. Ferguson, Oxford University.*)

outer-membrane proteins PorA, PorB, FetA, Opa, and factor H–binding protein is available online (*www.neisseria.org*). The number of specialized iron-regulated proteins found in the meningococcal outer membrane (e.g., FetA and transferrin-binding proteins) highlights the organisms' dependence on iron from human sources. A thin peptidoglycan cell wall separates the outer membrane from the cytoplasmic membrane.

The structure of meningococcal populations involved in local and global spread has been studied with multilocus enzyme electrophoresis (MLEE), which characterizes isolates according to differences in the electrophoretic mobility of cytoplasmic enzymes. However, this technique has mostly been replaced by multilocus sequence typing (MLST), in which meningococci are characterized by sequence types assigned on the basis of sequences of internal fragments of seven housekeeping genes. The online MLST database currently includes more than 13,000 meningococcal isolates and 7600 unique sequence types (*http://pubmlst.org/neisseria/*). Seven hyperinvasive lineages of *N. meningitidis* have been identified and are responsible for the majority of cases of invasive meningococcal disease worldwide. The apparent genetic stability of these meningococcal clones over decades and during wide geographic spread indicates that they are well adapted to the nasopharyngeal environment of the host and to efficient transmission.

The group B meningococcal genome is >2 megabases in length and contains 2158 coding regions. Many genes undergo phase variation that makes it possible to control their expression; this capacity is likely to be important in meningococcal adaptation to the host environment and evasion of the immune response. Meningococci can obtain DNA from their environment and can acquire new genes—including the capsular operon—such that a switch from one serogroup to another can occur.

EPIDEMIOLOGY

Patterns of disease

Up to 500,000 cases of meningococcal disease are thought to occur worldwide each year, and ~10% of the individuals affected die. There are several patterns of disease: epidemic, outbreak (small clusters of cases), hyperendemic, and sporadic or endemic.

Epidemics have continued since the original descriptions of meningococcal disease, especially affecting the sub-Saharan meningitis belt of Africa, where tens to hundreds of thousands of cases

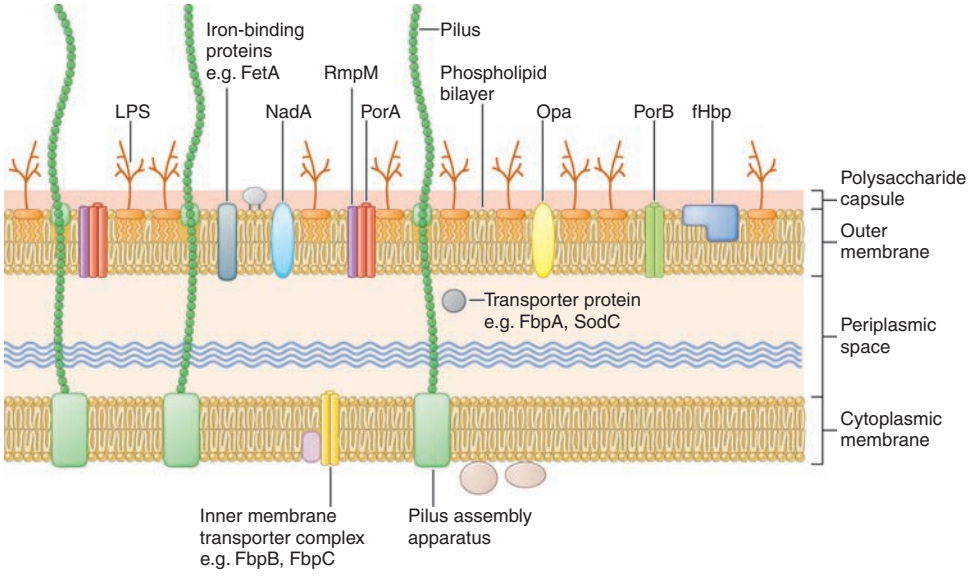


FIGURE 48-2
Cross-section through surface structures of *Neisseria meningitidis*. (*Reprinted with permission from M Sadarangani and AJ Pollard: Lancet Infect Dis 10:112, 2010.*)

(caused mainly by serogroup A but also by serogroups W135 and X) may be reported over a season and rates may be as high as 1000 cases per 100,000 population. Serogroup A epidemics took place in Europe and North America after the First and Second World Wars, and serogroup A outbreaks have been documented over the past 30 years in New Zealand, China, Nepal, Mongolia, India, Pakistan, Poland, and Russia.

Clusters of cases occur where there is an opportunity for increased transmission—i.e., in (semi-)closed communities such as schools, colleges, universities, military training centers, and refugee camps. Recently, such clusters have been especially strongly linked with a particular clone (sequence type 11) that is mainly associated with the serogroup C capsule. Wider and more prolonged community outbreaks (hyperendemic disease) due to single clones of serogroup B meningococci account for ≥10 cases per 100,000. Regions affected in the past decade include the U.S. Pacific Northwest, New Zealand (both islands), and the province of Normandy in France.

Most countries now experience predominantly sporadic cases (0.3–5 cases per 100,000 population), with many different disease-causing clones involved and usually no clear epidemiologic link between one case and another. The disease rate and the distribution of meningococcal strains vary in different regions of the world and also in any one location over time. For example, in the United States, the rate of meningococcal disease fell from 1.2 cases per 100,000 population in 1997 to <0.4 case per 100,000 in 2007 **(Fig. 48-3)**. Meningococcal disease in this country was previously dominated by serogroups B and C; however, serogroup Y emerged during the 1990s and became more common than serogroup C in 2007. In contrast, rates of disease in England and Wales rose to >5 cases per 100,000 during the 1990s because of an increase in cases caused by the ST11 serogroup C clone. As a result of a mass immunization program against serogroup C in 1999, almost all cases in the United Kingdom are now attributed to serogroup B **(Fig. 48-4)**.

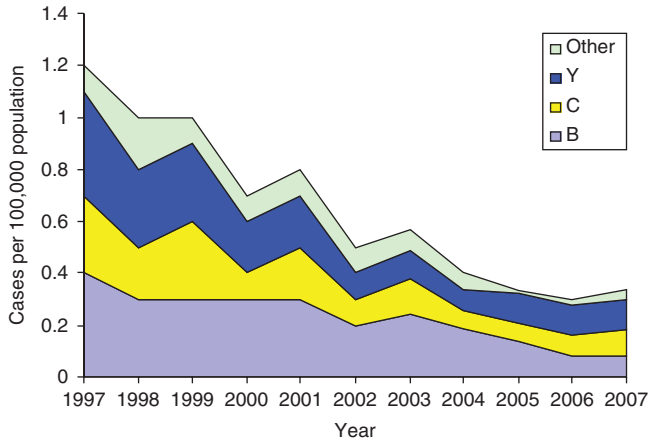


FIGURE 48-3
Meningococcal disease in the United States over time. (*Adapted from ABC Surveillance data, Centers for Disease Control and Prevention; www.cdc.gov.*)

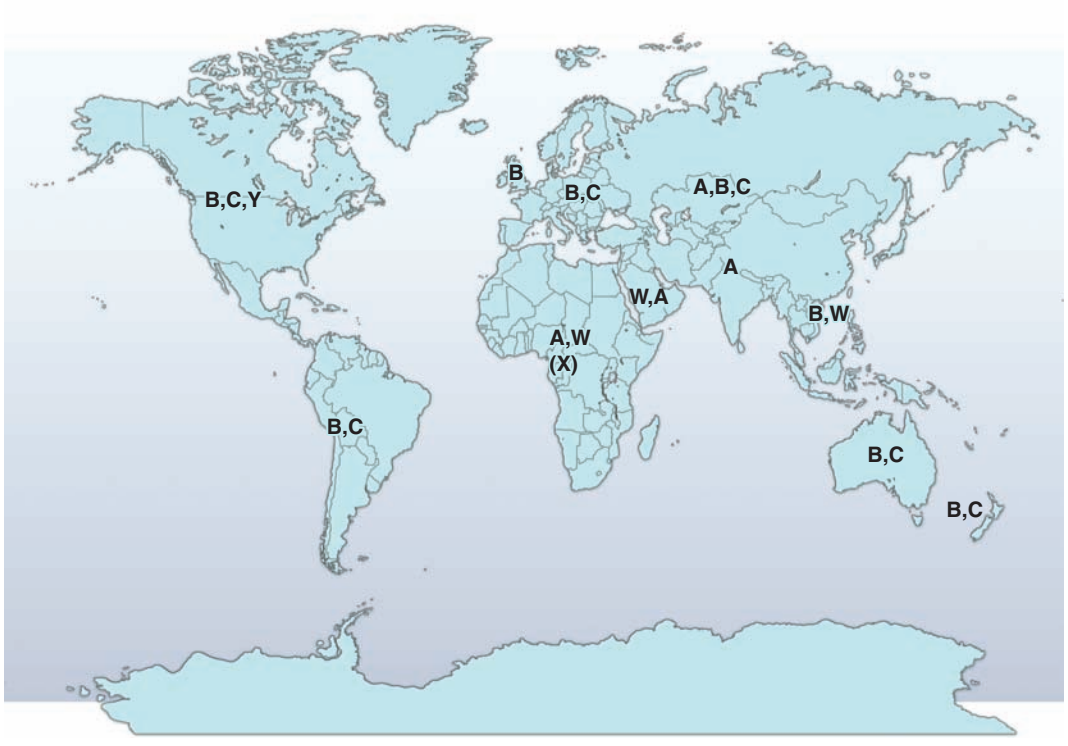


FIGURE 48-4
Global distribution of meningococcal serogroups, 1999–2009.

Factors associated with disease risk and susceptibility

The principal determinant of disease susceptibility is age, with the peak incidence in the first year of life (Fig. 48-5). The susceptibility of the very young presumably results from an absence of specific adaptive immunity in combination with very close contact with colonized individuals, including parents. Compared with other age groups, infants appear to be particularly susceptible to serogroup B disease: >30% of serogroup B cases in the United States occur during the first year of life. In the early 1990s in North America, the median ages for patients with disease due to serogroups B, C, Y, and W135 were 6, 17, 24, and 33 years, respectively.

After early childhood, a second peak of disease occurs in adolescents and young adults (15–25 years of age) in Europe and North America. It is thought that this peak relates to social behaviors and environmental exposures in this age group, as discussed below. Most cases of infection with *N. meningitidis* in developed countries today are sporadic, and the rarity of the disease suggests that individual susceptibility may be important. A number of factors probably contribute to individual susceptibility, including the host's genetic constitution, environment, and contact with a carrier or a case.

The best-documented genetic association with meningococcal disease is complement deficiency, chiefly of the terminal complement components (C5–9), properdin, or factor D; such a deficiency increases the risk of disease by up to 600-fold and may result in recurrent attacks. Complement components are believed to be important for the bactericidal activity of serum, which is considered the principal mechanism of immunity against invasive meningococcal disease. However, when investigated, complement deficiency is found in only a very small proportion of individuals with meningococcal disease (0.3%). Conversely, 7–20% of persons whose disease is caused by the less common serogroups (W135, X, Y, Z, 29E) have a complement deficiency. Complement deficiency appears to be associated with serogroup B disease only rarely. Individuals with recurrences of meningococcal disease, particularly those caused by non-B serogroups, should be assessed for complement deficiency by measurement of total hemolytic complement activity. There is also limited evidence that hyposplenism (through reduction in phagocytic capacity) and hypogammaglobulinemia (through absence of specific antibody) increase the risk of meningococcal disease. Genetic studies have revealed various associations with disease susceptibility, including complement and mannose-binding lectin deficiency, single-nucleotide polymorphisms in Toll-like receptor (TLR) 4 and complement factor H, and variants of Fc gamma receptors.

Factors that increase the chance of a susceptible individual acquiring *N. meningitidis* via the respiratory route also increase the risk of meningococcal disease. Acquisition occurs through close contact with carriers as a result of overcrowding (e.g., in poor socioeconomic settings, in refugee camps, during the Hajj pilgrimage to Mecca, and during freshman-year residence in college dormitories) and certain social behaviors (e.g., attendance at bars and nightclubs, kissing). Secondary cases may occur in close contacts of an index case (e.g., household members and persons kissing the infected individual); the risk to these contacts may be as high as 1000 times the background rate in the population. Factors that damage the nasopharyngeal epithelium also increase the risk of both colonization with *N. meningitidis* and invasive disease. The most important of these factors are cigarette smoking (odds ratio, 4.1) and passive exposure to cigarette smoke. In addition, recent viral respiratory tract infection, infection with *Mycoplasma* species, and winter or the dry season have been associated with meningococcal disease; all of these factors presumably either increase the expression of adhesion molecules in the nasopharynx, thus enhancing meningococcal adhesion, or facilitate meningococcal invasion of the bloodstream.

PATHOGENESIS

N. meningitidis has evolved as an effective colonizer of the human nasopharynx, with asymptomatic infection rates of >25% described in some series of adolescents and young adults and among residents of crowded communities.

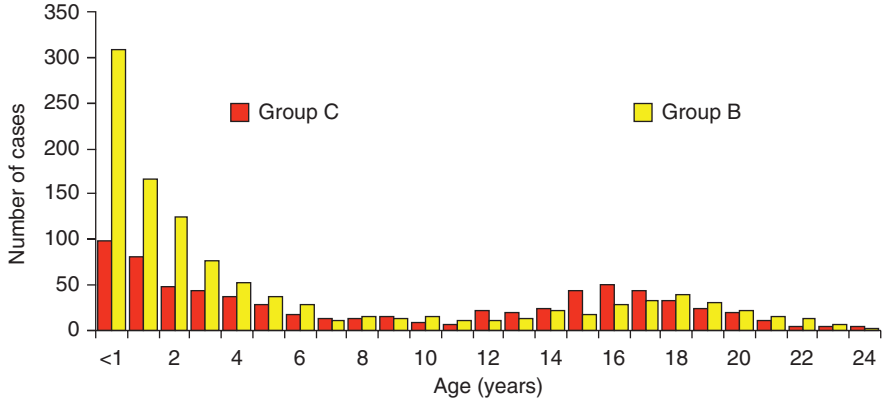


FIGURE 48-5
Age distribution of serogroups B and C meningococcal disease in England and Wales, 1998/1999. (*Health Protection Agency, UK; www.hpa.org.uk.*)

Point-prevalence studies reveal widely divergent rates of carriage for different types of meningococci. This variation suggests that some types may be adapted to a short duration of carriage with frequent transmission to maintain the population, while others may be less efficiently transmitted but may overcome this disadvantage by colonizing for a long period. Despite the high rates of carriage among adolescents and young adults, only ~10% of adults carry meningococci, and colonization is very rare in early childhood. Many of the same factors that increase the risk of meningococcal disease also increase the risk of carriage, including smoking, crowding, and respiratory viral infection. Colonization of the nasopharynx involves a series of interactions of meningococcal adhesins (e.g., Opa proteins and pili) with their ligands on the epithelial mucosa. *N. meningitidis* produces an IgA1 protease that is likely to reduce interruption of colonization by mucosal IgA.

Colonization should be considered the normal state of meningococcal infection, with an increased risk of invasion the unfortunate consequence (for both host and organism) of adaptations of hyperinvasive meningococcal lineages. The meningococcal capsule is an important virulence factor: acapsular strains rarely cause invasive disease. The capsule provides resistance to phagocytosis and may be important in preventing desiccation during transmission between hosts. Antigenic diversity in surface structures and an ability to vary levels of their expression have probably evolved as important factors in maintaining meningococcal populations within and between individual hosts.

Invasion through the mucosa into the blood occurs rarely, usually within a few days of acquisition of an invasive strain by a susceptible individual. Only occasional cases of prolonged colonization prior to invasion have been documented. Once the organism is in the bloodstream, its growth may be limited if the individual is partially immune, although bacteremia may allow seeding of another site, such as the meninges or the joints. Alternatively, unchecked proliferation may continue, resulting in high bacterial counts in the circulation. During growth, meningococci release blebs of outer membrane (Fig. 48-1) containing outer-membrane proteins and endotoxin (LPS). Endotoxin binds cell-bound CD14 in association with TLR4 to initiate an inflammatory cascade with the release of high levels of various mediators, including tumor necrosis factor α, soluble tumor necrosis factor receptor, interleukin (IL) 1, IL-1 receptor antagonist, IL-1β, IL-6, IL-8, IL-10, plasminogen-activator inhibitor 1 (PAI-1), and leukemia inhibitory factor. Soluble CD14-bound endotoxin acts as a mediator of endothelial activation. The severity of meningococcal disease is related both to the levels of endotoxin in the blood and to the magnitude of the inflammatory response. The latter is determined to some extent by polymorphisms in the inflammatory response genes (and their inhibitors), and the release of the inflammatory cascade heralds the development of meningococcal septicemia (meningococcemia). Endothelial injury is central to many clinical features of meningococcemia, including increased vascular permeability, pathologic changes in vascular tone, loss of thromboresistance, intravascular coagulation, and myocardial dysfunction. Endothelial injury leads to increased vascular permeability (attributed to loss of glycosaminoglycans and endothelial proteins), with subsequent gross proteinuria. Leakage of fluid and electrolytes into the tissues from capillaries leads to hypovolemia, tissue edema, and pulmonary edema. Initial compensation results in vasoconstriction and tachycardia, although cardiac output eventually falls. While resuscitation fluids may restore circulating volume, tissue edema will continue to increase, and, in the lung, the consequence may be respiratory failure.

Intravascular thrombosis (caused by activation of procoagulant pathways in association with upregulation of tissue factor on the endothelium) occurs in some patients with meningococcal disease and results in purpura fulminans and infarction of areas of skin or even of whole limbs. At the same time, multiple anticoagulant pathways are downregulated through loss of endothelial thrombomodulin and protein C receptors and decreases in levels of antithrombin III, protein C, protein S, and tissue factor pathway inhibitor. Thrombolysis is also profoundly impaired in meningococcal sepsis through the release of high levels of PAI-1.

Shock in meningococcal septicemia appears to be attributable to a combination of factors, including hypovolemia, which results from the capillary leak syndrome secondary to endothelial injury, and myocardial depression, which is driven by hypovolemia, hypoxia, metabolic derangements (e.g., hypocalcemia), and cytokines (e.g., IL-6). Decreased perfusion of tissues as a result of intravascular thrombosis, vasoconstriction, tissue edema, and reduced cardiac output in meningococcal septicemia can cause widespread organ dysfunction, including renal impairment and—later in the disease—a decreased level of consciousness due to central nervous system involvement.

Bacteria that reach the meninges cause a local inflammatory response, with release of a spectrum of cytokines similar to that seen in septicemia, that presents clinically as meningitis and is believed to determine the severity of neuronal injury. Local endothelial injury may result in cerebral edema and rapid onset of raised intracranial pressure in some cases.

CLINICAL MANIFESTATIONS

As discussed above, the most common form of infection with *N. meningitidis* is asymptomatic carriage of the organism in the nasopharynx. Despite the location of infection in the upper airway, meningococcal pharyngitis is rarely reported; however, upper respiratory tract symptoms are common prior to presentation with invasive disease. It is not clear whether these symptoms relate to preceding viral infection (which may promote meningococcal acquisition) or to meningococcal acquisition itself. After acquiring the organism, susceptible individuals develop disease manifestations in 1–10 days (usually <4 days, although colonization for 11 weeks has been documented).

Along the spectrum of presentations of meningococcal disease, the most common clinical syndromes are meningitis and meningococcal septicemia. In fulminant cases, death may occur within hours of the first symptoms. Occult bacteremia is also recognized and, if untreated, progresses in two-thirds of cases to focal infection including meningitis or septicemia. Meningococcal disease may also present as pneumonia, pyogenic arthritis or osteomyelitis, purulent pericarditis, endophthalmitis, conjunctivitis, primary peritonitis, or (rarely) urethritis. Perhaps because it is difficult to diagnose, pneumococcal pneumonia is not commonly reported but is associated with serogroups Y, W135, and Z and appears most often to affect individuals >10 years of age.

Rash

A nonblanching rash (petechial or purpuric) develops in >80% of cases of meningococcal disease; however, the rash is often absent early in the illness. Usually initially blanching in nature (macules, maculopapules, or urticaria) and indistinguishable from more common viral rashes, the rash of meningococcal infection becomes petechial or frankly purpuric over the hours after onset. In the most severe cases, large purpuric lesions develop (purpura fulminans). Some patients (including those with overwhelming sepsis) may have no rash. While petechial rash and fever are important signs of meningococcal disease, fewer than 10% of children (and, in some clinical settings, fewer than 1% of patients) with this presentation are found to have meningococcal disease. Most patients presenting with a petechial or purpuric rash have a viral infection **(Table 48-2)**. The skin lesions exhibit widespread endothelial necrosis and occlusion of small vessels in the dermis and subcutaneous tissues, with a neutrophilic infiltrate.

Meningitis

Meningococcal meningitis commonly presents as nonspecific manifestations, including fever, vomiting, and (especially in infants and young children) irritability, and is indistinguishable from other forms of bacterial meningitis unless there is an associated petechial or purpuric rash, which occurs in two-thirds of cases. Headache is rarely reported in early childhood but is more common in later childhood and adulthood. When headache is present, the following features, in association with fever or a history of fever, are suggestive of bacterial meningitis: neck stiffness, photophobia, decreased level of consciousness, seizures or status epilepticus, and focal neurologic signs. Classic signs of meningitis, such as neck stiffness and photophobia, are often absent in infants and young children with bacterial meningitis.

While 30–50% of patients present with a meningitis syndrome alone, up to 40% of meningitis patients also present with some features of septicemia. Most deaths from meningococcal meningitis alone (i.e., without septicemia) are associated with raised intracranial pressure presenting as a reduced level of consciousness, relative bradycardia and hypertension, focal neurologic signs, abnormal posturing, and signs of brainstem involvement—e.g., unequal, dilated, or poorly reactive pupils; abnormal eye movement; and impaired corneal responses.

TABLE 48-2

COMMON CAUSES OF PETECHIAL OR PURPURIC RASHES
Enteroviruses
Influenza and other respiratory viruses
Measles virus
Epstein-Barr virus
Cytomegalovirus
Parvovirus
Deficiency of protein C or S (including postvaricella protein S deficiency)
Platelet disorders (e.g., idiopathic thrombocytopenic purpura, drug effects, bone marrow infiltration)
Henoch-Schönlein purpura, connective tissue disorders, trauma (including nonaccidental injuries in children)
Pneumococcal, streptococcal, staphylococcal, or gram-negative bacterial sepsis

Septicemia

Meningococcal septicemia alone accounts for up to 20% of cases of meningococcal disease. The condition may progress from early nonspecific symptoms to death within hours. Mortality rates among children with this syndrome have been high (25–40%), but aggressive management (as discussed below) may reduce the figure to <10%. Early symptoms are nonspecific and suggest an influenza-like illness with fever, headache, and myalgia accompanied by vomiting and abdominal pain. As discussed above, the rash, if present, may appear to be viral early in the course until petechiae or purpuric lesions develop. Purpura fulminans occurs in severe cases, with multiple large purpuric lesions and signs of peripheral ischemia. Surveys of patients have indicated that limb pain, pallor (including a mottled appearance and cyanosis), and cold hands and feet may be prominent. Shock is manifested by tachycardia, poor peripheral perfusion, tachypnea, and oliguria. Decreased cerebral perfusion leads to confusion, agitation, or decreased level of consciousness. With progressive shock, multiorgan failure ensues; hypotension is a late sign in children, who more commonly present with compensated shock. Poor outcome is associated with an absence of meningismus, hypotension, young age, coma, relatively low temperature (< 38°C), leukopenia, and thrombocytopenia. Spontaneous hemorrhage (pulmonary, gastric, or cerebral) may result from consumption of coagulation factors and thrombocytopenia.

Chronic meningococcemia

Chronic meningococcemia, which is rarely recognized, presents as repeated episodes of petechial rash associated with fever, joint pain, features of arthritis, and

splenomegaly that may progress to acute meningococcal septicemia if untreated. During the relapsing course, bacteremia characteristically clears without treatment and then recurs. The differential diagnosis includes bacterial endocarditis, acute rheumatic fever, Henoch-Schönlein purpura, infectious mononucleosis, disseminated gonococcal infection, and immune-mediated vasculitis. This condition has been associated with complement deficiencies in some cases and with inadequate sulfonamide therapy in others.

Postmeningococcal reactive disease

In a small proportion of patients, an immune complex disease develops ~4–10 days after the onset of meningococcal disease, with manifestations that include a maculopapular or vasculitic rash (2% of cases), arthritis (up to 8% of cases), iritis (1%), pericarditis, and/or polyserositis associated with fever. The immune complexes involve meningococcal polysaccharide antigen and result in immunoglobulin and complement deposition with an inflammatory infiltrate. These features resolve spontaneously without sequelae. It is important to recognize this condition since a new onset of fever and rash can lead to concerns about relapse of meningococcal disease and unnecessarily prolonged antibiotic treatment.

DIAGNOSIS

Like other invasive bacterial infections, meningococcal disease may produce elevations of the white blood cell (WBC) count and of values for inflammatory markers (e.g., C-reactive protein and procalcitonin levels or the erythrocyte sedimentation rate). Values may be normal or low in rapidly progressive disease, and lack of these elevations does not exclude the diagnosis. However, in the presence of fever and a petechial rash, these elevations are suggestive of meningococcal disease. In patients with severe meningococcal septicemia, common laboratory findings include hypoglycemia, acidosis, hypokalemia, hypocalcemia, hypomagnesemia, hypophosphatemia, anemia, and coagulopathy.

Although meningococcal disease is often diagnosed on clinical grounds, in suspected meningococcal meningitis or meningococcemia, blood should routinely be sent for culture to confirm the diagnosis and to facilitate public health investigations; blood cultures are positive in up to 75% of cases. Culture media containing sodium polyanethol sulfonate, which may inhibit meningococcal growth, should be avoided. Meningococcal viability is reduced if there is a delay in transport of the specimen to the microbiology laboratory for culture or in plating of cerebrospinal fluid (CSF) samples. In countries where treatment with antibiotics before hospitalization is recommended for meningococcal disease, the majority of clinically suspected cases are culture negative. Real-time polymerase chain reaction (PCR) analysis of whole-blood samples increases the diagnostic yield by >40%, and results obtained with this method may remain positive for several days after administration of antibiotics. Indeed, in the United Kingdom, more than half of clinically suspected cases are currently identified by PCR.

Unless contraindications exist (raised intracranial pressure, uncorrected shock, disordered coagulation, thrombocytopenia, respiratory insufficiency, local infection, ongoing convulsions), lumbar puncture should be undertaken to identify and confirm the etiology of suspected meningococcal meningitis, whose presentation cannot be distinguished from that of meningitis of other bacterial causes. Some authorities have recommended a CT brain scan prior to lumbar puncture because of the risk of cerebral herniation in patients with raised intracranial pressure. However, a normal CT scan is not uncommon in the presence of raised intracranial pressure in meningococcal meningitis, and the decision to perform a lumbar puncture should be made on clinical grounds. CSF features of meningococcal meningitis (elevated protein level and WBC count, decreased glucose level) are indistinguishable from those of other types of bacterial meningitis unless a gram-negative diplococcus is identified. (Gram's staining is up to 80% sensitive for meningococcal meningitis.) CSF should be submitted for culture (sensitivity, 90%) and (where available) PCR analysis. CSF antigen testing with latex agglutination is insensitive and should be replaced by molecular diagnosis when possible.

Lumbar puncture should generally be avoided in meningococcal septicemia, as positioning for the procedure may critically compromise the patient's circulation in the context of hypovolemic shock. Delayed lumbar puncture may still be useful when the diagnosis is uncertain, particularly if molecular technology is available.

In other types of focal infection, culture and PCR analysis of normally sterile body fluids (e.g., synovial fluid) may aid in the diagnosis. Although some authorities have recommended cultures of scrapings or aspirates from skin lesions, this procedure adds little to the diagnostic yield when compared with a combination of blood culture and PCR analysis. Urinary antigen testing is also insensitive, and serologic testing for meningococcal infection has not been adequately studied. Because *N. meningitidis* is a component of the normal human nasopharyngeal flora, identification of the organism on throat swabs has no diagnostic value.

TREATMENT **Meningococcal Infections**

Death from meningococcal disease is associated most commonly with hypovolemic shock (meningococcemia) and occasionally with raised intracranial pressure (meningococcal meningitis). Therefore, management should focus on the treatment of these urgent clinical issues in addition to the administration of specific antibiotic therapy. Delayed recognition of meningococcal disease or its associated physiologic derangements, together with inadequate emergency management, is associated with poor outcome. Since the disease is rare, protocols for emergency management have been developed (see *www.meningitis.org*).

Airway patency may be compromised if the level of consciousness is depressed as a result of shock (impaired cerebral perfusion) or raised intracranial pressure; this situation may require intervention. In meningococcemia, pulmonary edema and pulmonary oligemia (presenting as hypoxia) require oxygen therapy or elective endotracheal intubation. In cases with shock, aggressive fluid resuscitation (with replacement of the circulating volume several times in severe cases) and inotropic support may be necessary to maintain cardiac output. If shock persists after volume resuscitation at 40 mL/kg, the risk of pulmonary edema is high, and elective intubation is recommended to improve oxygenation and decrease the work of breathing. Metabolic derangements including hypoglycemia, acidosis, hypokalemia, hypocalcemia, hypomagnesemia, hypophosphatemia, anemia, and coagulopathy should be anticipated and corrected. In the presence of raised intracranial pressure, management includes correction of coexistent shock and neurointensive care to maintain cerebral perfusion.

Empirical antibiotic therapy for suspected meningococcal disease consists of a third-generation cephalosporin such as ceftriaxone (75–100 mg/kg per day [maximum, 4 g/d] in one or two divided IV doses) or cefotaxime (200 mg/kg per day [maximum, 8 g/d] in four divided IV doses) to cover the various other (potentially penicillin-resistant) bacteria that may produce an indistinguishable clinical syndrome. Although unusual in most countries, reduced meningococcal sensitivity to penicillin (a minimal inhibitory concentration of 0.12–1.0 µg/mL) has been reported from Africa, the United Kingdom, Spain, Argentina, the United States, and Canada.

Both meningococcal meningitis and meningococcal septicemia are conventionally treated for 7 days, although courses of 3–5 days may be equally effective. Furthermore, a single dose of ceftriaxone or an oily suspension of chloramphenicol has been used successfully in resource-poor settings. No data are available to guide the duration of treatment for meningococcal infection at other foci (e.g., pneumonia, arthritis); antimicrobial therapy is usually continued until clinical and laboratory evidence of infection has resolved.

The use of glucocorticoids for adjunctive treatment of meningococcal meningitis remains controversial since no relevant studies have had sufficient power to determine true efficacy. One large study in adults did indicate a trend toward benefit, and in clinical practice a decision to use glucocorticoids usually precedes a definite diagnosis. Therapeutic doses of glucocorticoids are not recommended in meningococcal septicemia, but many intensivists recommend replacement glucocorticoid doses for patients who have refractory shock in association with impaired adrenal gland responsiveness.

Various other adjunctive therapies for meningococcal disease have been considered, but few have been subjected to clinical trials and none can currently be recommended. An antibody to LPS (HA1A) failed to confer a demonstrable benefit. Recombinant bactericidal/permeability-increasing protein was tested in a study that had inadequate power to show an effect on mortality rates; however, there were trends toward lower mortality rates among patients who received a complete infusion, and this group also had fewer amputations, fewer blood-product transfusions, and a significantly improved functional outcome. Given that protein C concentrations are reduced in meningococcal disease, the use of activated protein C has been considered since a survival benefit was demonstrated in adult sepsis trials; however, trials in pediatric sepsis (of particular relevance for meningococcal disease) found no benefit and indicated a potential risk of bleeding complications with use of activated protein C.

The postmeningococcal immune-complex inflammatory syndrome has been treated with nonsteroidal anti-inflammatory agents until spontaneous resolution occurs.

COMPLICATIONS

About 10% of patients with meningococcal disease die despite the availability of antimicrobial therapy and other intensive medical interventions. The most common complication of meningococcal disease (10% of cases) is scarring after necrosis of purpuric skin lesions, for which skin grafting may be necessary. The lower limbs are most often affected; next in frequency are the upper limbs, the trunk, and the face. On average, 13% of the skin surface area is involved. Amputations are necessary in ~2% of survivors of meningococcal disease because of a loss of tissue viability after peripheral ischemia or compartment syndromes. Unless there is local infection, amputation should usually be delayed to allow the demarcation between viable and nonviable tissue to become apparent. Approximately 4% of patients with meningococcal disease suffer hearing loss, and 7% have neurologic complications. In one study, pain was reported by 21% of survivors. In some investigations, the rate of complications is higher for serogroup C disease (mostly associated with the ST11 clone) than for serogroup B disease. In patients with severe hypovolemic shock, renal perfusion may be impaired and prerenal failure is common, but permanent renal replacement therapy is rarely needed.

Several studies suggest adverse psychosocial outcomes after meningococcal disease, with reduced quality of life, lowered self-esteem, and poorer neurologic development, including increased rates of attention deficit/hyperactivity disorder and special educational needs. Other studies have not found evidence of such outcomes.

PROGNOSIS

Several prognostic scoring systems have been developed to identify patients with meningococcal disease who are least likely to survive. Factors associated with a poorer prognosis are shock; young age (infancy), old age, and adolescence; coma; purpura fulminans; disseminated intravascular coagulation; thrombocytopenia;

leukopenia; absence of meningitis; metabolic acidosis; low plasma concentrations of antithrombin and proteins S and C; high blood levels of PAI-1; and a low erythrocyte sedimentation rate or C-reactive protein level. The Glasgow Meningococcal Septicaemia Prognostic Score is probably the best-performing scoring system studied so far and may be clinically useful for severity assessment in meningococcal disease. However, scoring systems do not direct the clinician to specific interventions, and the priority in management should be recognition of compromised airways, breathing, or circulation and direct, urgent intervention. Most patients improve rapidly with appropriate antibiotics and supportive therapy. Fulminant meningococcemia is more likely to result in death or ischemic skin loss than is meningitis; optimal emergency management may reduce mortality rates among the most severely affected patients.

PREVENTION

Since mortality rates in meningococcal disease remain high despite improvements in intensive care management, immunization is the only rational approach to prevention on a population level. Secondary cases are common among household and "kissing" contacts of cases, and secondary prophylaxis with antibiotic therapy is widely recommended for these contacts (see below).

Polysaccharide vaccines

Purified capsular polysaccharide has been used for immunization since the 1960s. Meningococcal polysaccharide vaccines are currently formulated as either bivalent (serogroups A and C) or quadrivalent (serogroups A, C, Y, and W135), with 50 μg of each polysaccharide per dose. Local reactions (erythema, induration, and tenderness) may occur in up to 40% of vaccinees, but serious adverse events (including febrile convulsions in young children) are very rarely reported. In adults, the vaccines are immunogenic, but immunity appears to be relatively short-lived (with antibody levels above baseline for only 2–10 years), and booster doses do not induce a further rise in antibody concentration. Indeed, a state of immunologic hyporesponsiveness has been widely reported to follow booster doses of plain polysaccharide vaccines. The repeating units of these vaccines cross-link B cell receptors to drive specific memory B cells to become plasma cells and produce antibody. Because polysaccharides are T cell–independent antigens, no memory B cells are produced after immunization, and the memory B cell pool is depleted such that fewer polysaccharide-specific cells are available to respond to a subsequent dose of vaccine **(Fig. 48-6)**. The clinical relevance of hyporesponsiveness is unknown. Plain polysaccharide vaccines generally are not immunogenic in early childhood, possibly because marginal-zone B cells are involved in polysaccharide responses and maturation of the splenic marginal zone is not complete until 18 months to 2 years of age. The efficacy of the meningococcal serogroup C component is >90% in young adults; no efficacy data are available for the serogroup Y and W135 polysaccharides in this age group.

Group A meningococcal polysaccharides are exceptional in that they are effective in preventing disease at all ages. Two doses administered 2–3 months apart to children 3–18 months of age or a single dose administered to older children or adults has a protective efficacy rate of >95%. The vaccine has been widely used in the control of meningococcal disease in the African meningitis belt. The duration of protection appears to be only 3–5 years.

There is no meningococcal serogroup B plain polysaccharide vaccine because α-2,8-*N*-acetylneuraminic acid is expressed on the surface of neural cells in the fetus such that the B polysaccharide is perceived as "self" and therefore is not immunogenic in humans.

Conjugate vaccines

The poor immunogenicity of plain polysaccharide vaccines in infancy has been overcome by chemical conjugation of the polysaccharides to a carrier protein (CRM_{197}, tetanus toxoid, or diphtheria toxoid). Conjugates that contain monovalent serogroup C polysaccharide and quadrivalent vaccines with A, C, Y, and W135 polysaccharides have been developed, as have vaccines including various other antigen combinations. After immunization, peptides from the carrier protein are conventionally believed to be presented to peptide-specific T cells in association with major histocompatibility complex (MHC) class II molecules (some recent data suggesting that carrier protein peptide may actually be presented in association with an oligosaccharide and MHCII) by polysaccharide-specific B cells; the result is a T cell–dependent immune response that allows production of antibody and generation of an expanded B cell memory pool. Unlike responses to booster doses of plain polysaccharides, responses to booster doses of conjugate vaccines have the characteristics of memory responses. Indeed, conjugate vaccines overcome the hyporesponsiveness induced by plain polysaccharides by replenishing the memory pool. The reactogenicity of conjugate vaccines is similar to that of plain polysaccharide vaccines.

The first widespread use of serogroup C meningococcal conjugate vaccine (MenC) came in 1999 in the United Kingdom after a rise in serogroup C disease. A mass vaccination campaign involving all individuals <19 years of age was undertaken, and the number of cases fell from >1000 in 1999 to just 28 in 2006. The effectiveness of the immunization program was attributed both to direct protection of immunized persons and to reduced transmission of the organism in the population as a result of decreased rates of colonization among the immunized (herd immunity). Data on immunogenicity and effectiveness have shown that the duration of protection is short when the vaccine is administered in early childhood; thus, booster doses are needed to maintain population immunity. In contrast, immunity after a dose of vaccine given in adolescence appears to be prolonged.

The first quadrivalent conjugate meningococcal vaccine containing A, C, Y, and W135 polysaccharides

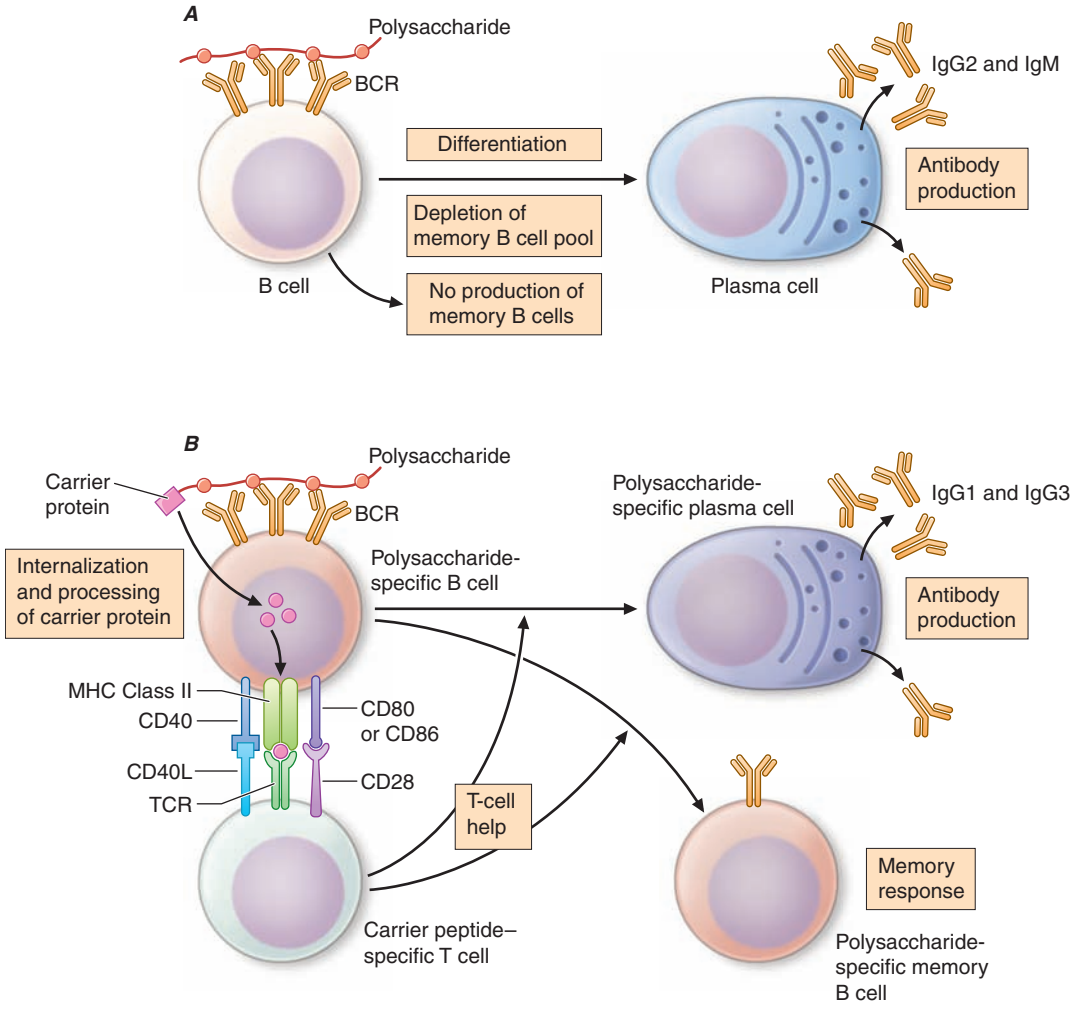


FIGURE 48-6

A. Polysaccharides from the encapsulated bacteria that cause disease in early childhood stimulate B cells by cross-linking the BCR and driving the production of immunoglobulins. There is no production of memory B cells, and the B cell pool may be depleted by this process such that subsequent immune responses are decreased. ***B.*** The carrier protein from protein-polysaccharide conjugate vaccines is processed by the polysaccharide-specific B cell, and peptides are presented to carrier peptide–specific T cells, with the consequent production of both plasma cells and memory B cells. BCR, B cell receptor; MHC, major histocompatibility complex; TCR, T cell receptor. (*Reprinted from AJ Pollard et al: Nat Rev Immunol 9:213, 2009.*)

conjugated to diphtheria toxoid was initially recommended for all children >11 years of age in the United States in 2005. In 2007 the license was extended to high-risk children 2–10 years of age. In the same year, the vaccine was licensed in Canada for persons 2–55 years of age. Uptake was slow, but preliminary data suggest an efficacy rate of >80%. Limited data from the U.S. Vaccine Adverse Events Reporting System indicated that there might be a short-term increase in the risk of Guillain-Barré syndrome after immunization with the diphtheria conjugate vaccine; however, further investigation has not confirmed this finding. Another quadrivalent conjugate vaccine (CRM_{197} carrier protein) was licensed in 2010 in both Europe and North America, and a third vaccine is in late-stage development.

A monovalent serogroup A vaccine was developed and licensed in 2010 and is being rolled out in several countries in sub-saharan Africa. The goal for this vaccine is control of epidemic meningococcal disease in the African meningitis belt.

Vaccines based on subcapsular antigens

The lack of immunogenicity of the serogroup B capsule has led to the development of vaccines based on subcapsular antigens. Various surface components have been studied in early-phase clinical trials. Outer-membrane vesicles (OMVs) containing outer-membrane proteins, phospholipid, and lipopolysaccharide can be extracted from cultures of *N. meningitidis* by detergent treatment **(Fig. 48-7)**. OMVs prepared in this way were used in efficacy trials with a Norwegian outbreak strain and reduced the incidence of group B disease among 14- to 16-year-old schoolchildren by 53%. Similarly, OMV vaccines constructed from local outbreak strains in Cuba and New Zealand have had

FIGURE 48-7
Illustration of meningococcal outer-membrane vesicle containing outer-membrane structures.

reported efficacy rates of >70%. These OMV vaccines appear to produce strain-specific immune responses, with only limited cross-protection, and are therefore best suited to clonal outbreaks (e.g., those in Cuba and New Zealand as well as others in Norway and the province of Normandy in France).

Several purified surface proteins have been evaluated in phase 1 clinical trials but have not yet been developed further because of variability or poor immunogenicity (e.g., transferrin-binding proteins, neisserial surface protein A). Other vaccine candidates have been identified since sequencing of the meningococcal genome. A combination vaccine that includes the New Zealand OMV vaccine and three proteins (neisserial adhesin A, factor H–binding protein, and neisserial heparin-binding antigen) is immunogenic in infancy and was recently submitted for licensure. Finally, a highly immunogenic vaccine based on two variants of factor H–binding protein is undergoing clinical evaluation.

MANAGEMENT OF CONTACTS

Close (household and kissing) contacts of individuals with meningococcal disease are at increased risk (up to 1000 times the rate for the general population) of developing secondary disease; a secondary case follows as many as 3% of sporadic cases. About one-fifth of secondary cases are actually co-primary cases—i.e., cases that occur soon after the primary case and in which transmission is presumed to have originated from the same third party. The rate of secondary cases is highest during the week after presentation of the index case. The risk falls rapidly but remains above baseline for up to 1 year after the index case; 30% of secondary cases occur in the first week, 20% in the second week, and most of the remainder over the next 6 weeks. In outbreaks of meningococcal disease, mass prophylaxis has been used; however, limited data support population intervention, and significant concerns have arisen about adverse events and the development of resistance. For these reasons, prophylaxis is usually restricted to (1) persons at greatest risk who are intimate and/or household contacts of the index case and (2) health care workers who have been directly exposed to respiratory secretions. In most cases, members of wider communities (e.g., at schools or colleges) are not offered prophylaxis.

The aim of prophylaxis is to eradicate colonization of close contacts with the strain that has caused invasive disease in the index case. Prophylaxis should be given to all contacts at the same time to avoid recolonization by meningococci transmitted from untreated contacts and should also be used as soon as possible to treat early disease in secondary cases. If the index patient is treated with an antibiotic that does not reliably clear colonization (e.g., penicillin), he or she should be given a prophylactic agent at the end of treatment to prevent relapse or onward transmission. Although rifampin has been most widely used and studied, it is not the optimal agent because it fails to eradicate carriage in 15–20% of cases, rates of adverse events have been high, compliance is affected by the need for four doses, and emerging resistance has been reported. Ceftriaxone as a single IM or IV injection is highly (97%) effective in carriage eradication and can be used at all ages and in pregnancy. Reduced susceptibility of isolates to ceftriaxone has occasionally been reported. Ciprofloxacin or ofloxacin is preferred in some countries; this agent is also highly effective and can be administered by mouth but is not recommended in pregnancy. Resistance to fluoroquinolones has been reported in some meningococci in North America, Europe, and Asia.

In documented serogroup A, C, Y, or W135 disease, contacts may be offered immunization (preferably with a conjugate vaccine) in addition to chemoprophylaxis to provide protection beyond the duration of antibiotic therapy. Mass vaccination has been used successfully to control disease during outbreaks in closed communities (educational and military establishments) as well as during epidemics in open communities.

CHAPTER 49

GONOCOCCAL INFECTIONS

Sanjay Ram ■ Peter A. Rice

DEFINITION

Gonorrhea is a sexually transmitted infection (STI) of epithelium and commonly manifests as cervicitis, urethritis, proctitis, and conjunctivitis. If untreated, infections at these sites can lead to local complications such as endometritis, salpingitis, tuboovarian abscess, bartholinitis, peritonitis, and perihepatitis in female patients; periurethritis and epididymitis in male patients; and ophthalmia neonatorum in newborns. Disseminated gonococcemia is an uncommon event whose manifestations include skin lesions, tenosynovitis, arthritis, and (in rare cases) endocarditis or meningitis.

MICROBIOLOGY

Neisseria gonorrhoeae is a gram-negative, nonmotile, nonspore-forming organism that grows singly and in pairs (i.e., as monococci and diplococci, respectively). Exclusively a human pathogen, the gonococcus contains, on average, three genome copies per coccal unit; this polyploidy permits a high level of antigenic variation and the survival of the organism in its host. Gonococci, like all other *Neisseria* species, are oxidase positive. They are distinguished from other neisseriae by their ability to grow on selective media and to utilize glucose but not maltose, sucrose, or lactose.

EPIDEMIOLOGY

The incidence of gonorrhea has declined significantly in the United States, but there were still ~299,000 newly reported cases in 2008. Gonorrhea remains a major public health problem worldwide, is a significant cause of morbidity in developing countries, and may play a role in enhancing transmission of HIV.

Gonorrhea predominantly affects young, nonwhite, unmarried, less educated members of urban populations. The number of reported cases probably represents half of the true number of cases—a discrepancy resulting from underreporting, self-treatment, and nonspecific treatment without a laboratory-proven diagnosis. The number of reported cases of gonorrhea in the United States rose from ~250,000 in the early 1960s to a high of 1.01 million in 1978. The recorded incidence of gonorrhea in modern times peaked in 1975, with 468 reported cases per 100,000 population in the United States. This peak was attributable to the interaction of several variables, including improved accuracy of diagnosis, changes in patterns of contraceptive use, and changes in sexual behavior. The incidence of the disease has since declined gradually and is currently estimated at 120 cases per 100,000, a figure that is still the highest among industrialized countries. A further decline in the overall incidence of gonorrhea in the United States over the past two decades may reflect increased condom use resulting from public health efforts to curtail HIV transmission. At present, the attack rate in the United States is highest among 15- to 19-year-old women and 20- to 24-year-old men; 40% of all reported cases occur in the preceding two groups together. From the standpoint of ethnicity, rates are highest among African Americans and lowest among persons of Asian or Pacific Island descent.

The incidence of gonorrhea is higher in developing countries than in industrialized nations. The exact incidence of any STI is difficult to ascertain in developing countries because of limited surveillance and variable diagnostic criteria. Studies in Africa have clearly demonstrated that nonulcerative STIs such as gonorrhea (in addition to ulcerative STIs) are an independent risk factor for the transmission of HIV (Chap. 93).

Gonorrhea is transmitted from males to females more efficiently than in the opposite direction. The rate of transmission to a woman during a single unprotected sexual encounter with an infected man is ~40–60%. Oropharyngeal gonorrhea occurs in ~20% of women who practice fellatio with infected partners. Transmission in either direction by cunnilingus is rare.

In any population, there exists a small minority of individuals who have high rates of new-partner acquisition. These "core-group members" or "high-frequency transmitters" are vital in sustaining STI transmission at the population level. Another instrumental factor in sustaining gonorrhea in the population is the large

number of infected individuals who are asymptomatic or have minor symptoms that are ignored. These persons, unlike symptomatic individuals, may not cease sexual activity and therefore continue to transmit the infection. This situation underscores the importance of contact tracing and empirical treatment of the sex partners of index cases.

PATHOGENESIS, IMMUNOLOGY, AND ANTIMICROBIAL RESISTANCE

Outer-membrane proteins

Pili

Fresh clinical isolates of *N. gonorrhoeae* initially form piliated (fimbriated) colonies distinguishable on translucent agar. Pilus expression is rapidly switched off with unselected subculture because of rearrangements in pilus genes. This change is a basis for antigenic variation of gonococci. Piliated strains adhere better to cells derived from human mucosal surfaces and are more virulent in organ culture models and human inoculation experiments than nonpiliated variants. In a fallopian tube explant model, pili mediate gonococcal attachment to nonciliated columnar epithelial cells. This event initiates gonococcal phagocytosis and transport through these cells to intercellular spaces near the basement membrane or directly into the subepithelial tissue. Pili are also essential for genetic competence and transformation of *N. gonorrhoeae*, which permit horizontal transfer of genetic material between different gonococcal lineages in vivo.

Opacity-associated protein

Another gonococcal surface protein that is important in adherence to epithelial cells is opacity-associated protein (Opa, formerly called protein II). Opa contributes to intergonococcal adhesion, which is responsible for the opaque nature of gonococcal colonies on translucent agar and the organism's adherence to a variety of eukaryotic cells, including polymorphonuclear leukocytes (PMNs). Certain Opa variants promote invasion of epithelial cells, and this effect has been linked with the ability of Opa to bind vitronectin, glycosaminoglycans, and several members of the carcinoembryonic antigen–related cell adhesion molecule (CEACAM) receptor family. *N. gonorrhoeae* Opa proteins that bind CEACAM 1, which is expressed by primary CD4+ T lymphocytes, suppress the activation and proliferation of these lymphocytes. This phenomenon may serve to explain the transient decrease in CD4+ T lymphocyte counts associated with gonococcal infection.

Porin

Porin (previously designated protein I) is the most abundant gonococcal surface protein, accounting for >50% of the organism's total outer-membrane protein. Porin molecules exist as trimers that provide anion-transporting aqueous channels through the otherwise-hydrophobic outer membrane. Porin shows stable interstrain antigenic variation and forms the basis for gonococcal serotyping. Two main serotypes have been identified: PorB.1A strains are often associated with disseminated gonococcal infection (DGI), while PorB.1B strains usually cause local genital infections only. DGI strains are generally resistant to the killing action of normal human serum and do not incite a significant local inflammatory response; therefore, they may not cause symptoms at genital sites. These characteristics may be related to the ability of PorB.1A strains to bind to complement-inhibitory molecules, resulting in a diminished inflammatory response. Porin can translocate to the cytoplasmic membrane of host cells—a process that could initiate gonococcal endocytosis and invasion.

Other outer-membrane proteins

Other notable outer-membrane proteins include H.8, a lipoprotein that is present in high concentration on the surface of all gonococcal strains and is an excellent target for antibody-based diagnostic testing. Transferrin-binding proteins (Tbp1 and Tbp2) and lactoferrin-binding protein are required for scavenging iron from transferrin and lactoferrin in vivo. Transferrin and iron have been shown to enhance the attachment of iron-deprived *N. gonorrhoeae* to human endometrial cells. IgA1 protease is produced by *N. gonorrhoeae* and may protect the organism from the action of mucosal IgA.

Lipooligosaccharide

Gonococcal lipooligosaccharide (LOS) consists of a lipid A and a core oligosaccharide that lacks the repeating O-carbohydrate antigenic side chain seen in other gram-negative bacteria (Chap. 2). Gonococcal LOS possesses marked endotoxic activity and contributes to the local cytotoxic effect in a fallopian tube model. LOS core sugars undergo a high degree of phase variation under different conditions of growth; this variation reflects genetic regulation and expression of glycotransferase genes that dictate the carbohydrate structure of LOS. These phenotypic changes may affect interactions of *N. gonorrhoeae* with elements of the humoral immune system (antibodies and complement) and may also influence direct binding of organisms to both professional phagocytes and nonprofessional phagocytes (epithelial cells). For example, gonococci that are sialylated at their LOS sites bind complement factor H and inhibit the alternative pathway of complement. LOS sialylation may also decrease nonopsonic Opa-mediated association with neutrophils and inhibit the oxidative burst in PMNs. The unsialylated terminal lactosamine residue of LOS binds to an asialoglycoprotein receptor on male epithelial cells, which facilitates binding and subsequent gonococcal invasion of these cells. Moreover, LOS oligosaccharide structures can modulate host immune responses. For example, the terminal monosaccharide expressed by LOS determines the C-type lectin receptor on dendritic cells that is targeted by the bacteria. In turn, the specific C-type lectin receptor engaged influences whether a T_H1- or T_H2-type response is elicited; the latter response may be less favorable for clearance of gonococcal infection.

Host factors

In addition to gonococcal structures that interact with epithelial cells, host factors seem to be important in mediating entry of gonococci into nonphagocytic cells. Activation of phosphatidylcholine-specific phospholipase C and acidic sphingomyelinase by *N. gonorrhoeae*, which results in the release of diacylglycerol and ceramide, is a requirement for the entry of *N. gonorrhoeae* into epithelial cells. Ceramide accumulation within cells leads to apoptosis, which may disrupt epithelial integrity and facilitate entry of gonococci into subepithelial tissue. Release of chemotactic factors as a result of complement activation contributes to inflammation, as does the toxic effect of LOS in provoking the release of inflammatory cytokines.

The importance of humoral immunity in host defenses against neisserial infections is best illustrated by the predisposition of persons deficient in terminal complement components (C5 through C9) to recurrent bacteremic gonococcal infections and to recurrent meningococcal meningitis or meningococcemia. Gonococcal porin induces T cell–proliferative responses in persons with urogenital gonococcal disease. A significant increase in porin-specific interleukin (IL) 4–producing CD4+ as well as CD8+ T lymphocytes is seen in individuals with mucosal gonococcal disease. A portion of these lymphocytes that show a porin-specific T_H2-type response could traffic to mucosal surfaces and play a role in immune protection against the disease. Few data clearly indicate that protective immunity is acquired from a previous gonococcal infection, although bactericidal and opsonophagocytic antibodies to porin and LOS may offer partial protection. On the other hand, women who are infected and acquire high levels of antibody to another outer-membrane protein, Rmp (reduction modifiable protein, formerly called protein III), may be especially likely to become reinfected with *N. gonorrhoeae* because Rmp antibodies block the effect of bactericidal antibodies to porin and LOS. Rmp shows little, if any, interstrain antigenic variation; therefore, Rmp antibodies potentially may block antibody-mediated killing of all gonococci. The mechanism of blocking has not been fully characterized, but Rmp antibodies noncompetitively inhibit binding of porin and LOS antibodies because of the proximity of these structures in the gonococcal outer membrane. In male volunteers who have no history of gonorrhea, the net effect of these events may influence the outcome of experimental challenge with *N. gonorrhoeae*. Because Rmp bears extensive homology to enterobacterial OmpA and meningococcal class 4 proteins, it is possible that these blocking antibodies result from prior exposure to cross-reacting proteins from these species and also play a role in first-time infection with *N. gonorrhoeae*.

Gonococcal resistance to antimicrobial agents

It is no surprise that *N. gonorrhoeae*, with its remarkable capacity to alter its antigenic structure and adapt to changes in the microenvironment, has become resistant to numerous antibiotics. The first effective agents against gonorrhea were the sulfonamides, which were introduced in the 1930s and became ineffective within a decade. Penicillin was then employed as the drug of choice for the treatment of gonorrhea. By 1965, 42% of gonococcal isolates had developed low-level resistance to penicillin G. Resistance due to the production of penicillinase arose later.

Gonococci become fully resistant to antibiotics either by chromosomal mutations or by acquisition of R factors (plasmids). Two types of chromosomal mutations have been described. The first type, which is drug specific, is a single-step mutation leading to high-level resistance. The second type involves mutations at several chromosomal loci that combine to determine the level as well as the pattern of resistance. Strains with mutations in chromosomal genes were first observed in the late 1950s. As recently as 2004, chromosomal mutations accounted for resistance to penicillin, tetracycline, or both in ~12% of strains surveyed in the United States.

β-Lactamase (penicillinase)–producing strains of *N. gonorrhoeae* (PPNG) carrying plasmids with the Pc^r determinant had rapidly spread worldwide by the early 1980s. *N. gonorrhoeae* strains with plasmid-borne tetracycline resistance (TRNG) can mobilize some β-lactamase plasmids, and PPNG and TRNG occur together, sometimes along with strains exhibiting chromosomally mediated resistance (CMRNG). Penicillin, ampicillin, and tetracycline are no longer reliable for the treatment of gonorrhea and should not be used.

Quinolone-containing regimens were also recommended for treatment of gonococcal infections; the fluoroquinolones offered the advantage of antichlamydial activity when administered for 7 days. However, quinolone-resistant *N. gonorrhoeae* (QRNG) appeared soon after these agents were first used to treat gonorrhea. QRNG is particularly common in the Pacific Islands (including Hawaii) and Asia, where, in certain areas, all gonococcal strains are now resistant to quinolones. At present, QRNG is also common in parts of Europe and the Middle East. In the United States, QRNG has been identified in midwestern and eastern areas as well as in states on the Pacific coast, where resistant strains were first seen. Alterations in DNA gyrase and topoisomerase IV have been implicated as mechanisms of fluoroquinolone resistance.

Resistance to spectinomycin, which has been used in the past as an alternative agent, has been reported. Since this agent usually is not associated with resistance to other antibiotics, spectinomycin can be reserved for use against multiresistant strains of *N. gonorrhoeae*. Nevertheless, outbreaks caused by strains resistant to spectinomycin have been documented in Korea and England when the drug has been used for primary treatment of gonorrhea.

Third-generation cephalosporins have remained highly effective as single-dose therapy for gonorrhea despite recent evidence that their minimal inhibitory concentrations (MICs) against strains of *N. gonorrhoeae* are increasing. Even though the MICs of ceftriaxone against

certain strains may reach 0.015–0.125 μg/mL (higher than the MICs of 0.0001–0.008 μg/mL for fully susceptible strains), these levels are greatly exceeded in the blood, the urethra, and the cervix when the routinely recommended parenteral dose of ceftriaxone is administered. All *N. gonorrhoeae* strains with reduced susceptibility to ceftriaxone and cefixime (termed *cephalosporin intermediate/resistant strains*) contain (1) a mosaic *penA* allele encoding a penicillin-binding protein 2 (PBP 2) whose sequence differs in nearly 60 amino acids from that of wild-type PBP 2 and (2) additional genetic resistance determinants that are also required for high-level penicillin resistance.

CLINICAL MANIFESTATIONS

Gonococcal infections in males

Acute urethritis is the most common clinical manifestation of gonorrhea in males. The usual incubation period after exposure is 2–7 days, although the interval can be longer and some men remain asymptomatic. Strains of the PorB.1A serotype tend to cause a greater proportion of cases of mild and asymptomatic urethritis than do PorB.1B strains. Urethral discharge and dysuria, usually without urinary frequency or urgency, are the major symptoms. The discharge initially is scant and mucoid but becomes profuse and purulent within a day or two. Gram's stain of the urethral discharge may reveal PMNs and gram-negative intracellular monococci and diplococci **(Fig. 49-1)**. The clinical manifestations of gonococcal urethritis are usually more severe and overt than those of nongonococcal urethritis, including urethritis caused by *Chlamydia trachomatis* (Chap. 81); however, exceptions are common, and it is often impossible to differentiate the causes of urethritis on clinical grounds alone. The majority of cases of urethritis seen in the United States today are not caused by *N. gonorrhoeae* and/or *C. trachomatis*. Although a number of other organisms may be responsible, many cases do not have a specific etiologic agent identified.

Most symptomatic men with gonorrhea seek treatment and cease to be infectious. The remaining men, who are largely asymptomatic, accumulate in number over time and constitute about two-thirds of all infected men at any point in time. Together with men incubating the organism (who shed the organism but are asymptomatic), they serve as the source of spread of infection. Before the antibiotic era, symptoms of urethritis persisted for ~8 weeks. Epididymitis is now an uncommon complication, and gonococcal prostatitis occurs rarely, if at all. Other unusual local complications of gonococcal urethritis include edema of the penis due to dorsal lymphangitis or thrombophlebitis, submucous inflammatory "soft" infiltration of the urethral wall, periurethral abscess or fistula, inflammation or abscess of Cowper's gland, and seminal vesiculitis. Balanitis may develop in uncircumcised men.

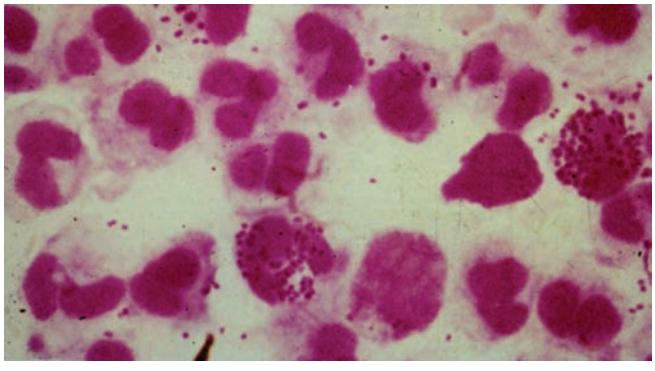


FIGURE 49-1
Gram's stain of urethral discharge from a male patient with gonorrhea shows gram-negative intracellular monococci and diplococci. (*From the Public Health Agency of Canada.*)

Gonococcal infections in females

Gonococcal cervicitis

Mucopurulent cervicitis is the most common STI diagnosis in American women and may be caused by *N. gonorrhoeae*, *C. trachomatis*, and other organisms. Cervicitis may coexist with candidal or trichomonal vaginitis. *N. gonorrhoeae* primarily infects the columnar epithelium of the cervical os. Bartholin's glands occasionally become infected.

Women infected with *N. gonorrhoeae* usually develop symptoms. However, the women who either remain asymptomatic or have only minor symptoms may delay in seeking medical attention. These minor symptoms may include scant vaginal discharge issuing from the inflamed cervix (without vaginitis or vaginosis per se) and dysuria (often without urgency or frequency) that may be associated with gonococcal urethritis. Although the incubation period of gonorrhea is less well defined in women than in men, symptoms usually develop within 10 days of infection and are more acute and intense than those of chlamydial cervicitis.

The physical examination may reveal a mucopurulent discharge (mucopus) issuing from the cervical os. Because Gram's stain is not sensitive for the diagnosis of gonorrhea in women, specimens should be submitted for culture or a nonculture assay (see next). Edematous and friable cervical ectopy as well as endocervical bleeding induced by gentle swabbing are more often seen in chlamydial infection. Gonococcal infection may extend deep enough to produce dyspareunia and lower abdominal or back pain. In such cases, it is imperative to consider a diagnosis of pelvic inflammatory disease (PID) and to administer treatment for that disease (Chaps. 30 and 81).

N. gonorrhoeae may be recovered from the urethra and rectum of women with cervicitis, but these are rarely the only infected sites. Urethritis in women may produce symptoms of internal dysuria, which is often attributed to "cystitis." Pyuria in the absence of bacteriuria seen on Gram's stain of unspun urine, accompanied by urine cultures that fail to yield $>10^2$ colonies of bacteria usually associated with urinary tract infection, signifies the possibility of urethritis due to *C. trachomatis*. Urethral infection with *N. gonorrhoeae* may also occur

in this context, but in this instance urethral cultures are usually positive.

Gonococcal vaginitis

The vaginal mucosa of healthy women is lined by stratified squamous epithelium and is rarely infected by *N. gonorrhoeae*. However, gonococcal vaginitis can occur in anestrogenic women (e.g., prepubertal girls and postmenopausal women), in whom the vaginal stratified squamous epithelium is often thinned down to the basilar layer, which can be infected by *N. gonorrhoeae*. The intense inflammation of the vagina makes the physical (speculum and bimanual) examination extremely painful. The vaginal mucosa is red and edematous, and an abundant purulent discharge is present. Infection in the urethra and in Skene's and Bartholin's glands often accompanies gonococcal vaginitis. Inflamed cervical erosion or abscesses in nabothian cysts may also occur. Coexisting cervicitis may result in pus in the cervical os.

Anorectal gonorrhea

Because the female anatomy permits the spread of cervical exudate to the rectum, *N. gonorrhoeae* is sometimes recovered from the rectum of women with uncomplicated gonococcal cervicitis. The rectum is the sole site of infection in only 5% of women with gonorrhea. Such women are usually asymptomatic, but occasionally have acute proctitis manifested by anorectal pain or pruritus, tenesmus, purulent rectal discharge, and rectal bleeding. Among men who have sex with men (MSM), the frequency of gonococcal infection, including rectal infection, fell by ≥90% throughout the United States in the early 1980s, but a resurgence of gonorrhea among MSM has been documented in several cities since the 1990s. Gonococcal isolates from the rectum of MSM tend to be more resistant to antimicrobial agents than are gonococcal isolates from other sites. Gonococcal isolates with a mutation in *mtrR* (multiple transferable resistance repressor) or in the promoter region of the gene that encodes for this transcriptional repressor develop increased resistance to antimicrobial hydrophobic agents such as bile acids and fatty acids in feces and thus are found with increased frequency in MSM. This situation may have been responsible for higher rates of failure of treatment for rectal gonorrhea with older regimens consisting of penicillin or tetracyclines.

Pharyngeal gonorrhea

Pharyngeal gonorrhea is usually mild or asymptomatic, although symptomatic pharyngitis does occasionally occur with cervical lymphadenitis. The mode of acquisition is oral-genital sexual exposure, with fellatio being a more efficient means of transmission than cunnilingus. Most cases resolve spontaneously, and transmission from the pharynx to sexual contacts is rare. Pharyngeal infection almost always coexists with genital infection. Swabs from the pharynx should be plated directly onto gonococcal selective media. Pharyngeal colonization with *Neisseria meningitidis* needs to be differentiated from that with other *Neisseria* species.

Ocular gonorrhea in adults

Ocular gonorrhea in an adult usually results from autoinoculation from an infected genital site. As in genital infection, the manifestations range from severe to occasionally mild or asymptomatic disease. The variability in clinical manifestations may be attributable to differences in the ability of the infecting strain to elicit an inflammatory response. Infection may result in a markedly swollen eyelid, severe hyperemia and chemosis, and a profuse purulent discharge. The massively inflamed conjunctiva may be draped over the cornea and limbus. Lytic enzymes from the infiltrating PMNs occasionally cause corneal ulceration and rarely cause perforation.

Prompt recognition and treatment of this condition are of paramount importance. Gram's stain and culture of the purulent discharge establish the diagnosis. Genital cultures should also be performed.

Gonorrhea in pregnant women, neonates, and children

Gonorrhea in pregnancy can have serious consequences for both the mother and the infant. Recognition of gonorrhea early in pregnancy also identifies a population at risk for other STIs, particularly chlamydial infection, syphilis, and trichomoniasis. The risks of salpingitis and PID—conditions associated with a high rate of fetal loss—are highest during the first trimester. Pharyngeal infection, most often asymptomatic, may be more common during pregnancy because of altered sexual practices. Prolonged rupture of the membranes, premature delivery, chorioamnionitis, funisitis (infection of the umbilical cord stump), and sepsis in the infant (with *N. gonorrhoeae* detected in the newborn's gastric aspirate during delivery) are common complications of maternal gonococcal infection at term. Other microorganisms and conditions, including *Mycoplasma hominis*, *Ureaplasma urealyticum*, *C. trachomatis*, and bacterial vaginosis (often accompanied by infection with *Trichomonas vaginalis*), have been associated with similar complications.

The most common form of gonorrhea in neonates is ophthalmia neonatorum, which results from exposure to infected cervical secretions during parturition. Ocular neonatal instillation of a prophylactic agent (e.g., 1% silver nitrate eyedrops or ophthalmic preparations containing erythromycin or tetracycline) prevents ophthalmia neonatorum but is not effective for its treatment, which requires systemic antibiotics. The clinical manifestations are acute and usually begin 2–5 days after birth. An initial nonspecific conjunctivitis with a serosanguineous discharge is followed by tense edema of the eyelids, chemosis, and a profuse, thick, purulent discharge. Corneal ulcerations that result in nebulae or perforation may lead to anterior synechiae, anterior staphyloma, panophthalmitis, and blindness. Infections described at other mucosal sites in infants, including vaginitis, rhinitis, and

anorectal infection, are likely to be asymptomatic. Pharyngeal colonization has been demonstrated in 35% of infants with gonococcal ophthalmia, and coughing is the most prominent symptom in these cases. Septic arthritis (see next section) is the most common manifestation of systemic infection or DGI in the newborn. The onset usually comes at 3–21 days of age, and polyarticular involvement is common. Sepsis, meningitis, and pneumonia are seen in rare instances.

Any STI in children beyond the neonatal period raises the possibility of sexual abuse. Gonococcal vulvovaginitis is the most common manifestation of gonococcal infection in children beyond infancy. Anorectal and pharyngeal infections are common in these children and are frequently asymptomatic. The urethra, Bartholin's and Skene's glands, and the upper genital tract are rarely involved. All children with gonococcal infection should also be evaluated for chlamydial infection, syphilis, and possibly HIV infection.

Gonococcal arthritis (DGI)

DGI (gonococcal arthritis) results from gonococcal bacteremia. In the 1970s, DGI occurred in ~0.5–3% of persons with untreated gonococcal mucosal infection. The lower incidence of DGI at present is probably attributable to a decline in the prevalence of particular strains that are likely to disseminate. DGI strains resist the bactericidal action of human serum and generally do not incite inflammation at genital sites, probably because of limited generation of chemotactic factors. Strains recovered from DGI cases in the 1970s were often of the PorB.1A serotype, were highly susceptible to penicillin, and had special growth requirements—including arginine, hypoxanthine, and uracil—that made the organism more fastidious and more difficult to isolate.

Menstruation is a risk factor for dissemination, and approximately two-thirds of cases of DGI are in women. In about half of affected women, symptoms of DGI begin within 7 days of onset of menses. Complement deficiencies, especially of the components involved in the assembly of the membrane attack complex (C5 through C9), predispose to neisserial bacteremia, and persons with more than one episode of DGI should be screened with an assay for total hemolytic complement activity.

The clinical manifestations of DGI have sometimes been classified into two stages: a bacteremic stage, which is less common today, and a joint-localized stage with suppurative arthritis. A clear-cut progression usually is not evident. Patients in the bacteremic stage have higher temperatures, and chills more frequently accompany their fever. Painful joints are common and often occur together with tenosynovitis and skin lesions. Polyarthralgias usually include the knees, elbows, and more distal joints; the axial skeleton is generally spared. Skin lesions are seen in ~75% of patients and include papules and pustules, often with a hemorrhagic component (Fig. 49-2; see also Fig. 11-44). Other manifestations of noninfectious dermatitis, such as nodular

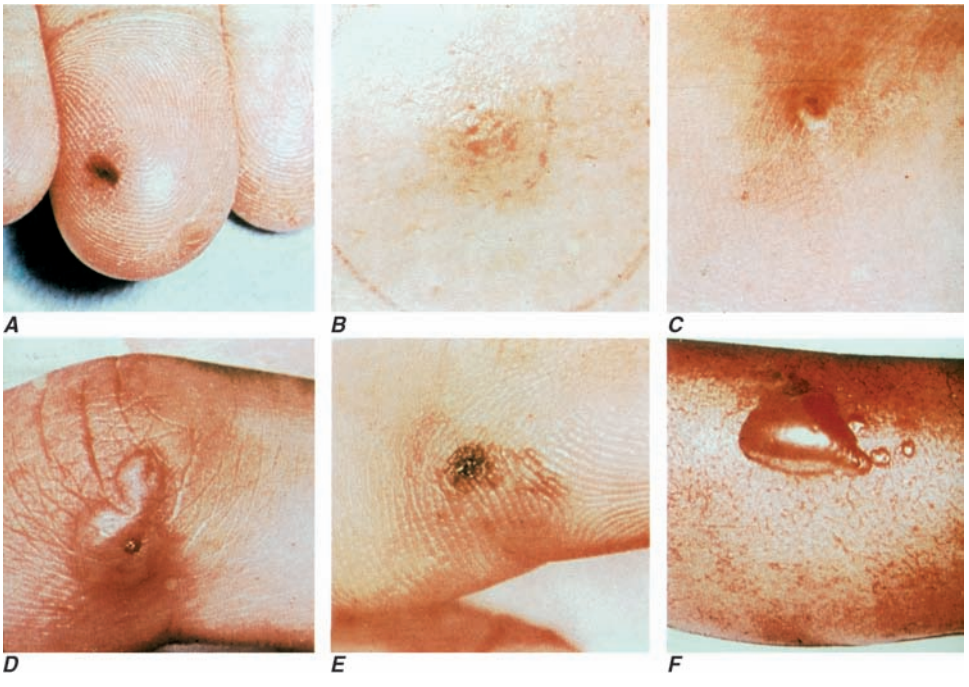


FIGURE 49-2

Characteristic skin lesions in patients with proven gonococcal bacteremia. The lesions are in various stages of evolution. ***A.*** Very early petechia on finger. ***B.*** Early papular lesion, 7 mm in diameter, on lower leg. ***C.*** Pustule with central eschar resulting from early petechial lesion. ***D.*** Pustular lesion on finger. ***E.*** Mature lesion with central necrosis (black) on hemorrhagic base. ***F.*** Bullae on anterior tibial surface. (*Reprinted with permission from KK Holmes et al: Ann Intern Med 74:979, 1971.*)

lesions, urticaria, and erythema multiforme, have been described. These lesions are usually on the extremities and number between 5 and 40. The differential diagnosis of the bacteremic stage of DGI includes reactive arthritis, acute rheumatoid arthritis, sarcoidosis, erythema nodosum, drug-induced arthritis, and viral infections (e.g., hepatitis B and acute HIV infection). The distribution of joint symptoms in reactive arthritis differs from that in DGI **(Fig. 49-3)**, as do the skin and genital manifestations.

Suppurative arthritis involves one or two joints, most often the knees, wrists, ankles, and elbows (in decreasing order of frequency); other joints occasionally are involved. Most patients who develop gonococcal septic arthritis do so without prior polyarthralgias or skin lesions; in the absence of symptomatic genital infection, this disease cannot be distinguished from septic arthritis caused by other pathogens. Rarely, osteomyelitis complicates septic arthritis involving small joints of the hand.

Gonococcal endocarditis, although rare today, was a relatively common complication of DGI in the preantibiotic era, accounting for about one-quarter of reported cases of endocarditis. Another unusual complication of DGI is meningitis.

Gonococcal infections in HIV-infected persons

The association between gonorrhea and the acquisition of HIV has been demonstrated in several well-controlled studies, mainly in Kenya and Zaire. The nonulcerative STIs enhance the transmission of HIV by three- to fivefold, possibly because of increased viral shedding by persons with urethritis or cervicitis (Chap. 93). HIV has been detected by polymerase chain reaction (PCR) more commonly in ejaculates from HIV-positive men with gonococcal urethritis than in those from HIV-positive men with nongonococcal urethritis. PCR positivity diminishes by twofold after appropriate therapy for urethritis. Not only does gonorrhea enhance the transmission of HIV, it may also increase the individual's risk for acquisition of HIV. A proposed mechanism is the significantly greater number of CD4+ T lymphocytes and dendritic cells that can be infected by HIV in endocervical secretions of women with nonulcerative STIs than in those of women with ulcerative STIs.

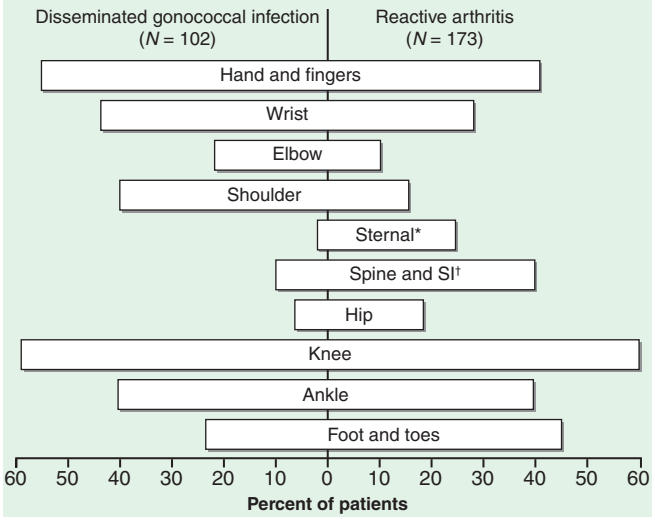


FIGURE 49-3
Distribution of joints with arthritis in 102 patients with disseminated gonococcal infection and 173 patients with reactive arthritis. *Includes the sternoclavicular joints. †SI, sacroiliac joint. (*Reprinted with permission from M Kousa et al: Sex Transm Dis 5:57, 1978.*)

LABORATORY DIAGNOSIS

A rapid diagnosis of gonococcal infection in men may be obtained by Gram's staining of urethral exudates (Fig. 49-1). The detection of gram-negative intracellular monococci and diplococci is usually highly specific and sensitive in diagnosing gonococcal urethritis in symptomatic males but is only ~50% sensitive in diagnosing gonococcal cervicitis. Samples should be collected with Dacron or rayon swabs. Part of the sample should be inoculated onto a plate of modified Thayer-Martin or other gonococcal selective medium for culture. It is important to process all samples immediately because gonococci do not tolerate drying. If plates cannot be incubated immediately, they can be held safely for several hours at room temperature in candle extinction jars prior to incubation. If processing is to occur within 6 h, transport of specimens may be facilitated by the use of nonnutritive swab transport systems such as Stuart or Amies medium. For longer holding periods (e.g., when specimens for culture are to be mailed), culture media with self-contained CO_2-generating systems (such as the JEMBEC or Gono-Pak systems) may be used. Specimens should also be obtained for the diagnosis of chlamydial infection (Chap. 81).

PMNs are often seen in the endocervix on a Gram's stain, and an abnormally increased number (≥30 PMNs per field in five 1000× oil-immersion microscopic fields) establishes the presence of an inflammatory discharge. Unfortunately, the presence or absence of gram-negative intracellular monococci or diplococci in cervical smears does not accurately predict which patients have gonorrhea, and the diagnosis in this setting should be made by culture or another suitable nonculture diagnostic method. The sensitivity of a single endocervical culture is ~80–90%. If a history of rectal sex is elicited, a rectal wall swab (uncontaminated with feces) should be cultured. A presumptive diagnosis of gonorrhea cannot be made on the basis of gram-negative diplococci in smears from the pharynx, where other *Neisseria* species are components of the normal flora.

Increasingly, nucleic acid probe tests are being substituted for culture for the direct detection of *N. gonorrhoeae* in urogenital specimens. A common assay employs a nonisotopic chemiluminescent DNA probe that hybridizes specifically with gonococcal 16S ribosomal RNA; this assay is as sensitive as conventional culture techniques. A disadvantage of non-culture-based

assays is that *N. gonorrhoeae* cannot be grown from the transport systems. Thus a culture-confirmatory test and formal antimicrobial susceptibility testing, if needed, cannot be performed. Nucleic acid amplification tests (NAATs), including Roche Amplicor, Gen-Probe APTIMA Combo2 (which also detects *Chlamydia*), and BD ProbeTec ET, offer an advantage: urine samples can be tested with a sensitivity similar to that obtained when urethral or cervical swab samples are assessed by culture and other non-NAATs.

Because of the legal implications, the preferred method for the diagnosis of gonococcal infection in children is a standardized culture. Two positive NAATs, each targeting a different nucleic acid sequence, may be substituted for culture of the cervix or the urethra as legal evidence of infection; however, cervical specimens are not recommended for prepubertal girls. Nonculture tests for gonococcal infection have not been approved by the U.S. Food and Drug Administration for use with specimens obtained from the pharynx and rectum of infected children. Cultures should be obtained from the pharynx and anus of both girls and boys, the vagina of girls, and the urethra of boys. For boys with a urethral discharge, a meatal specimen of the discharge is adequate for culture. Presumptive colonies of *N. gonorrhoeae* should be identified definitively by at least two independent methods.

Blood should be cultured in suspected cases of DGI. The use of Isolator blood culture tubes may enhance the yield. The probability of positive blood cultures decreases after 48 h of illness. Synovial fluid should be inoculated into blood culture broth medium and plated onto chocolate agar rather than selective medium because this fluid is not likely to be contaminated with commensal bacteria. Gonococci are infrequently recovered from early joint effusions containing <20,000 leukocytes/μL, but may be recovered from effusions containing >80,000 leukocytes/μL. The organisms are seldom recovered from blood and synovial fluid of the same patient.

TREATMENT Gonococcal Infections

Treatment failure can lead to continued transmission and the emergence of antibiotic resistance. The importance of adequate treatment with a regimen that the patient will adhere to cannot be overemphasized. Thus, highly effective single-dose regimens have been developed for uncomplicated gonococcal infections. The 2010 treatment guidelines for gonococcal infections from the Centers for Disease Control and Prevention are summarized in Table 49-1; the recommendations for uncomplicated gonorrhea apply to HIV-infected as well as HIV-uninfected patients.

Single-dose regimens of the third-generation cephalosporins ceftriaxone (given IM) and cefixime (given orally) currently are the mainstays of therapy for uncomplicated gonococcal infection of the urethra, cervix, rectum, or pharynx and almost always result in an effective cure. Outside the United States, cefixime has been associated with rare treatment failures caused by strains of *N. gonorrhoeae* with elevated MICs of third-generation cephalosporins. Quinolone-containing regimens are no longer recommended in the United States as first-line treatment because of widespread resistance to these agents.

Because co-infection with *C. trachomatis* occurs frequently, initial treatment regimens must also incorporate an agent (e.g., azithromycin or doxycycline) that is effective against chlamydial infection. Pregnant women with gonorrhea, who should not take doxycycline, should receive concurrent treatment with a macrolide antibiotic for possible chlamydial infection. A single 1-g dose of azithromycin, which is effective therapy for uncomplicated chlamydial infections, results in an unacceptably low cure rate (93%) for gonococcal infections and should not be used alone. A single 2-g dose of azithromycin, particularly in the extended-release microsphere formulation, delivers azithromycin to the lower gastrointestinal tract, thereby improving tolerability. Azithromycin is effective against sensitive strains, but this drug is expensive, causes gastrointestinal distress, and is not recommended for routine or first-line treatment of gonorrhea. Spectinomycin has been used as an alternative regimen for the treatment of uncomplicated gonococcal infections in penicillin-allergic persons outside the United States but is not currently available in this country. Of note, the limited effectiveness of spectinomycin for the treatment of pharyngeal infection reduces its utility in populations among whom such infection is common, such as MSM.

Persons with uncomplicated infections who receive a recommended regimen do not need a test of cure. Cultures for *N. gonorrhoeae* should be performed if symptoms persist after therapy with an established regimen, and any gonococci isolated should be tested for antimicrobial susceptibility.

Symptomatic gonococcal pharyngitis is more difficult to eradicate than genital infection. Persons who cannot tolerate cephalosporins and those in whom quinolones are contraindicated may be treated with spectinomycin if it is available, but this agent results in a cure rate of ≥52%. Persons given spectinomycin should have a pharyngeal sample cultured 3–5 days after treatment as a test of cure. A single 2-g dose of azithromycin may be used in areas where rates of resistance to azithromycin are low.

Treatments for gonococcal epididymitis and PID are discussed in Chap. 30. Ocular gonococcal infections in older children and adults should be managed with a single dose of ceftriaxone combined with saline irrigation of the conjunctivae (both undertaken expeditiously), and patients should undergo a careful ophthalmologic evaluation that includes a slit-lamp examination.

DGI may require higher dosages and longer durations of therapy (Table 49-1). Hospitalization is indicated if the diagnosis is uncertain, if the patient has localized joint disease that requires aspiration, or if the patient

TABLE 49-1

RECOMMENDED TREATMENT FOR GONOCOCCAL INFECTIONS: 2010 GUIDELINES OF THE CENTERS FOR DISEASE CONTROL AND PREVENTION

DIAGNOSIS	TREATMENT OF CHOICE[a]
Uncomplicated gonococcal infection of the cervix, urethra, pharynx[b], or rectum	
First-line regimens	Ceftriaxone (250 mg IM, single dose) *or* Cefixime (400 mg PO, single dose) *plus* Treatment for *Chlamydia* if chlamydial infection is not ruled out: Azithromycin (1 g PO, single dose) *or* Doxycycline (100 mg PO bid for 7 days)
Alternative regimens	Ceftizoxime (500 mg IM, single dose) *or* Cefotaxime (500 mg IM, single dose) *or* Spectinomycin (2 g IM, single dose)[c,d] *or* Cefotetan (1 g IM, single dose) plus probenecid (1 g PO, single dose)[c] *or* Cefoxitin (2 g IM, single dose) plus probenecid (1 g PO, single dose)[c]
Epididymitis	See Chap. 30
Pelvic inflammatory disease	See Chap. 30
Gonococcal conjunctivitis in an adult	Ceftriaxone (1 g IM, single dose)[e]
Ophthalmia neonatorum[f]	Ceftriaxone (25–50 mg/kg IV, single dose, not to exceed 125 mg)
Disseminated gonococcal infection[g]	
Initial therapy[h]	
Patient tolerant of β-lactam drugs	Ceftriaxone (1 g IM or IV q24h; recommended) *or* Cefotaxime (1 g IV q8h) *or* Ceftizoxime (1 g IV q8h)
Patients allergic to β-lactam drugs	Spectinomycin (2 g IM q12h)[d]
Continuation therapy	Cefixime (400 mg PO bid)
Meningitis or endocarditis	See text[i]

[a]True failure of treatment with a recommended regimen is rare and should prompt an evaluation for reinfection or consideration of an alternative diagnosis.
[b]Ceftriaxone is the only agent recommended for treatment of pharyngeal infection.
[c]Spectinomycin, cefotetan, and cefoxitin, which are alternative agents, currently are unavailable or in short supply in the United States.
[d]Spectinomycin may be ineffective for the treatment of pharyngeal gonorrhea.
[e]Plus lavage of the infected eye with saline solution (once).
[f]Prophylactic regimens are discussed in the text.
[g]Hospitalization is indicated if the diagnosis is uncertain, if the patient has frank arthritis with an effusion, or if the patient cannot be relied on to adhere to treatment.
[h]All initial regimens should be continued for 24–48 h after clinical improvement begins, at which time the switch may be made to one of the continuation regimens to complete a full week of antimicrobial treatment. Treatment for chlamydial infection (as above) should be given if this infection has not been ruled out. Fluoroquinolones may be an option if antimicrobial susceptibility can be documented by culture of the causative organism.
[i]Hospitalization is indicated to exclude suspected meningitis or endocarditis.

cannot be relied on to comply with treatment. Open drainage is necessary only occasionally—e.g., for management of hip infections that may be difficult to drain percutaneously. Nonsteroidal anti-inflammatory agents may be indicated to alleviate pain and hasten clinical improvement of affected joints. Gonococcal meningitis and endocarditis should be treated in the hospital with high-dose IV ceftriaxone (1–2 g every 12 h); therapy should continue for 10–14 days for meningitis and for at least 4 weeks for endocarditis. All persons who experience more than one episode of DGI should be evaluated for complement deficiency.

PREVENTION AND CONTROL

Condoms, if properly used, provide effective protection against the transmission and acquisition of gonorrhea as well as other infections that are transmitted to and from genital mucosal surfaces. Spermicidal preparations used with a diaphragm or cervical sponges impregnated with nonoxynol 9 offer some protection against gonorrhea and chlamydial infection. However, the frequent use of preparations that contain nonoxynol 9 is associated with mucosal disruption that paradoxically may enhance the risk of HIV infection in the event of exposure. All patients should be instructed to refer sex partners for evaluation and treatment. All sex partners of persons with gonorrhea should be evaluated and treated for *N. gonorrhoeae* and *C. trachomatis* infections if their last contact with the patient took place within 60 days before the onset of symptoms or the diagnosis of infection in the patient. If the patient's last sexual encounter was >60 days before onset of symptoms or diagnosis, the patient's most recent sex partner should be treated. Partner-delivered medications or prescriptions for medications to treat gonorrhea and chlamydial infection diminish the likelihood of reinfection (or relapse) in the infected patient. In states where it is legal, this approach is an option for partner management. Patients should be instructed to abstain from sexual intercourse until therapy is completed and until they and their sex partners no longer have symptoms. Greater emphasis must be placed on prevention by public health education, individual patient counseling, and behavior modification. Sexually active persons, especially adolescents, should be offered screening for STIs. For males, a NAAT on urine or a urethral swab may be used for screening. Preventing the spread of gonorrhea may help reduce the transmission of HIV. No effective vaccine for gonorrhea is yet available, but efforts to test several candidates are under way.

ACKNOWLEDGMENTS

The authors acknowledge the contributions of Dr. King K. Holmes and Dr. Stephen A. Morse to the chapter on this subject in earlier editions of Harrison's Principles of Internal Medicine.

CHAPTER 50

HAEMOPHILUS AND *MORAXELLA* INFECTIONS

Timothy F. Murphy

HAEMOPHILUS INFLUENZAE

MICROBIOLOGY

Haemophilus influenzae was first recognized in 1892 by Pfeiffer, who erroneously concluded that the bacterium was the cause of influenza. The bacterium is a small (1- by 0.3-μm) gram-negative organism of variable shape; hence, it is often described as a pleomorphic coccobacillus. In clinical specimens such as cerebrospinal fluid (CSF) and sputum, it frequently stains only faintly with safranin and therefore can easily be overlooked.

H. influenzae grows both aerobically and anaerobically. Its aerobic growth requires two factors: hemin (X factor) and nicotinamide adenine dinucleotide (V factor). These requirements are used in the clinical laboratory to identify the bacterium. Caution must be used to distinguish *H. influenzae* from *H. haemolyticus*, a respiratory tract commensal that has identical growth requirements.*H. haemolyticus* has classically been distinguished from *H. influenzae* by hemolysis on horse blood agar. However, a significant proportion of isolates of *H. haemolyticus* have now been recognized as nonhemolytic. Analysis of 16S ribosomal sequences is one reliable method to distinguish these two species.

Six major serotypes of *H. influenzae* have been identified; designated *a* through *f*, they are based on antigenically distinct polysaccharide capsules. In addition, some strains lack a polysaccharide capsule and are referred to as *nontypable* strains. Type b and nontypable strains are the most relevant strains clinically **(Table 50-1)**, although encapsulated strains other than type b can cause disease. *H. influenzae* was the first free-living organism to have its entire genome sequenced.

TABLE 50-1

CHARACTERISTICS OF TYPE b AND NONTYPABLE STRAINS OF *HAEMOPHILUS INFLUENZAE*

FEATURE	TYPE b STRAINS	NONTYPABLE STRAINS
Capsule	Ribosyl-ribitol phosphate	Unencapsulated
Pathogenesis	Invasive infections due to hematogenous spread	Mucosal infections due to contiguous spread
Clinical manifestations	Meningitis and invasive infections in incompletely immunized infants and children	Otitis media in infants and children; lower respiratory tract infections in adults with chronic bronchitis
Evolutionary history	Basically clonal	Genetically diverse
Vaccine	Highly effective conjugate vaccines	None available; under development

The antigenically distinct type b capsule is a linear polymercomposed of ribosyl-ribitol phosphate. Strains of *H. influenzae* type b (Hib) cause disease primarily in infants and children <6 years of age. Nontypable strains are primarily mucosal pathogens but occasionally cause invasive disease.

EPIDEMIOLOGY AND TRANSMISSION

H. influenzae, an exclusively human pathogen, is spread by airborne droplets or by direct contact with secretions or fomites. Colonization with nontypable *H. influenzae* is a dynamic process; new strains are acquired and other strains are replaced periodically.

The widespread use of Hib conjugate vaccines in many industrialized countries has resulted in striking decreases in the rate of nasopharyngeal colonization by Hib and in the incidence of Hib infection **(Fig. 50-1)**. However, the majority of the world's children remain unimmunized. Worldwide, invasive Hib disease occurs predominantly in unimmunized children and in those who have not completed the primary immunization series. Certain groups have a higher incidence of invasive Hib disease than the general population, including black children and Native American groups. Although this increased incidence has not yet been accounted for, several factors may be relevant, including age at exposure to the bacterium, socioeconomic conditions, and genetic differences.

PATHOGENESIS

Hib strains cause systemic disease by invasion and hematogenous spread from the respiratory tract to distant sites such as the meninges, bones, and joints. The type b polysaccharide capsule is an important virulence factor affecting the bacterium's ability to avoid opsonization and cause systemic disease.

Nontypable strains cause disease by local invasion of mucosal surfaces. Otitis media results when bacteria reach the middle ear by way of the eustachian tube. Adults with chronic bronchitis experience recurrent lower respiratory tract infection due to nontypable strains. In addition, persistent nontypable *H. influenzae* colonization of the lower airways of adults with chronic obstructive pulmonary disease (COPD) contributes to the airway inflammation that is a hallmark of the disease. Nontypable strains that cause infection in adults with COPD differ in pathogenic potential and genome content from strains that cause otitis media. The incidence of invasive disease caused by nontypable strains is low. Strains that cause invasive disease are genetically and phenotypically diverse.

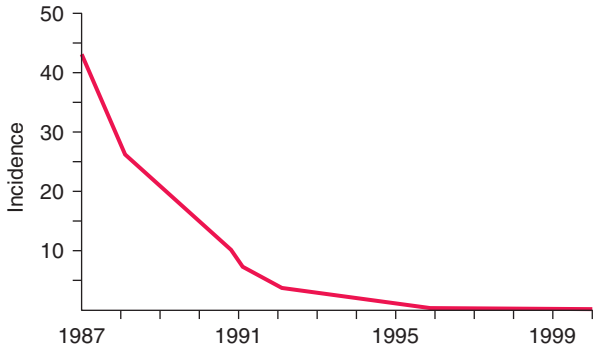


FIGURE 50-1

Estimated incidence (rate per 100,000) of invasive disease due to *Haemophilus influenzae* type b among children <5 years of age: 1987–2000. Fewer than 40 cases per year have been reported since 2000. (*Data from the Centers for Disease Control and Prevention.*)

IMMUNE RESPONSE

Antibody to the capsule is important in protection from infection by Hib strains. The level of (maternally acquired) serum antibody to the capsular polysaccharide, which is a polymer of polyribitol ribose phosphate (PRP), declines from birth to 6 months of age and, in the absence of vaccination, remains low until ~2 or 3 years of age. The age at the antibody nadir correlates with that of the peak incidence of type b disease. Antibody to PRP then appears partly as a result of exposure to Hib or cross-reacting antigens. Systemic Hib disease is unusual after the age of 6 years because of the presence of protective antibody. Vaccines in which PRP is conjugated to protein carrier molecules have been developed and are now used widely. These vaccines generate an antibody response to PRP in infants and effectively prevent invasive infections in infants and children.

Since nontypable strains lack a capsule, the immune response to infection is directed at noncapsular antigens. These antigens have generated considerable interest as immune targets and potential vaccine components. The human immune response to nontypable strains appears to be strain-specific, accounting in part for the propensity of these strains to cause recurrent otitis media and recurrent exacerbations of chronic bronchitis in immunocompetent hosts.

CLINICAL MANIFESTATIONS

Hib

The most serious manifestation of infection with Hib is *meningitis* (Chap. 31), which primarily affects children <2 years of age. The clinical manifestations of Hib meningitis are similar to those of meningitis caused by other bacterial pathogens. Fever and altered central nervous system function are the most common features at presentation. Nuchal rigidity may or may not be evident. Subdural effusion, the most common complication, is suspected when, despite 2 or 3 days of appropriate antibiotic therapy, the infant has seizures, hemiparesis, or continued obtundation. The overall mortality rate from Hib meningitis is ~5%, and the morbidity rate is high. Of survivors, 6% have permanent sensorineural hearing loss, and about one-fourth have a significant handicap of some type. If more subtle handicaps are sought, up to half of survivors are found to have some neurologic sequelae, such as partial hearing loss and delayed language development.

Epiglottitis (Chap. 17) is a life-threatening Hib infection involving cellulitis of the epiglottis and supraglottic tissues. It can lead to acute upper airway obstruction. Its unique epidemiologic features are its occurrence in an older age group (2–7 years old) than other Hib infections and its absence among Navajo Indians and Alaskan Eskimos. Sore throat and fever rapidly progress to dysphagia, drooling, and airway obstruction. Epiglottitis also occurs in adults.

Cellulitis (Chap. 22) due to Hib occurs in young children. The most common location is on the head or neck, and the involved area sometimes takes on a characteristic bluish-red color. Most patients have bacteremia, and 10% have an additional focus of infection.

Hib causes *pneumonia* in infants. The infection is clinically indistinguishable from other types of bacterial pneumonia (e.g., pneumococcal pneumonia) except that Hib is more likely to involve the pleura.

Several less common invasive conditions can be important clinical manifestations of Hib infection in children. These include osteomyelitis, septic arthritis, pericarditis, orbital cellulitis, endophthalmitis, urinary tract infection, abscesses, and bacteremia without an identifiable focus.

Nontypable H. influenzae

Nontypable *H. influenzae* is the most common bacterial cause of exacerbations of COPD; these exacerbations are characterized by increased cough, sputum production, and shortness of breath. Fever is low-grade, and no infiltrates are evident on chest x-ray. Nontypable strains also cause community-acquired bacterial pneumonia in adults, especially among patients with COPD or AIDS. The clinical features of *H. influenzae* pneumonia are similar to those of other types of bacterial pneumonia (including pneumococcal pneumonia).

Nontypable *H. influenzae* is one of the three most common causes of childhood otitis media (the other two being *Streptococcus pneumoniae* and *Moraxella catarrhalis*) (Chap. 17). Infants are febrile and irritable, while older children report ear pain. Symptoms of viral upper respiratory infection often precede otitis media. The diagnosis is made by pneumatic otoscopy. An etiologic diagnosis, although not routinely sought, can be established by tympanocentesis and culture of middle-ear fluid. Clinical features associated with *H. influenzae* otitis media include a history of recurrent episodes, treatment failure, concomitant conjunctivitis, bilateral otitis media, and recent antimicrobial therapy. The increasing use of pneumococcal polysaccharide conjugate vaccines in infants is resulting in a relative increase in the proportion of otitis media cases that are caused by *H. influenzae*.

Nontypable *H. influenzae* also causes puerperal sepsis and is an important cause of neonatal bacteremia. These nontypable strains, which are closely related to *H. haemolyticus*, tend to be of biotype IV and cause invasive disease after colonizing the female genital tract.

Nontypable *H. influenzae* causes sinusitis (Chap. 17) in adults and children. In addition, the bacterium is a less common cause of various invasive infections. These infections include empyema, adult epiglottitis, pericarditis, cellulitis, septic arthritis, osteomyelitis, endocarditis, cholecystitis, intraabdominal infections, urinary tract infections, mastoiditis, aortic graft infection, and bacteremia without a detectable focus. Most *H. influenzae* invasive infections in countries where Hib vaccines are used widely are caused by nontypable strains. Many patients with *H. influenzae* bacteremia have an underlying condition, such as HIV infection, cardiopulmonary disease, alcoholism, or cancer.

DIAGNOSIS

The most reliable method for establishing a diagnosis of Hib infection is recovery of the organism in culture. The presence of gram-negative coccobacilli in Gram-stained CSF is strong evidence for Hib meningitis. Recovery of the organism from CSF confirms the diagnosis. Cultures of other normally sterile body fluids, such as blood, joint fluid, pleural fluid, pericardial fluid, and subdural effusion, are confirmatory in other infections.

Detection of PRP is an important adjunct to culture in rapid diagnosis of Hib meningitis. Immunoelectrophoresis, latex agglutination, coagglutination, and enzyme-linked immunosorbent assay are effective in detecting PRP. These assays are particularly helpful when patients have received prior antimicrobial therapy and thus are especially likely to have negative cultures.

Because nontypable *H. influenzae* is primarily a mucosal pathogen, it is a component of a mixed flora; thus etiologic diagnosis is challenging. Nontypable *H. influenzae* infection is strongly suggested by the predominance of gram-negative coccobacilli among abundant polymorphonuclear leukocytes in a Gram-stained sputum specimen from a patient in whom pneumonia is suspected. Although bacteremia is detectable in a small proportion of patients with pneumonia due to nontypable *H. influenzae*, most such patients have negative blood cultures.

A diagnosis of otitis media is based on the detection by pneumatic otoscopy of fluid in the middle ear. An etiologic diagnosis requires tympanocentesis but is not routinely sought. An invasive procedure is also required to determine the etiology of sinusitis; thus, treatment is often empirical once the diagnosis is suspected in light of clinical symptoms and sinus radiographs.

TREATMENT Haemophilus influenzae

Initial therapy for meningitis due to Hib should consist of a cephalosporin such as ceftriaxone or cefotaxime. For children, the dosage of ceftriaxone is 75–100 mg/kg daily given in two doses 12 h apart. The pediatric dosage of cefotaxime is 200 mg/kg daily given in four doses 6 h apart. Adult dosages are 2 g every 12 h for ceftriaxone and 2 g every 4–6 h for cefotaxime. An alternative regimen for initial therapy is ampicillin (200–300 mg/kg daily in four divided doses) plus chloramphenicol (75–100 mg/kg daily in four divided doses). Therapy should continue for a total of 1–2 weeks.

Administration of glucocorticoids to patients with Hib meningitis reduces the incidence of neurologic sequelae. The presumed mechanism is reduction of the inflammation induced by bacterial cell-wall mediators of inflammation when cells are killed by antimicrobial agents. Dexamethasone (0.6 mg/kg per day intravenously in four divided doses for 2 days) is recommended for the treatment of Hib meningitis in children >2 months of age.

Invasive infections other than meningitis are treated with the same antimicrobial agents. For epiglottitis, the dosage of ceftriaxone is 50 mg/kg daily, and the dosage of cefotaxime is 150 mg/kg daily, given in three divided doses 8 h apart. Epiglottitis constitutes a medical emergency, and maintenance of an airway is critical. The duration of therapy is determined by the clinical response. A course of 1–2 weeks is usually appropriate.

Many infections caused by nontypable strains of *H. influenzae*, such as otitis media, sinusitis, and exacerbations of COPD, can be treated with oral antimicrobial agents. Approximately 20–35% of nontypable strains produce β-lactamase (with the exact proportion depending on geographic location), and these strains are resistant to ampicillin. Several agents have excellent activity against nontypable *H. influenzae*, including amoxicillin/clavulanic acid, various extended-spectrum cephalosporins, and the macrolides azithromycin and clarithromycin. Fluoroquinolones are highly active against *H. influenzae* and are useful in adults with exacerbations of COPD. However, fluoroquinolones are not currently recommended for the treatment of children or pregnant women because of possible effects on articular cartilage.

In addition to β-lactamase production, alteration of penicillin-binding proteins—a second mechanism of ampicillin resistance—has been detected in isolates of *H. influenzae*. Although rare in the United States, these β-lactamase–negative ampicillin-resistant strains are increasing in prevalence in Europe and Japan. Continued monitoring of the evolving antimicrobial susceptibility patterns of *H. influenzae* will be important.

PREVENTION

Vaccination

(See also Chap. 4) Two conjugate vaccines that prevent invasive infections with Hib in infants and children are licensed in the United States. In addition to eliciting protective antibody, these vaccines prevent disease by reducing rates of pharyngeal colonization with Hib. The widespread use of conjugate vaccines has dramatically reduced the incidence of Hib disease in developed countries. Even though the manufacture of Hib vaccines is costly, vaccination is cost-effective. The Global Alliance for Vaccines and Immunizations has recognized the underuse of Hib conjugate vaccines. The disease burden has been reduced in developing countries that have implemented routine vaccination (e.g., The Gambia, Chile). An important obstacle to more widespread vaccination is the lack of data on the epidemiology and burden of Hib disease in many developing countries.

All children should be immunized with an Hib conjugate vaccine, receiving the first dose at ~2 months of age, the rest of the primary series at 2–6 months of age, and a booster dose at 12–15 months of age. Specific recommendations vary for the different conjugate vaccines. The reader is referred to the recommendations of the American Academy of Pediatrics (Chap. 4 and *www.cispimmunize.org*).

Currently, no vaccines are available for the prevention of disease caused by nontypable *H. influenzae*. However, a vaccine that contains a surface protein of *H. influenzae* conjugated to pneumococcal polysaccharides has shown partial efficacy in preventing *H. influenzae* otitis media. Additional progress in the development of vaccines against nontypable *H. influenzae* is anticipated.

Chemoprophylaxis

The risk of secondary disease is greater than normal among household contacts of patients with Hib disease. Therefore, all children and adults (except pregnant women) in households with at least one incompletely immunized contact <4 years of age should receive

prophylaxis with oral rifampin. When two or more cases of invasive Hib disease have occurred within 60 days at a child-care facility attended by incompletely vaccinated children, administration of rifampin to all attendees and personnel is indicated, as is recommended for household contacts. Chemoprophylaxis is not indicated in nursery and child-care contacts of a single index case. The reader is referred to the recommendations of the American Academy of Pediatrics.

HAEMOPHILUS DUCREYI

Haemophilus ducreyi is the etiologic agent of chancroid (Chap. 30), a sexually transmitted disease characterized by genital ulceration and inguinal adenitis. *H. ducreyi* poses a significant health problem in developing countries. In addition to being a cause of morbidity in itself, chancroid is associated with HIV infection because of the role played by genital ulceration in HIV transmission. Chancroid increases both the efficiency of, transmission of, and the degree of susceptibility to HIV infection.

MICROBIOLOGY

H. ducreyi is a highly fastidious coccobacillary gram-negative bacterium whose growth requires X factor (hemin). Although, in light of this requirement, the bacterium has been classified in the genus *Haemophilus*, DNA homology and chemotaxonomic studies have established substantial differences between *H. ducreyi* and other *Haemophilus* species. Taxonomic reclassification of the organism is likely in the future but awaits further study. Ulcers contain predominantly T cells. The fact that patients who have had chancroid may have repeated infections indicates that infection does not confer protection.

EPIDEMIOLOGY AND PREVALENCE

Chancroid is a common cause of genital ulcers in developing countries. In the United States, several large outbreaks have occurred since 1981. Recurring epidemiologic themes have been apparent in these outbreaks: (1) transmission has been predominantly heterosexual; (2) males have outnumbered females by ratios of 3:1 to 25:1; (3) prostitutes have been important in transmission of the infection; and (4) chancroid has been strongly associated with illicit drug use. The annual number of cases reported in the United States has remained stable since 2000.

CLINICAL MANIFESTATIONS

Infection is acquired as the result of a break in the epithelium during sexual contact with an infected individual. After an incubation period of 4–7 days, the initial lesion—a papule with surrounding erythema—appears.

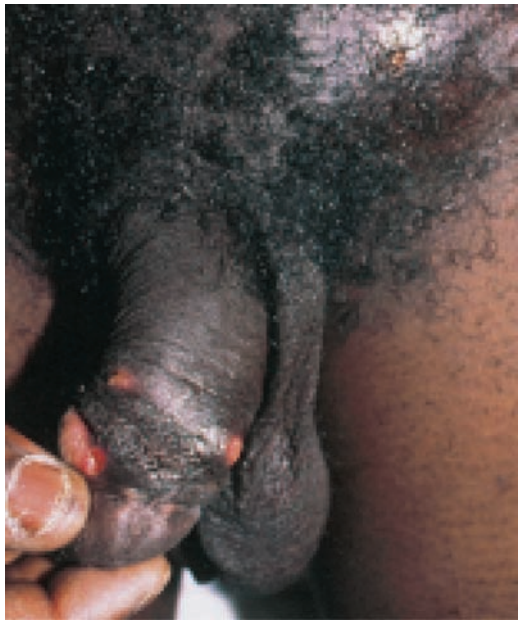


FIGURE 50-2
Chancroid with characteristic penile ulcers and associated left inguinal adenitis (bubo).

In 2 or 3 days, the papule evolves into a pustule, which spontaneously ruptures and forms a sharply circumscribed ulcer that is generally not indurated **(Fig. 50-2)**. The ulcers are painful and bleed easily; little or no inflammation of the surrounding skin is evident. Approximately half of patients develop enlarged, tender inguinal lymph nodes, which frequently become fluctuant and spontaneously rupture. Patients usually seek medical care after 1–3 weeks of painful symptoms.

The presentation of chancroid does not usually include all of the typical clinical features and is sometimes atypical. Multiple ulcers can coalesce to form giant ulcers. Ulcers can appear and then resolve, with inguinal adenitis (Fig. 50-2) and suppuration following 1–3 weeks later; this clinical picture can be confused with that of lymphogranuloma venereum (Chap. 81). Multiple small ulcers can resemble folliculitis. Other differential diagnostic considerations include the various infections causing genital ulceration, such as primary syphilis, secondary syphilis (condyloma latum), genital herpes, and donovanosis. In rare cases, chancroid lesions become secondarily infected with bacteria; the result is extensive inflammation.

DIAGNOSIS

Clinical diagnosis of chancroid is often inaccurate, and laboratory confirmation should be attempted in suspected cases. An accurate diagnosis of chancroid relies on culture of *H. ducreyi* from the lesion. In addition, aspiration and culture of suppurative lymph nodes should be considered. Since the organism can be difficult to grow, the use of selective and supplemented media is necessary. A multiplex polymerase chain reaction assay has been developed

for simultaneous amplification of DNA targets from *H. ducreyi*, *Treponema pallidum*, and herpes simplex virus types 1 and 2. When this assay becomes commercially available, it will be a useful diagnostic tool with which to identify the etiology of genital ulcers.

TREATMENT ***Haemophilus ducreyi***

Treatment regimens recommended by the Centers for Disease Control and Prevention include (1) a single 1-g oral dose of azithromycin; (2) ceftriaxone (250 mg intramuscularly in a single dose); (3) ciprofloxacin (500 mg by mouth twice a day for 3 days); and (4) erythromycin base (500 mg by mouth three times a day for 7 days). Isolates from patients who do not respond promptly to treatment should be tested for antimicrobial resistance. In patients with HIV infection, healing may be slow and longer courses of treatment may be necessary. Clinical treatment failure in HIV-seropositive patients may reflect co-infection, especially with herpes simplex virus. Contacts of patients with chancroid should be identified and treated, whether or not symptoms are present, if they have had sexual contact with the patient during the 10 days preceding the patient's onset of symptoms.

MORAXELLA CATARRHALIS

MICROBIOLOGY

M. catarrhalis is an unencapsulated gram-negative diplococcus the ecologic of which niche is the human respiratory tract. The organism was initially designated *Micrococcus catarrhalis*, but its name was changed to *Neisseria catarrhalis* in 1970 because of phenotypic similarities to commensal *Neisseria* species. On the basis of more rigorous analysis of genetic relatedness, *Moraxella catarrhalis* is now the widely accepted name for this species.

EPIDEMIOLOGY

Nasopharyngeal colonization by *M. catarrhalis* is common in infancy, with colonization rates ranging between 33% and 100% and depending on geographic location. Several factors probably account for this geographic variation, including living conditions, day-care attendance, hygiene, household smoking, and population genetics. The prevalence of colonization decreases steadily with age.

The widespread use of pneumococcal conjugate vaccines in some countries has resulted in alterations in patterns of nasopharyngeal colonization in resident populations. A relative increase in colonization by nonvaccine pneumococcal serotypes, nontypable *H. influenzae*, and *M. catarrhalis* has occurred. These changes in colonization patterns may be altering the distribution of pathogens of both otitis media and sinusitis in children.

PATHOGENESIS

M. catarrhalis causes mucosal infections of the respiratory tract. Strains exhibit substantial genetic diversity and differences in virulence properties. The species is composed of two distinct genetic lineages; the complement-resistant lineage is more strongly associated with virulence than are complement-sensitive strains.

The expression of several adhesin molecules with differing specificities for various host cell receptors reflects the importance of adherence to the respiratory epithelial surface in the pathogenesis of infection. *M. catarrhalis* invades multiple cell types. Its intracellular residence in lymphoid tissue provides a potential reservoir for persistence in the human respiratory tract.

CLINICAL MANIFESTATIONS

In children, *M. catarrhalis* causes predominantly mucosal infections when the bacterium migrates from the nasopharynx to the middle ear or the sinuses (Chap. 17). The inciting event for both otitis media and sinusitis is often a preceding viral infection. Overall, cultures of middle-ear fluid obtained by tympanocentesis indicate that *M. catarrhalis* causes 15–20% of cases of acute otitis media. Acute otitis media caused by *M. catarrhalis* or nontypable *H. influenzae* is clinically milder than otitis media caused by *S. pneumoniae*, with less fever and a lower prevalence of a red bulging tympanic membrane. However, substantial overlap makes it impossible to predict etiology in an individual child on the basis of clinical features.

A small proportion of viral upper respiratory tract infections are complicated by bacterial sinusitis. Cultures of sinus puncture aspirates show that *M. catarrhalis* accounts for ~20% of cases of acute bacterial sinusitis in children and for a smaller proportion in adults.

M. catarrhalis is a common cause of exacerbations in adults with COPD. The bacterium has been overlooked in this clinical setting because it has long been considered to be a commensal and because it is easily mistaken for commensal *Neisseria* species in cultures of respiratory secretions (see "Diagnosis," next). Several independent lines of evidence have established *M. catarrhalis* as a pathogen in COPD. These include (1) the demonstration of *M. catarrhalis* in the lower airways during exacerbations, (2) the association of exacerbation with acquisition of new strains, (3) elevations of inflammatory markers in association with *M. catarrhalis*, and (4) the development of specific immune responses following infection. *M. catarrhalis* is the second most common bacterial cause of COPD exacerbations (after *H. influenzae*), as shown in a 10-year prospective study; the distribution of new-strain acquisitions is shown in **Fig. 50-3**. Not included are culture-negative cases or cases from which a pathogen had been previously isolated. With the application of rigorous clinical criteria for defining the etiology of exacerbations (both culture-positive and culture-negative), ~10% of all exacerbations in the same study were caused by *M. catarrhalis*.

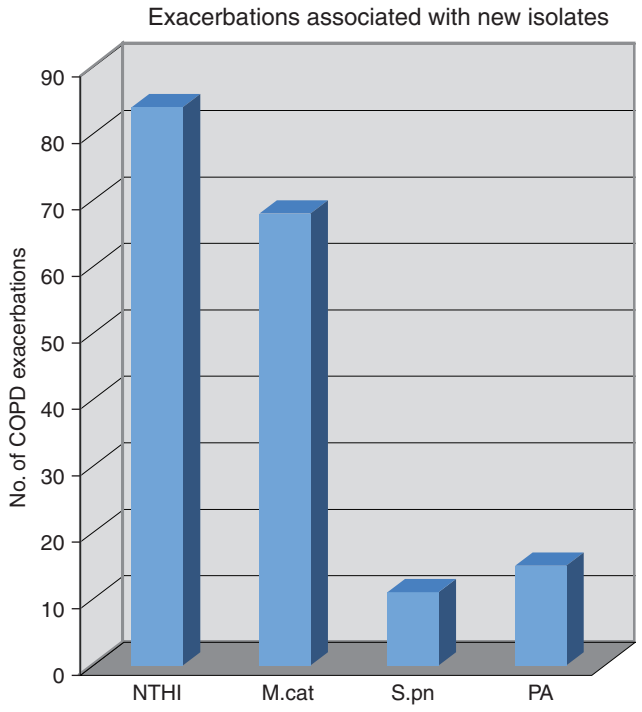


FIGURE 50-3
Cumulative results of a prospective study (1994–2004) of bacterial infection in COPD showing etiology of exacerbations. The numbers of exacerbations shown indicate the acquisition of a new strain simultaneous with clinical symptoms of an exacerbation. NTHI, nontypable *H. influenzae*; M.cat, *M. catarrhalis*; S.pn, *Streptococcus pneumoniae*; PA, *Pseudomonas aeruginosa*. (*Adapted from TF Murphy, GI Parameswaran: Clin Infect Dis 49:124, 2009, with permission.© 2009 Infectious Diseases Society of America.*)

The clinical features of an exacerbation due to *M. catarrhalis* are similar to those of exacerbations due to other bacterial pathogens, including *H. influenzae* and *S. pneumoniae*. The cardinal symptoms are cough with increased sputum production, sputum purulence, and dyspnea in comparison with baseline symptoms.

Pneumonia due to *M. catarrhalis* occurs in the elderly, particularly in the setting of underlying cardiopulmonary disease, but is infrequent. Invasive infections, such as bacteremia, endocarditis, neonatal meningitis, and septic arthritis, are rare.

DIAGNOSIS

Tympanocentesis is required for etiologic diagnosis of otitis media, but this procedure is not performed routinely. Therefore, treatment of otitis media is generally empirical. Similarly, an etiologic diagnosis of sinusitis requires an invasive procedure and thus is usually not available to the clinician. Isolation of *M. catarrhalis* from an expectorated sputum sample from an adult experiencing clinical symptoms of an exacerbation is suggestive, but not diagnostic, of *M. catarrhalis* as the cause.

Upon culture, colonies of *M. catarrhalis* resemble commensal neisseriae that are part of the normal upper airway flora. As mentioned earlier, the difficulty in distinguishing colonies of *M. catarrhalis* from neisserial colonies in cultures of respiratory secretions explains in part why *M. catarrhalis* has been overlooked as a pathogen. In contrast to these *Neisseria* species, *M. catarrhalis* colonies can be slid across the agar surface without disruption (the "hockey puck sign"). In addition, after 48 h of growth, *M. catarrhalis* colonies take on a pink color and tend to be larger than neisserial colonies. A variety of biochemical tests can distinguish M. catarrhalis from neisseriae. Kits that rely on these biochemical reactions are commercially available.

TREATMENT ***Moraxella catarrhalis***

M. catarrhalis rapidly acquired β-lactamases during the 1970s and 1980s; antimicrobial susceptibility patterns have remained relatively stable since that time, with >90% of strains now producing β-lactamase and thus resistant to amoxicillin. Otitis media in children and exacerbations of COPD in adults are generally managed empirically with antimicrobial agents that are active against *S. pneumoniae, H. influenzae*, and *M. catarrhalis*. Most strains of *M. catarrhalis* are susceptible to amoxicillin/clavulanic acid, extended-spectrum cephalosporins, newer macrolides (azithromycin, clarithromycin), trimethoprim-sulfamethoxazole, and fluoroquinolones.

CHAPTER 51

INFECTIONS DUE TO THE HACEK GROUP AND MISCELLANEOUS GRAM-NEGATIVE BACTERIA

Tamar F. Barlam ■ Dennis L. Kasper

THE HACEK GROUP

HACEK organisms are a group of fastidious, slow-growing, gram-negative bacteria, the growth of which requires an atmosphere of carbon dioxide. Species belonging to this group include several ***H****aemophilus* species, ***A****ggregatibacter* (formerly ***A****ctinobacillus*) *actinomycetemcomitans*, ***C****ardiobacterium hominis*, ***E****ikenella corrodens*, and ***K****ingella kingae*. HACEK bacteria normally reside in the oral cavity and have been associated with local infections in the mouth. They are also known to cause severe systemic infections—most often bacterial endocarditis, which can develop on either native or prosthetic valves (Chap. 20).

HACEK ENDOCARDITIS

In large series, up to 3% of cases of infective endocarditis are attributable to HACEK organisms, most often *A. actinomycetemcomitans, Haemophilus* species, and *C. hominis*. Invasive infection typically occurs in patients with a history of cardiac valvular disease, often in the setting of a recent dental procedure, nasopharyngeal infection, or tongue piercing or scraping. The aortic and mitral valves are most commonly affected. The clinical course of HACEK endocarditis tends to be subacute; however, embolization is common. The overall prevalence of major emboli associated with HACEK endocarditis ranges from 28% to 71% in different series. On echocardiography, valvular vegetations are seen in up to 85% of patients. The vegetations are frequently large, although vegetation size has not been directly correlated with the risk of embolization. Cultures of blood from patients with suspected HACEK endocarditis may require up to 30 days to become positive, and the microbiology laboratory should be alerted when a HACEK organism is being considered. However, most cultures that ultimately yield a HACEK organism become positive within the first week, especially with improved culture systems such as BACTEC. In addition, polymerase chain reaction techniques (e.g., of cardiac valves) are facilitating the diagnosis of HACEK infections. Because of the organisms' slow growth, antimicrobial testing may be difficult, and β-lactamase production may not be detected. E-test methodology may increase the accuracy of susceptibility testing.

Haemophilus species

Haemophilus species are differentiated by their in vitro growth requirements for X factor (hemin) and V factor (nicotinamide adenine dinucleotide). *H. aphrophilus* requires only X factor for growth, while species designated *para-* require only V factor. *H. aphrophilus* and *H. parainfluenzae* are the *Haemophilus* species most commonly isolated from cases of HACEK endocarditis; *H. paraphrophilus* is less common. Of patients with HACEK endocarditis due to *Haemophilus* species, 60% have been ill for <2 months before presentation, and 19–50% develop congestive heart failure. Mortality rates as high as 30–50% were reported in older series; however, more recent studies have documented mortality rates of <5%. *H. aphrophilus* also causes invasive bone and joint infections, and *H. parainfluenzae* has been isolated from other infections, such as meningitis; brain, dental, and liver abscess; pneumonia; and septicemia.

Aggregatibacter actinomycetemcomitans

A. actinomycetemcomitans can be isolated from soft tissue infections and abscesses in association with *Actinomyces israelii*. Typically, patients who develop endocarditis with *A. actinomycetemcomitans* have severe periodontal disease or have recently undergone dental procedures in the setting of underlying cardiac valvular damage. The disease is insidious; patients may be sick for several months before diagnosis. Frequent complications include embolic phenomena, congestive heart failure, and renal failure. *A. actinomycetemcomitans* has been isolated from patients with brain abscess, meningitis, endophthalmitis,

parotitis, osteomyelitis, urinary tract infection, pneumonia, and empyema, among other infections.

Cardiobacterium hominis

C. hominis primarily causes endocarditis in patients with underlying valvular heart disease or with prosthetic valves. This organism most frequently affects the aortic valve. Many patients have signs and symptoms of long-standing infection before diagnosis, with evidence of arterial embolization, vasculitis, cerebrovascular accidents, immune complex glomerulonephritis, or arthritis at presentation. Embolization, mycotic aneurysms, and congestive heart failure are common complications. A second species, *C. valvarum*, has now been described in association with endocarditis.

Eikenella corrodens

E. corrodens is most frequently recovered from sites of infection in conjunction with other bacterial species. Clinical sources of *E. corrodens* include sites of human bite wounds (clenched-fist injuries), endocarditis, soft tissue infections, osteomyelitis, head and neck infections, respiratory infections, chorioamnionitis, gynecologic infections associated with intrauterine devices, meningitis and brain abscesses, and visceral abscesses.

Kingella kingae

Because of improved microbiologic methodology, isolation of *K. kingae* is increasingly common. Inoculation of clinical specimens (e.g., synovial fluid) into aerobic blood culture bottles enhances recovery of this organism. Specific real-time PCR studies of joint fluid can identify *K. kingae* in culture-negative cases. Invasive *K. kingae* infections with bacteremia are associated with upper respiratory tract infections and stomatitis in 80% of cases. Rates of oropharyngeal colonization with *K. kingae* are highest in the first 3 years of life, coinciding with increased incidence of skeletal infections due to this organism. *K. kingae* bacteremia can present with a petechial rash similar to that seen in *Neisseria meningitidis* sepsis.

Infective endocarditis, unlike other infections with *K. kingae*, occurs in older children and adults. The majority of patients have preexisting valvular disease. There is a high incidence of complications, including arterial emboli, cerebrovascular accidents, tricuspid insufficiency, and congestive heart failure with cardiovascular collapse.

TREATMENT **Endocarditis Caused by HACEK Organisms**

See Table 51-1. Native-valve endocarditis should be treated for 4 weeks with antibiotics, whereas prosthetic-valve endocarditis requires 6 weeks of therapy. The cure rates for HACEK prosthetic-valve endocarditis appear to be high. Unlike prosthetic-valve endocarditis caused by other gram-negative organisms, HACEK endocarditis is often cured with antibiotic treatment alone—i.e., without surgical intervention.

TABLE 51-1

TREATMENT OF ENDOCARDITIS CAUSED BY HACEK GROUP ORGANISMS[a]

ORGANISM	INITIAL THERAPY	ALTERNATIVE AGENTS	COMMENTS
Haemophilus species, *Aggregatibacter actinomycetemcomitans*	Ceftriaxone (2 g/d)	Ampicillin/sulbactam (3 g of ampicillin q6h) **or** fluoroquinolones[b]	Ampicillin ± an aminoglycoside can be used if the organism does not produce β-lactamase.[c]
Cardiobacterium hominis	Ceftriaxone (2 g/d)	Ampicillin/sulbactam (3 g of ampicillin q6h)	Penicillin (16–18 mU q4h) or ampicillin (2 g q4h) should be used if the organism is susceptible.
Eikenella corrodens	Ampicillin (2 g q4h)	Ceftriaxone (2 g/d) **or** fluoroquinolones[b]	The organism is typically resistant to clindamycin, metronidazole, and aminoglycosides.
Kingella kingae	Ceftriaxone (2 g/d) **or** ampicillin/sulbactam (3 g of ampicillin q6h)	Fluoroquinolones[b]	The prevalence of β-lactamase-producing strains is increasing. Efficacy for invasive infections is best demonstrated for first-line treatments.

[a]Susceptibility testing should be performed in all cases to guide therapy. See text for recommended durations of treatment.
[b]Fluoroquinolones are not recommended for treatment of children <18 years of age.
[c]European guidelines for endocarditis recommend the addition of gentamicin (3 mg/kg per day in 3 divided doses for 2–4 weeks).

OTHER GRAM-NEGATIVE BACTERIA

Achromobacter xylosoxidans

Achromobacter (previously *Alcaligenes*) *xylosoxidans* is probably part of the endogenous intestinal flora and has been isolated from a variety of water sources, including well water, IV fluids, and humidifiers. Immunocompromised hosts, including patients with cancer and postchemotherapy neutropenia, cirrhosis, chronic renal failure, and cystic fibrosis, are at increased risk. Nosocomial outbreaks and pseudo-outbreaks of *A. xylosoxidans* infection have been attributed to contaminated fluids, and clinical illness has been associated with isolates from many sites, including blood (often in the setting of intravascular devices). Community-acquired *A. xylosoxidans* bacteremia usually occurs in the setting of pneumonia. Metastatic skin lesions are present in one-fifth of cases. The reported mortality rate is 67%—a figure similar to rates for other bacteremic gram-negative pneumonias.

TREATMENT ***Achromobacter xylosoxidans* Infections**

Treatment is based on in vitro susceptibility testing of all clinically relevant isolates. Imipenem, piperacillin-tazobactam, and trimethoprim-sulfamethoxazole (TMP-SMX) are typically the most active agents, but multidrug-resistant isolates sensitive only to colistin have been reported.

Aeromonas species

More than 85% of *Aeromonas* infections are caused by *A. hydrophila*, *A. caviae*, and *A. veronii* biovar *sobria*. *Aeromonas* proliferates in potable water, freshwater, and soil. It remains controversial whether *Aeromonas* is a cause of bacterial gastroenteritis; asymptomatic colonization of the intestinal tract with *Aeromonas* occurs frequently. However, rare cases of hemolytic-uremic syndrome following bloody diarrhea have been shown to be secondary to the presence of *Aeromonas*.

Aeromonas causes sepsis and bacteremia in infants with multiple medical problems and in immunocompromised hosts, particularly those with cancer or hepatobiliary disease. *Aeromonas* infection and sepsis can occur in patients with trauma (including severe trauma with myonecrosis) and in burn patients exposed to *Aeromonas* by environmental (freshwater or soil) contamination of their wounds. Reported mortality rates range from 25% among immunocompromised adults with sepsis to >90% among patients with myonecrosis. *Aeromonas* can produce ecthyma gangrenosum (hemorrhagic vesicles surrounded by a rim of erythema with central necrosis and ulceration; see Fig. 11-35) resembling the lesions seen in *Pseudomonas aeruginosa* infection. *Aeromonas* causes nosocomial infections related to catheters, surgical incisions, or use of leeches. Other manifestations include necrotizing fasciitis, meningitis, peritonitis, pneumonia, and ocular infections.

TREATMENT ***Aeromonas* Infections**

Aeromonas species are generally susceptible to fluoroquinolones (e.g., ciprofloxacin at a dosage of 500 mg every 12 h PO or 400 mg every 12 h IV), third-generation cephalosporins, carbapenems, and aminoglycosides. Because *Aeromonas* can produce various β-lactamases, including carbapenemases, susceptibility testing must be used to guide therapy. Antibiotic prophylaxis (e.g., with ciprofloxacin) is indicated when medicinal leeches are used.

Capnocytophaga species

This genus of fastidious, fusiform, gram-negative coccobacilli is facultatively anaerobic and requires an atmosphere enriched in carbon dioxide for optimal growth. *C. ochracea*, *C. gingivalis*, *C. haemolytica*, and *C. sputigena* have been associated with sepsis in immunocompromised hosts, particularly neutropenic patients with oral ulcerations. These species have been isolated from many other sites as well, usually as part of a polymicrobial infection. Most *Capnocytophaga* infections are contiguous with the oropharynx (e.g., periodontal disease, respiratory tract infections, cervical abscesses, and endophthalmitis).

C. canimorsus and *C. cynodegmi* are endogenous to the canine mouth (Chap. 35). Patients infected with these species frequently have a history of dog bites or of exposure to dogs without scratches or bites. Asplenia, glucocorticoid therapy, and alcohol abuse are predisposing conditions that can be associated with severe sepsis with shock and disseminated intravascular coagulation. Patients typically have a petechial rash that can progress from purpuric lesions to gangrene. Meningitis, endocarditis, cellulitis, osteomyelitis, and septic arthritis have also been associated with these organisms.

TREATMENT ***Capnocytophaga* Infections**

Because of increasing β-lactamase production, a penicillin derivative plus a β-lactamase inhibitor—such as ampicillin/sulbactam (1.5–3.0 g of ampicillin every 6 h)—is currently recommended for empirical treatment of infections caused by *Capnocytophaga* species. If the isolate is known to be susceptible, infections with *C. canimorsus* should be treated with penicillin (12–18 million units every 4 h). *Capnocytophaga* is also susceptible to clindamycin (600–900 mg every 6–8 h). This regimen or ampicillin/sulbactam should be given prophylactically to asplenic patients who have sustained dog-bite injuries.

Chryseobacterium species

Chryseobacterium (formerly *Flavobacterium*) *meningosepticum* is an important cause of nosocomial infections, including

outbreaks due to contaminated fluids (e.g., disinfectants and aerosolized antibiotics) and sporadic infections due to indwelling devices, feeding tubes, and other fluid-associated apparatuses. Nosocomial *C. meningosepticum* infection usually involves neonates or patients with underlying immunosuppression (e.g., related to malignancy). *C. meningosepticum* has been reported to cause meningitis (primarily in neonates), pneumonia, sepsis, endocarditis, bacteremia, and soft tissue infections. *C. indologenes* has caused bacteremia, sepsis, and pneumonia, typically in immunocompromised patients with indwelling devices.

TREATMENT ***Chryseobacterium*** **Infections**

Chryseobacteria are often susceptible to fluoroquinolones and TMP-SMX. They may be susceptible to β-lactam/β-lactamase inhibitor agents such as piperacillin-tazobactam but can possess extended-spectrum β-lactamases and metallo-β-lactamases. Susceptibility testing should be performed.

Pasteurella multocida

P. multocida is a bipolar-staining, gram-negative coccobacillus that colonizes the respiratory and gastrointestinal tracts of domestic animals; oropharyngeal colonization rates are 70–90% in cats and 50–65% in dogs. *P. multocida* can be transmitted to humans through bites or scratches, via the respiratory tract from contact with contaminated dust or infectious droplets, or via deposition of the organism on injured skin or mucosal surfaces during licking. Most human infections affect skin and soft tissue; almost two-thirds of these infections are caused by cats. Patients at the extremes of age or with serious underlying disorders (e.g., cirrhosis, diabetes) are at increased risk for systemic manifestations, including meningitis, peritonitis, osteomyelitis and septic arthritis, endocarditis, and septic shock, but cases have also occurred in healthy individuals. If inhaled, *P. multocida* can cause acute respiratory tract infection, particularly in patients with underlying sinus and pulmonary disease.

TREATMENT ***Pasteurella multocida*** **Infections**

P. multocida is susceptible to penicillin, ampicillin, ampicillin/sulbactam, second- and third-generation cephalosporins, tetracyclines, and fluoroquinolones. β-Lactamase-producing strains have been reported.

MISCELLANEOUS ORGANISMS

Rhizobium (formerly *Agrobacterium) radiobacter* has usually been associated with infection in the presence of medical devices, including intravascular catheter–related infections, prosthetic-joint and prosthetic-valve infections, and peritonitis caused by dialysis catheters. Most cases occur in immunocompromised hosts, especially individuals with malignancy or HIV infection. Strains are usually susceptible to fluoroquinolones, third- and fourth-generation cephalosporins, and carbapenems.

Shewanella putrefaciens and *S. algae* are ubiquitous organisms found primarily in seawater. Devitalized tissues can become colonized with *Shewanella* and serve as a nidus for systemic infection. *Shewanella* species cause skin and soft tissue infections, chronic ulcers of the lower extremities, ear infections, biliary tract infections, pneumonia, necrotizing fasciitis, bacteremia, and sepsis. A fulminant course is associated with cirrhosis, malignancy, or other severe underlying conditions. Organisms are often susceptible to fluoroquinolones, third- and fourth-generation cephalosporins, and aminoglycosides.

Chromobacterium violaceum has been responsible for life-threatening infections with severe sepsis and metastatic abscesses, particularly in children with defective neutrophil function (e.g., those with chronic granulomatous disease). *Ochrobactrum anthropi* causes infections related to central venous catheters in compromised hosts; other invasive infections have been described. Other organisms implicated in human infections include *Weeksella* species; various CDC groups, such as EF4 and Ve-2; *Flavimonas* species; *Sphingobacterium* species; *Protomonas* species; and *Oligella urethralis*. The reader is advised to consult subspecialty texts and references for further guidance on these organisms.

CHAPTER 52

LEGIONELLA INFECTIONS

Miguel Sabria ■ Victor L. Yu

Legionellosis refers to the two clinical syndromes caused by bacteria of the genus *Legionella*. *Pontiac fever* is an acute, febrile, self-limited illness that has been serologically linked to *Legionella* species, whereas *Legionnaires' disease* is the designation for pneumonia caused by these species. Legionnaires' disease was first recognized in 1976, when an outbreak of pneumonia took place at a Philadelphia hotel during an American Legion convention.

MICROBIOLOGY

The family Legionellaceae comprises more than 50 species with more than 70 serogroups. The species *L. pneumophila* causes 80–90% of human infections and includes at least 16 serogroups; serogroups 1, 4, and 6 are most commonly implicated in human infections. To date, 18 species other than *L. pneumophila* have been associated with human infections, among which *L. micdadei* (Pittsburgh pneumonia agent), *L. bozemanii*, *L. dumoffii*, and *L. longbeachae* are the most common. Members of the Legionellaceae are aerobic gram-negative bacilli that do not grow on routine microbiologic media. Buffered charcoal yeast extract (BCYE) agar is the medium used to grow *Legionella*.

ECOLOGY AND TRANSMISSION

The natural habitats for *L. pneumophila* are aquatic bodies, including lakes and streams. *L. longbeachae* has been isolated from natural soil and commercial potting soil. Legionellae can survive under a wide range of environmental conditions; for example, the organisms can live for years in refrigerated water samples. Natural bodies of water contain only small numbers of legionellae. However, once the organisms enter human-constructed aquatic reservoirs (such as drinking-water systems), they can grow and proliferate. Factors known to enhance colonization by and amplification of legionellae include warm temperatures (25°–42°C) and scale and sediment. *L. pneumophila* can form microcolonies within biofilms; its eradication from drinking-water systems requires disinfectants that can penetrate the biofilm. The presence of symbiotic microorganisms, including algae, amebas, ciliated protozoa, and other water-dwelling bacteria, promotes the growth of legionellae. The organisms can invade and multiply within free-living protozoa. Rainfall and humidity have been identified as environmental risk factors.

Sporadic community-acquired Legionnaires' disease has been linked to colonization of residential, hotel, and industrial water supplies. Drinking-water systems in hospitals and extended-care facilities have been linked to health care–associated Legionnaires' disease.

Cooling towers and evaporative condensers have been overestimated as sources of *Legionella*. Early investigations that implicated cooling towers antedated the discovery that the organism could also exist in drinking water. In many outbreaks attributed to cooling towers, cases of Legionnaires' disease continued to occur despite disinfection of the cooling towers; drinking water was the actual source. Koch's postulates have never been fulfilled for cooling tower–associated outbreaks as they have been for hospital-acquired Legionnaires' disease. Nevertheless, cooling towers have occasionally been identified in community-acquired outbreaks, including an outbreak in Murcia, Spain, in which several hundred suspected cases of Legionnaires' disease occurred over a 3-week period. As mentioned above, *L. longbeachae* infections have been linked to potting soil, but the mode of transmission remains to be clarified.

Multiple modes of transmission of *Legionella* to humans exist, including aerosolization, aspiration, and direct instillation into the lungs during respiratory tract manipulations. Aspiration is now known to be the predominant mode of transmission, but it is unclear whether *Legionella* enters the lungs via oropharyngeal colonization or directly via the drinking of contaminated water. Oropharyngeal colonization has been demonstrated in patients undergoing transplantation. Nasogastric tubes have been linked to hospital-acquired Legionnaires' disease; microaspiration of contaminated water was the hypothesized mode of transmission. Surgery with general anesthesia is a known risk factor that is consistent with aspiration. Especially compelling is the

reported 30% incidence of postoperative Legionnaires' disease among patients undergoing head and neck surgery at a hospital with a contaminated water supply; aspiration is a recognized sequela in such cases. Studies of patients with hospital-acquired Legionnaires' disease have shown that these individuals underwent endotracheal intubation significantly more often and for a significantly longer duration than patients with hospital-acquired pneumonia of other etiologies.

Aerosolization of *Legionella* by devices filled with tap water, including whirlpools, nebulizers, and humidifiers, has been implicated. An ultrasonic mist machine in the produce section of a grocery store was the source in a community outbreak. Pontiac fever has been linked to *Legionella*-containing aerosols from water-using machinery, a cooling tower, air-conditioners, and whirlpools.

EPIDEMIOLOGY

The incidence of Legionnaires' disease depends on the degree of contamination of the aquatic reservoir, the immune status of the persons exposed to water from that reservoir, the intensity of exposure, and the availability of specialized laboratory tests on which the correct diagnosis can be based. Numerous prospective studies have ranked *Legionella* among the top four microbial causes of community-acquired pneumonia, accounting for 2–9% of cases. (*Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Chlamydia pneumoniae* are usually ranked first, second, and third, respectively.) On the basis of a multihospital study of community-acquired pneumonia in Ohio, the Centers for Disease Control and Prevention (CDC) estimated that as many as 18,000 cases of sporadic community-acquired Legionnaires' disease occur annually in the United States and that only 3% of these cases are correctly diagnosed. *Legionella* is responsible for 10–50% of cases of nosocomial pneumonia when a hospital's water system is colonized with the organisms. The incidence of hospital-acquired Legionnaires' disease depends on the degree of contamination of drinking water as defined by the rate of positivity of distal water sites (not as defined quantitatively by the number of colony-forming units per milliliter).

Risk factors for Legionnaires' disease include cigarette smoking; chronic lung disease; advanced age; prior hospitalization, with discharge within 10 days before onset of pneumonia symptoms; and immunosuppression. Immunosuppressive conditions that predispose to Legionnaires' disease include transplantation, HIV infection, and treatment with glucocorticoids or tumor necrosis factor α antagonists. However, in a large prospective study of community-acquired pneumonia, 28% of patients with Legionnaires' disease did not have these classic risk factors. Surgery is a prominent predisposing factor in hospital-acquired infection, with transplant recipients at highest risk. Hospital-acquired cases are now being recognized among neonates and immunosuppressed children.

Pontiac fever occurs in epidemics. The high attack rate (>90%) reflects airborne transmission.

PATHOGENESIS AND IMMUNITY

Legionella enters the lungs through aspiration or direct inhalation. Attachment to host cells is mediated by bacterial type IV pili, heat-shock proteins, a major outer-membrane protein, and complement. Because the organism possesses pili that mediate adherence to respiratory tract epithelial cells, conditions that impair mucociliary clearance, including cigarette smoking, lung disease, or alcoholism, predispose to Legionnaires' disease.

Both the innate and adaptive immune responses play a role in host defense. Toll-like receptors mediate recognition of *L. pneumophila* in alveolar macrophages and enhance early neutrophil recruitment to the site of infection. Alveolar macrophages phagocytose legionellae by a conventional or a coiling mechanism. The macrophage infectivity potentiation (MIP) surface protein enhances infection of the macrophages. After phagocytosis, *L. pneumophila* evades intracellular killing by inhibiting phagosome-lysosome fusion. Although many legionellae are killed, some proliferate intracellularly until the cells rupture; the bacteria are then phagocytosed again by newly recruited phagocytes, and the cycle begins anew. The role of neutrophils in immunity appears to be minimal: neutropenic patients are not predisposed to Legionnaires' disease. Although *L. pneumophila* is susceptible to oxygen-dependent microbiologic systems in vitro, it resists killing by neutrophils. The humoral immune system is active against *Legionella*. Type-specific IgM and IgG antibodies are measurable within weeks of infection. In vitro, antibodies promote killing of *Legionella* by phagocytes (neutrophils, monocytes, and alveolar macrophages). Immunized animals develop a specific antibody response, with subsequent resistance to *Legionella* challenge. However, antibodies neither enhance lysis by complement nor inhibit intracellular multiplication within phagocytes.

Some *L. pneumophila* strains are clearly more virulent than others, although the precise factors mediating virulence remain uncertain. For example, although multiple strains may colonize water-distribution systems, only a few cause disease in patients exposed to water from these systems. At least one surface epitope of *L. pneumophila* serogroup 1 is associated with virulence. Monoclonal antibody subtype mAb2 has been linked to virulence. *L. pneumophila* serogroup 6 is more commonly involved in hospital-acquired Legionnaires' disease and is more likely to be associated with a poor outcome.

The genome of *L. pneumophila* has been sequenced. A broad range of membrane transporters within the genome are thought to optimize the use of nutrients in water and soil.

CLINICAL AND LABORATORY FEATURES

Pontiac fever

Pontiac fever is an acute, self-limiting, flu-like illness with an incubation period of 24–48 h. Pneumonia does not develop. Malaise, fatigue, and myalgias are the most

common symptoms, occurring in 97% of cases. Fever (usually with chills) develops in 80–90% of cases and headache in 80%. Other symptoms (seen in <50% of cases) include arthralgias, nausea, cough, abdominal pain, and diarrhea. Modest leukocytosis with a neutrophilic predominance is sometimes detected. Complete recovery occurs within a few days; antibiotic therapy is unnecessary. A few patients may experience lassitude for many weeks after recovery. The diagnosis is established by antibody seroconversion.

Legionnaires' disease (pneumonia)

Legionnaires' disease is often included in the differential diagnosis of "atypical pneumonia," along with pneumonia due to *C. pneumoniae*, *Chlamydophila psittaci*, *Mycoplasma pneumoniae*, *Coxiella burnetii*, and some viruses. The clinical similarities among these types of pneumonia include a relatively nonproductive cough and a low incidence of grossly purulent sputum. However, the clinical manifestations of Legionnaires' disease are usually more severe than those of most "atypical" pneumonias, and the course and prognosis of *Legionella* pneumonia more closely resemble those of bacteremic pneumococcal pneumonia than those of pneumonia due to other "atypical" pathogens. Patients with community-acquired Legionnaires' disease are significantly more likely than patients with pneumonia of other etiologies to be admitted to an intensive care unit on presentation.

The incubation period for Legionnaires' disease is usually 2–10 days, although longer incubation periods have been documented. The symptoms and signs may range from a mild cough and a slight fever to stupor with widespread pulmonary infiltrates and multisystem failure. Nonspecific symptoms—malaise, fatigue, anorexia, and headache—are seen early in the illness. Myalgias and arthralgias are uncommon but are prominent in a few patients. Upper respiratory symptoms, including coryza, are rare.

The mild cough of Legionnaires' disease is only slightly productive. Sometimes the sputum is streaked with blood. Chest pain—either pleuritic or nonpleuritic—can be a prominent feature and, when coupled with hemoptysis, can lead to an incorrect diagnosis of pulmonary embolism. Shortness of breath is reported by one-third to one-half of patients. Gastrointestinal difficulties are often pronounced; abdominal pain, nausea, and vomiting affect 10–20% of patients. Diarrhea (watery rather than bloody) is reported in 25–50% of cases. The most common neurologic abnormalities are confusion or changes in mental status; however, the multitudinous neurologic symptoms reported range from headache and lethargy to encephalopathy.

Patients with Legionnaires' disease virtually always have fever. Temperatures in excess of 40.5°C (104.9°F) were recorded in 20% of the cases in one series. Relative bradycardia has been overemphasized as a useful diagnostic finding; it occurs primarily in older patients with severe pneumonia. Chest examination reveals rales early in the course and evidence of consolidations as the disease progresses. Abdominal examination may reveal generalized or local tenderness.

Although the clinical manifestations often considered classic for Legionnaires' disease **(Table 52-1)** may suggest the diagnosis, prospective comparative studies have shown that clinical manifestations are generally nonspecific and that Legionnaires' disease is not readily distinguishable from pneumonia of other etiologies. In a review of 13 studies of community-acquired pneumonia, clinical manifestations that occurred significantly more often in Legionnaires' disease included diarrhea, neurologic findings (including confusion), and a temperature of >39°C. Hyponatremia, elevated values in liver function tests, and hematuria also occurred more frequently in Legionnaires' disease. Other laboratory abnormalities include creatine phosphokinase elevation, hypophosphatemia, serum creatinine elevation, and proteinuria.

Sporadic cases of Legionnaires' disease appear to be more severe than outbreak-associated and hospital-acquired cases, presumably because their diagnosis is delayed. Results of the German CAPNETZ Study showed that, among cases of community-acquired *Legionella* pneumonia, ambulatory cases were as common as cases requiring hospitalization.

Extrapulmonary legionellosis

Since the portal of entry for *Legionella* is the lung in virtually all cases, extrapulmonary manifestations usually result from bloodborne dissemination from the lung. *Legionella* has been identified in lymph nodes, spleen, liver, or kidneys in autopsied cases. The most common extrapulmonary site of legionellosis is the heart; numerous reports have described myocarditis, pericarditis, postcardiotomy syndrome, and prosthetic-valve endocarditis. Most cases have been hospital-acquired. In some patients without overt evidence of pneumonia, the organisms may gain entry through a postoperative sternal wound exposed to contaminated tap water or through a mediastinal-tube insertion site. Sinusitis, peritonitis, pyelonephritis, skin and soft tissue infection, septic arthritis, and pancreatitis have been seen predominantly in immunosuppressed patients.

TABLE 52-1

CLINICAL CLUES SUGGESTIVE OF LEGIONNAIRES' DISEASE

Diarrhea
High fever (>40°C; >104°F)
Numerous neutrophils, but no organisms revealed by Gram's staining of respiratory secretions
Hyponatremia (serum sodium level <131 mg/dL)
Failure to respond to β-lactam drugs (penicillins or cephalosporins) and aminoglycoside antibiotics
Occurrence of illness in an environment in which the potable water supply is known to be contaminated with *Legionella*
Onset of symptoms within 10 days after discharge from the hospital

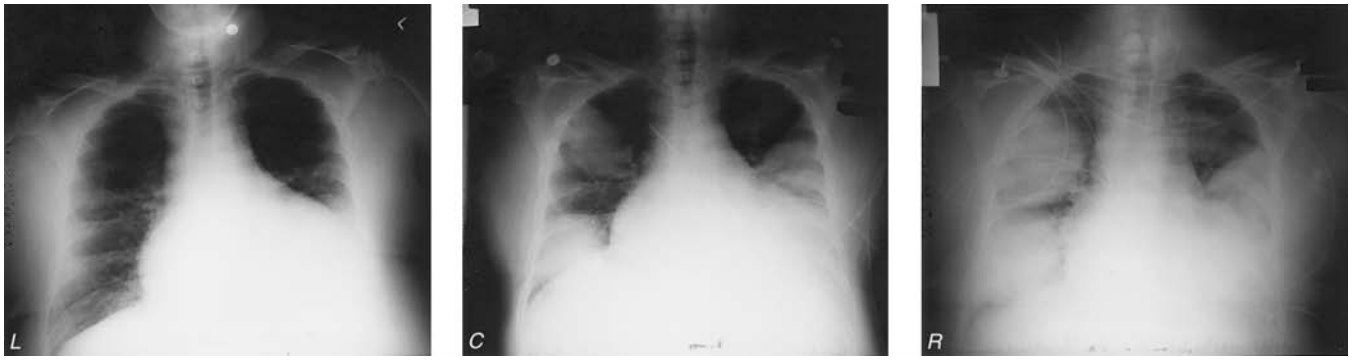


FIGURE 52-1
Chest radiographic findings in a 52-year-old man who presented with pneumonia subsequently diagnosed as Legionnaires' disease. The patient was a cigarette smoker with chronic obstructive pulmonary disease and alcoholic cardiomyopathy; he had received glucocorticoids. *L. pneumophila* was identified by direct fluorescent antibody staining and culture of sputum. ***Left:*** Baseline chest radiograph showing long-standing cardiomegaly. ***Center:*** Admission chest radiograph showing new rounded opacities. ***Right:*** Chest radiograph taken 3 days after admission, during treatment with erythromycin.

Chest radiography

Virtually all patients with Legionnaires' disease have abnormal chest radiographs showing pulmonary infiltrates at the time of clinical presentation. In a few cases of hospital-acquired disease, fever and respiratory tract symptoms have preceded the radiographic appearance of the infiltrate. Radiologic findings are nonspecific. Pleural effusion is evident in 28–63% of patients on hospital admission. In immunosuppressed patients, especially those receiving glucocorticoids, distinctive rounded nodular opacities may be seen; these lesions may expand and cavitate **(Fig. 52-1)**. Likewise, abscesses can occur in immunosuppressed hosts. The progression of infiltrates and pleural effusion on chest radiography despite appropriate antibiotic therapy within the first week is common, and radiographic improvement lags behind clinical improvement by several days. Complete clearing of infiltrates requires 1–4 months.

DIAGNOSIS

Given the nonspecific clinical manifestations of Legionnaires' disease and the high mortality rates for untreated Legionnaires' disease, the use of *Legionella* testing—especially the *Legionella* urinary antigen test—is recommended for all patients with community-acquired pneumonia, including patients with ambulatory pneumonia and hospitalized children. *Legionella* cultures should be made more widely available since the urinary antigen test can diagnose only *L. pneumophila* serogroup 1. Hospitals in which the drinking water is known to be colonized with *Legionella* species should have *Legionella* cultures routinely available for all patients with hospital-acquired pneumonia.

The diagnosis of Legionnaires' disease requires special microbiologic tests **(Table 52-2)**. The sensitivity of bronchoscopy specimens is similar to that of sputum samples for culture on selective media; if sputum is not available, bronchoscopy specimens may yield the organism. Bronchoalveolar lavage fluid gives higher yields than bronchial wash specimens. Thoracentesis should be performed if pleural effusion is found, and the fluid should be evaluated by direct fluorescent antibody (DFA) staining, culture, and the antigen assay designed for use with urine.

Staining

Gram's staining of material from normally sterile sites, such as pleural fluid or lung tissue, occasionally suggests the diagnosis; efforts to detect *Legionella* in sputum by Gram's staining typically reveal numerous leukocytes but no organisms. When they are visualized, the organisms appear as small, pleomorphic, faint, gram-negative bacilli. *L. micdadei* organisms can be detected as weakly or partially acid-fast bacilli in clinical specimens.

TABLE 52-2
UTILITY OF SPECIAL LABORATORY TESTS FOR THE DIAGNOSIS OF LEGIONNAIRES' DISEASE

TEST	SENSITIVITY, %	SPECIFICITY, %
Culture		
Sputum[a]	80	100
Transtracheal aspirate	90	100
Direct fluorescent antibody staining of sputum	50–70	96–99
Urinary antigen testing[b]	70	100
Antibody serology[c]	40–60	96–99

[a]Use of multiple selective media with dyes.
[b]Serogroup 1 only.
[c]IgG and IgM testing of both acute- and convalescent-phase sera. A single titer of ≥1:256 is considered presumptive, while fourfold seroconversion is considered definitive.

The DFA test is rapid and highly specific but is less sensitive than culture because large numbers of organisms are required for microscopic visualization. This test is more likely to be positive in advanced than in early disease.

Culture

The definitive method for diagnosis of *Legionella* infection is isolation of the organism from respiratory secretions, although culture for 3–5 days is required. Antibiotics added to the medium suppress the growth of competing flora from nonsterile sites, and dyes color the colonies and assist in identification. The use of multiple selective BCYE media is necessary for maximal sensitivity. When culture plates are overgrown with other microflora, pretreatment of the specimen with acid or heat can markedly improve the yield. *L. pneumophila* is often isolated from sputum that is not grossly or microscopically purulent; sputum containing more than 25 epithelial cells per high-power field (a finding that classically suggests contamination) may still yield *L. pneumophila*.

Antibody detection

Antibody testing of both acute- and convalescent-phase sera is necessary. A fourfold rise in titer is diagnostic; 12 weeks are often required for the detection of an antibody response. A single titer of 1:128 in a patient with pneumonia constitutes circumstantial evidence for Legionnaires' disease. Serology is of use primarily in epidemiologic studies. The specificity of serology for *Legionella* species other than *L. pneumophila* is uncertain; there is cross-reactivity with *Legionella* species and some gram-negative bacilli.

Urinary antigen

The assay for *Legionella* soluble antigen in urine is rapid, relatively inexpensive, easy to perform, second only to culture in terms of sensitivity, and highly specific. Several enzyme immunoassays and a rapid immunochromatographic assay are commercially available. The rapid immunochromatographic assay is relatively inexpensive and easy to perform. The urinary antigen test is available only for *L. pneumophila* serogroup 1, which causes ~80% of *Legionella* infections. Cross-reactivity with other *L. pneumophila* serogroups and other *Legionella* species has been detected in up to 22% of urine samples from patients with culture-proven cases. Antigen in urine is detectable 3 days after the onset of clinical disease and disappears over 2 months; positivity can be prolonged when patients receive glucocorticoids. The test is not affected by antibiotic administration.

Molecular methods

DFA stains can identify a number of *Legionella* species. Both polyclonal and monoclonal antibody stains are commercially available. Although its application is currently limited to research investigations, polymerase chain reaction (PCR) with DNA probes is theoretically more sensitive and specific than other methods. A molecular probe is undergoing evaluation. PCR has proven somewhat useful in the identification of *Legionella* from environmental water specimens. In PCR (unlike culture), epidemiologic links cannot be made since the infecting pathogen is not available for molecular subtyping.

TREATMENT *Legionella* Infection

Because *Legionella* is an intracellular pathogen, antibiotics that can attain high intracellular concentrations are most likely to be effective. The dosages for various drugs used in the treatment of *Legionella* infection are listed in Table 52-3.

The macrolides (especially azithromycin) and the respiratory quinolones are now the antibiotics of choice and are effective as monotherapy. Compared with erythromycin, the newer macrolides have superior in vitro activity, display greater intracellular activity, reach higher concentrations in respiratory secretions and lung tissue, and have fewer adverse effects. The pharmacokinetics

TABLE 52-3

ANTIBIOTIC THERAPY FOR *LEGIONELLA* INFECTION

ANTIMICROBIAL AGENT	DOSAGE[a]
Macrolides	
Azithromycin	500 mg[b] PO or IV[c] q24h
Clarithromycin	500 mg PO or IV[c] q12h
Quinolones	
Levofloxacin	750 mg IV q24h 500 mg[b] PO q24h
Ciprofloxacin	400 mg IV q8h 750 mg PO q12h
Moxifloxacin	400 mg[b] PO q24h
Ketolide	
Telithromycin	800 mg PO q24h
Tetracyclines	
Doxycycline	100 mg[b] PO or IV q12h
Minocycline	100 mg[b] PO or IV q12h
Tetracycline	500 mg PO or IV q6h
Tigecycline	100-mg IV load, then 50 mg IV q12h
Others	
Trimethoprim-sulfamethoxazole	160/800 mg IV q8h
Rifampin[d]	160/800 mg PO q12h 300–600 mg PO or IV q12h

[a]Dosages are derived from clinical experience.
[b]The authors recommend doubling the first dose.
[c]The IV formulation is not available in some countries.
[d]Rifampin should be used only in combination with a macrolide or a quinolone.

of the newer macrolides and quinolones also allow once- or twice-daily dosing. Quinolones are the preferred antibiotics for transplant recipients because both macrolides and rifampin interact pharmacologically with cyclosporine and tacrolimus. Retrospective uncontrolled studies have shown that complications of pneumonia are fewer and clinical response is more rapid in patients receiving quinolones than in those receiving macrolides. Alternative agents include tetracycline and its analogues doxycycline and minocycline. Tigecycline is active in vitro but clinical experience is minimal. Anecdotal reports have described both successes and failures with trimethoprim-sulfamethoxazole, imipenem, and clindamycin. For severely ill patients with extensive pulmonary infiltrates, a two-drug combination of a newer macrolide or a quinolone with rifampin may be considered for initial treatment. Rifampin is highly active in vitro and in cell models, but its interaction with many other medications, including macrolides, is problematic. Initial therapy should be given by the IV route. A clinical response usually occurs within 3–5 days, after which oral therapy can be substituted. The total duration of therapy in the immunocompetent host is 10–14 days; a longer course (3 weeks) may be appropriate for immunosuppressed patients and those with advanced disease. For azithromycin, with its long half-life, a 5- to 10-day course is sufficient.

Pontiac fever requires only symptom-based treatment, not antimicrobial therapy.

PROGNOSIS

Mortality rates for Legionnaires' disease vary with the patient's underlying disease and its severity, the patient's immune status, the severity of pneumonia, and the timing of administration of appropriate antimicrobial therapy. Mortality rates are highest (80%) among immunosuppressed patients who do not receive appropriate antimicrobial therapy early in the course of illness. With appropriate and timely antibiotic treatment, mortality rates from community-acquired Legionnaires' disease among immunocompetent patients range from 0% to 11%; without treatment, the figure may be as high as 31%. In a study of survivors of an outbreak of community-acquired Legionnaires' disease, sequelae of fatigue, neurologic symptoms, and weakness were found in 63–75% of patients 17 months after receipt of antibiotics.

PREVENTION

Routine environmental culture of hospital water supplies is recommended as an approach to the prevention of hospital-acquired Legionnaires' sease. Guidelines mandating this proactive approach have been adopted throughout Europe and in several U.S. states. Positive cultures from the water supply mandate the use of specialized laboratory tests (especially culture on selective media and the urinary antigen test) for patients with hospital-acquired pneumonia. Studies have shown that neither a high degree of outward cleanliness of the water system nor routine application of maintenance measures decreases the frequency or intensity of *Legionella* contamination. Thus, engineering guidelines and building codes, although routinely advocated as preventive measures, have little impact on the presence of *Legionella*.

Disinfection of the drinking water supply is effective. Two methods have proved reliable and cost-effective. The superheat-and-flush method requires heating of the water so that the distal-outlet temperature is 70–80°C and flushing of the distal outlets with hot water for at least 30 min. This method is ideal for emergency situations. Commercial copper and silver ionization systems have proven effective in numerous hospitals. Chlorine dioxide is a promising modality. Tap water filters have been effective for high-risk patient areas, such as transplantation or intensive care units. Hyperchlorination is no longer recommended because of its expense, carcinogenicity, corrosive effects on piping, and unreliable efficacy.

CHAPTER 53

PERTUSSIS AND OTHER *BORDETELLA* INFECTIONS

Scott A. Halperin

Pertussis is an acute infection of the respiratory tract caused by *Bordetella pertussis*. The name *pertussis* means "violent cough," which aptly describes the most consistent and prominent feature of the illness. The inspiratory sound made at the end of an episode of paroxysmal coughing gives rise to the common name for the illness, "whooping cough." However, this feature is variable: it is uncommon among infants ≥6 months of age and is frequently absent in older children and adults. The Chinese name for pertussis is "the 100-day cough," which accurately describes the clinical course of the illness. The identification of *B. pertussis* was first reported by Bordet and Gengou in 1906, and vaccines were produced over the following two decades.

MICROBIOLOGY

Of the 10 identified species in the genus *Bordetella*, only three are of major medical significance. *B. pertussis* infects only humans and is the most important *Bordetella* species causing human disease. *B. parapertussis* causes an illness in humans that is similar to pertussis but is typically milder; co-infections with *B. parapertussis* and *B. pertussis* have been documented. *B. bronchiseptica* is an important pathogen of domestic animals that causes kennel cough in dogs, atrophic rhinitis and pneumonia in pigs, and pneumonia in cats. Both respiratory infection and opportunistic infection due to *B. bronchiseptica* are occasionally reported in humans. Two additional species, *B. hinzii* and *B. holmesii*, are unusual causes of bacteremia; both have been isolated from patients with sepsis, most often from those who are immunocompromised.

Bordetella species are gram-negative pleomorphic aerobic bacilli that share common genotypic characteristics. *B. pertussis* and *B. parapertussis* are the most similar of the species, but *B. parapertussis* does not express the gene coding for pertussis toxin. *B. pertussis* is a slow-growing fastidious organism that requires selective medium and forms small glistening bifurcated colonies. Suspicious colonies are presumptively identified as *B. pertussis* by direct fluorescent antibody testing or by agglutination with species-specific antiserum. *B. pertussis* is further differentiated from other *Bordetella* species by biochemical and motility characteristics.

B. pertussis produces a wide array of toxins and biologically active products that are important in its pathogenesis and in immunity. Most of these virulence factors are under the control of a single genetic locus that regulates their production, resulting in antigenic modulation and phase variation. Although these processes occur both in vitro and in vivo, their importance in the pathobiology of the organism is unknown; they may play a role in intracellular persistence and person-to-person spread. The organism's most important virulence factor is *pertussis toxin*, which is composed of a B oligomer–binding subunit and an enzymatically active A protomer that ADP-ribosylates a guanine nucleotide-binding regulatory protein (G protein) in target cells, producing a variety of biologic effects. Pertussis toxin has important mitogenic activity, affects the circulation of lymphocytes, and serves as an adhesin for bacterial binding to respiratory ciliated cells. Other important virulence factors and adhesins are *filamentous hemagglutinin*, a component of the cell wall, and *pertactin*, an outer-membrane protein. *Fimbriae*, bacterial appendages that play a role in bacterial attachment, are the major antigens against which agglutinating antibodies are directed. These agglutinating antibodies have historically been the primary means of serotyping *B. pertussis* strains. Other virulence factors include tracheal cytotoxin, which causes respiratory epithelial damage; adenylate cyclase toxin, which impairs host immune-cell function; dermonecrotic toxin, which may contribute to respiratory mucosal damage; and lipooligosaccharide, which has properties similar to those of other gram-negative bacterial endotoxins.

EPIDEMIOLOGY

Pertussis is a highly communicable disease, with attack rates of 80–100% among unimmunized household contacts and 20% within households in well-immunized populations. The infection has a worldwide distribution, with cyclical outbreaks every 3–5 years (a pattern that has persisted despite widespread immunization). Pertussis occurs in all months; however, in North America, its activity peaks in summer and autumn.

In developing countries, pertussis remains an important cause of infant morbidity and death. The reported incidence of pertussis worldwide has decreased as a result of improved vaccine coverage. However, coverage rates are still <50% in many developing nations (Fig. 53-1); the World Health Organization (WHO) estimates that 90% of the burden of pertussis is in developing regions. In addition, overreporting of immunization coverage and underreporting of disease result in substantial underestimation of the global burden of pertussis. The WHO estimates that there were 254,000 deaths from pertussis among children in 2004.

Before the institution of widespread immunization programs in the developed world, pertussis was one of the most common infectious causes of morbidity and death. In the United States before the 1940s, between 115,000 and 270,000 cases of pertussis were reported annually, with an average yearly rate of 150 cases per 100,000 population. With universal childhood immunization, the number of reported cases fell by >95%, and mortality rates decreased even more dramatically. Only 1010 cases of pertussis were reported in 1976 (Fig. 53-2). After that historic low, rates of pertussis slowly increased, peaking at >25,000 cases annually in 2004 and 2005. In 2007, 10,454 cases of pertussis were reported in the United States.

Although thought of as a disease of childhood, pertussis can affect people of all ages and is increasingly being identified as a cause of prolonged coughing illness in adolescents and adults. In unimmunized populations, pertussis incidence peaks during the preschool years, and well over half of children have the disease before reaching adulthood. In highly immunized populations such as those in North America, the peak incidence is among infants <1 year of age who have not completed the three-dose primary immunization series. Recent trends, however, show an increasing incidence of pertussis among adolescents and adults. In the United States in 2007, although infants <6 months of age had the highest incidence of pertussis, most cases were reported in adolescents and adults. Moreover, the figures for adolescents and adults are likely to be underestimates because of a greater degree of underrecognition and underreporting in these age groups. A number of studies of prolonged coughing illness suggest that pertussis may be the etiologic agent in 12–30% of adults with cough that does not improve within 2 weeks. In one study of the efficacy of an acellular pertussis vaccine in adolescents and adults, the incidence of pertussis in the placebo group was 3.7–4.5 cases per 1000 person-years. Although this prospective cohort study yielded a lower estimate than the studies of cough illness, its results still translate to 600,000–800,000 cases of pertussis annually among adults in the United States. Severe morbidity and high mortality rates, however, are restricted almost entirely to infants. In Canada, there were 16 deaths from pertussis between 1991 and 2001; all those who died were infants ≥6 months of age. Although school-age children are the source of infection for

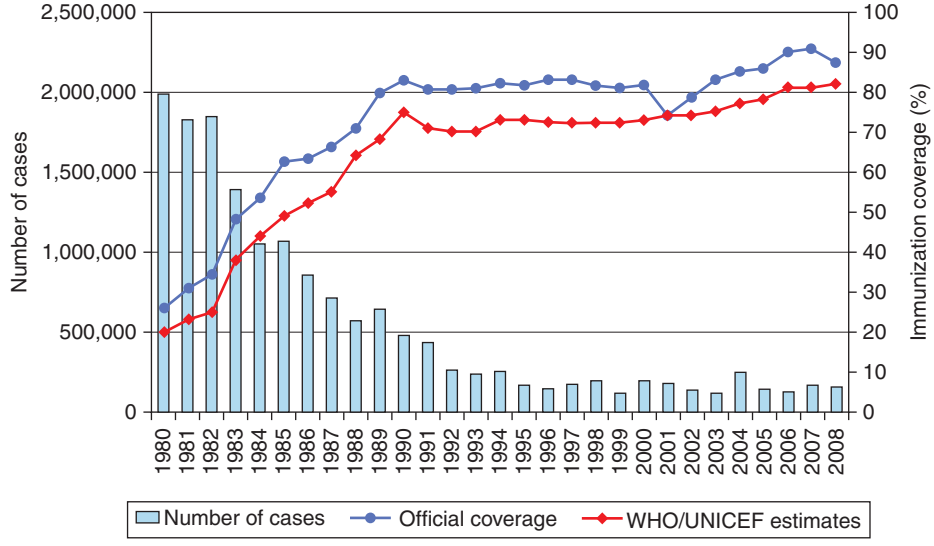


FIGURE 53-1
Global annual reported pertussis incidence and rate of coverage with DTP3 (diphtheria toxoid, tetanus toxoid, and pertussis vaccine; 3 doses), 1980–2008. (© *World Health Organization, 2009. All rights reserved. From http://www.who.int/immunization_monitoring/diseases/pertussis/en/index.html.* ***Source:*** *WHO/IVB database, 2009.*)

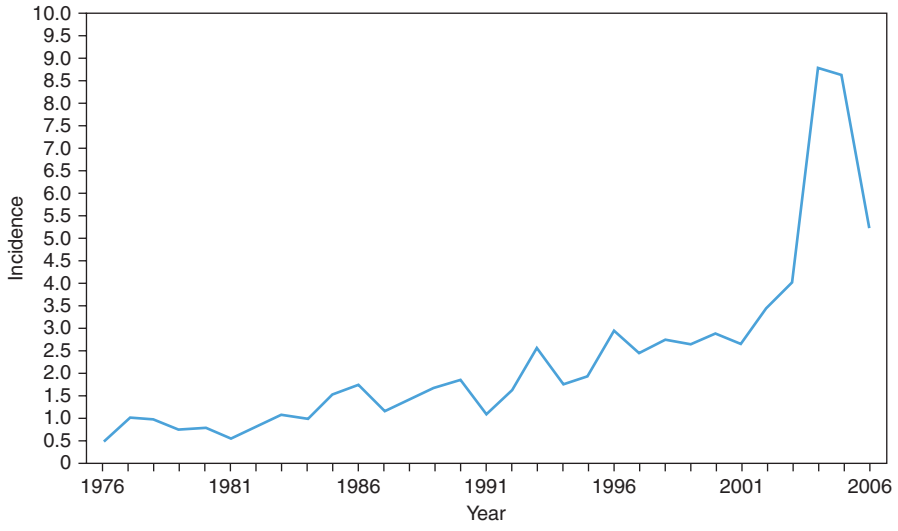


FIGURE 53-2

Pertussis incidence (per 100,000 population) by year—United States, 1976–2006. (*From the Centers for Disease Control and Prevention, MMWR Morb Mortal Wkly Rep 55[53]:60, 2008.*)

most households, adults are the likely source for high-risk infants and may serve as the reservoir of infection between epidemic years.

PATHOGENESIS

Infection with *B. pertussis* is initiated by attachment of the organism to the ciliated epithelial cells of the nasopharynx. Attachment is mediated by surface adhesins (e.g., pertactin and filamentous hemagglutinin), which bind to the integrin family of cell-surface proteins, probably in conjunction with pertussis toxin. The role of fimbriae in adhesion and in maintenance of infection has not been fully delineated. At the site of attachment, the organism multiplies, producing a variety of other toxins that cause local mucosal damage (tracheal cytotoxin, dermonecrotic toxin). Impairment of host defense by *B. pertussis* is mediated by pertussis toxin and adenylate cyclase toxin. There is local cellular invasion, with intracellular bacterial persistence; however, systemic dissemination does not occur. Systemic manifestations (lymphocytosis) result from the effects of the toxins.

The pathogenesis of the clinical manifestations of pertussis is poorly understood. It is not known what causes the hallmark paroxysmal cough. A pivotal role for pertussis toxin has been proposed. Proponents of this position point to the efficacy of preventing clinical symptoms with a vaccine containing only pertussis toxoid. Detractors counter that pertussis toxin is not the critical factor because paroxysmal cough also occurs in patients infected with *B. parapertussis*, which does not produce pertussis toxin. It is thought that neurologic events in pertussis, such as seizures and encephalopathy, are due to hypoxia from coughing paroxysms or apnea rather than to the effects of specific bacterial products. *B. pertussis* pneumonia, which occurs in up to 10% of infants with pertussis, is usually a diffuse bilateral primary infection. In older children and adults with pertussis, pneumonia is often due to secondary bacterial infection with streptococci or staphylococci.

IMMUNITY

Both humoral and cell-mediated immunity are thought to be important in pertussis. Antibodies to pertussis toxin, filamentous hemagglutinin, pertactin, and fimbriae are all protective in animal models. Pertussis agglutinins were correlated with protection in early studies of whole-cell pertussis vaccines. Serologic correlates of protection conferred by acellular pertussis vaccines have not been established, although antibody to pertactin, fimbriae, and (to a lesser degree) pertussis toxin correlated best with protection in two efficacy trials. The duration of immunity after whole-cell pertussis vaccination is short-lived, with little protection remaining after 10–12 years. After a three-dose infant primary series of acellular pertussis vaccine, protection persists for at least 5–6 years; the duration of immunity after a four- or five-dose schedule is not yet known, but serologic and modeling studies suggest that a booster may be needed after 10 years. Although immunity after natural infection was thought to be lifelong, seroepidemiologic evidence demonstrates that it clearly is not and that subsequent episodes of clinical pertussis are prevented by intermittent subclinical infection.

CLINICAL MANIFESTATIONS

Pertussis is a prolonged coughing illness with clinical manifestations that vary by age **(Table 53-1)**. Although not uncommon among adolescents and adults, classic pertussis is most often seen in preschool and school-age children. After an incubation period averaging 7–10 days,

TABLE 53-1

CLINICAL FEATURES OF PERTUSSIS, BY AGE GROUP AND DIAGNOSTIC STATUS

	PERCENTAGE OF PATIENTS		
	ADOLESCENTS AND ADULTS		
FEATURE	LABORATORY CONFIRMATION	NO LABORATORY CONFIRMATION	CHILDREN
Cough	95–100	95–100	95–100
Prolonged	60–80	60–80	60–95
Paroxysmal	60–90	50–90	80–95
Sleep-disturbing	50–80	50–80	90–100
Whoop	10–40	5–30	40–80
Posttussive vomiting	20–50	5–30	80–90

an illness develops that is indistinguishable from the common cold and is characterized by coryza, lacrimation, mild cough, low-grade fever, and malaise. After 1–2 weeks, this *catarrhal phase* evolves into the *paroxysmal phase*: the cough becomes more frequent and spasmodic with repetitive bursts of 5–10 coughs, often within a single expiration. Posttussive vomiting is frequent, with a mucous plug occasionally expelled at the end of an episode. The episode may be terminated by an audible whoop, which occurs upon rapid inspiration against a closed glottis at the end of a paroxysm. During a spasm, there may be impressive neck-vein distension, bulging eyes, tongue protrusion, and cyanosis. Paroxysms may be precipitated by noise, eating, or physical contact. Between attacks, the patient's appearance is normal but increasing fatigue is evident. The frequency of paroxysmal episodes varies widely, from several per hour to 5–10 per day. Episodes are often worse at night and interfere with sleep. Weight loss is not uncommon as a result of the illness's interference with eating. Most complications occur during the paroxysmal stage. Fever is uncommon and suggests bacterial superinfection.

After 2–4 weeks, the coughing episodes become less frequent and less severe—changes heralding the onset of the *convalescent phase*. This phase can last 1–3 months and is characterized by gradual resolution of coughing episodes. For 6–12 months, intercurrent viral infections may be associated with a recrudescence of paroxysmal cough.

Not all individuals who develop pertussis have classic disease. The clinical manifestations in adolescents and adults are more often atypical. In a German study of pertussis in adults, more than two-thirds had paroxysmal cough and more than one-third had whoop. Adult illness in North America differs from this experience: the cough may be severe and prolonged but is less frequently paroxysmal, and a whoop is uncommon. Vomiting with cough is the best predictor of pertussis as the cause of prolonged cough in adults. Other predictive features are a cough at night and exposure to other individuals with a prolonged coughing illness.

COMPLICATIONS

Complications are frequently associated with pertussis and are more common among infants than among older children or adults. Subconjunctival hemorrhages, abdominal and inguinal hernias, pneumothoraces, and facial and truncal petechiae can result from increased intrathoracic pressure generated by severe fits of coughing. Weight loss can follow decreased caloric intake. In a series of >1100 children <2 years of age who were hospitalized with pertussis, 27.1% had apnea, 9.4% had pneumonia, 2.6% had seizures, and 0.4% had encephalopathy; 10 children (0.9%) died. Pneumonia is reported in <5% of adolescents and adults and increases in frequency after 50 years of age. In contrast to the primary *B. pertussis* pneumonia that develops in infants, pneumonia in adolescents and adults with pertussis is usually caused by a secondary infection with encapsulated organisms such as *Streptococcus pneumoniae* or *Haemophilus influenzae*. Pneumothorax, severe weight loss, inguinal hernia, rib fracture, carotid artery aneurysm, and cough syncope have all been reported in adolescents and adults with pertussis.

DIAGNOSIS

If the classic symptoms of pertussis are present, clinical diagnosis is not difficult. However, particularly in older children and adults, it is difficult to differentiate infections caused by *B. pertussis* and *B. parapertussis* from other respiratory tract infections on clinical grounds. Therefore, laboratory confirmation should be attempted in all cases. Lymphocytosis—an absolute lymphocyte count of $>10^8$–10^9/L—is common among young children (in whom it is unusual with other infections) but not among adolescents and adults. Culture of nasopharyngeal secretions remains the gold standard of diagnosis, although DNA detection by polymerase chain reaction (PCR) has replaced culture in many laboratories because of increased sensitivity and quicker results. The best specimen is collected by nasopharyngeal aspiration, in which a fine flexible plastic catheter attached to a 10-mL syringe is passed into the nasopharynx and withdrawn while gentle suction is applied. Since *B. pertussis* is highly sensitive to drying, secretions for culture should be inoculated without delay onto appropriate medium (Bordet-Gengou or Regan-Lowe), or the catheter should be flushed with a phosphate-buffered saline solution for culture and/or PCR. An alternative to the aspirate is a Dacron or rayon nasopharyngeal swab; again, inoculation of culture plates should be immediate or an appropriate transport medium (e.g., Regan-Lowe charcoal medium) should be used. Results of PCR can be available within hours; cultures become positive by day 5 of incubation. *B. pertussis* and *B. parapertussis* can be differentiated by agglutination with specific antisera or by direct immunofluorescence.

Nasopharyngeal cultures in untreated pertussis remain positive for a mean of 3 weeks after the onset of illness;

these cultures become negative within 5 days of the institution of appropriate antimicrobial therapy. The duration of a positive PCR in untreated pertussis or after therapy is not known, but exceeds that of positive cultures. Since much of the period during which the organism can be recovered from the nasopharynx falls into the catarrhal phase, when the etiology of the infection is not suspected, there is only a small window of opportunity for culture-proven diagnosis. Cultures from infants and young children are more frequently positive than those from older children and adults; this difference may reflect earlier presentation of the former age group for medical care. Direct fluorescent antibody tests of nasopharyngeal secretions for direct diagnosis may still be available in some laboratories but should not be used because of poor sensitivity and specificity. Pseudo-outbreaks of pertussis have been reported as a result of false-positive PCR results. Greater standardization of PCR methodology can alleviate this problem.

As a result of the difficulties with laboratory diagnosis of pertussis in adolescents, adults, and patients who have been symptomatic for >4 weeks, increasing attention is being given to serologic diagnosis. Enzyme immunoassays detecting IgA and IgG antibodies to pertussis toxin, filamentous hemagglutinin, pertactin, and fimbriae have been developed and assessed for reproducibility. Two- or fourfold increases in antibody titer are suggestive of pertussis, although cross-reactivity of some antigens (such as filamentous hemagglutinin and pertactin) among *Bordetella* species makes it difficult to depend diagnostically on seroconversion involving a single type of antibody. Late presentation for medical care and prior immunization also complicate serologic diagnosis because the first sample obtained may in fact be a convalescent-phase specimen. Criteria for serologic diagnosis based on comparison of results for a single serum specimen with established population values are gaining acceptance, and serologic measurement of antibody to pertussis toxin will probably become more widely standardized and available for diagnostic purposes.

DIFFERENTIAL DIAGNOSIS

A child presenting with paroxysmal cough, posttussive vomiting, and whoop is likely to have an infection caused by *B. pertussis* or *B. parapertussis*; lymphocytosis increases the likelihood of a *B. pertussis* etiology. Viruses such as respiratory syncytial virus and adenovirus have been isolated from patients with clinical pertussis but probably represent co-infection.

In adolescents and adults, who often do not have paroxysmal cough or whoop, the differential diagnosis of a prolonged coughing illness is more extensive. Pertussis should be suspected when any patient has a cough that does not improve within 14 days, a paroxysmal cough of any duration, a cough followed by vomiting (adolescents and adults), or any respiratory symptoms after contact with a laboratory-confirmed case of pertussis. Other etiologies to consider include infections caused by *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, adenovirus, influenza virus, and other respiratory viruses. Use of angiotensin-converting enzyme (ACE) inhibitors, reactive airway disease, and gastroesophageal reflux disease are well-described noninfectious causes of prolonged cough in adults.

TREATMENT Pertussis

ANTIBIOTICS The purpose of antibiotic therapy for pertussis is to eradicate the infecting bacteria from the nasopharynx; therapy does not substantially alter the clinical course unless given early in the catarrhal phase. Macrolide antibiotics are the drugs of choice for treatment of pertussis (Table 53-2); macrolide-resistant *B. pertussis* strains have been reported but are rare. Trimethoprim-sulfamethoxazole is recommended as an alternative for individuals allergic to macrolides.

Supportive Care Young infants have the highest rates of complication and death from pertussis; therefore, most infants (and older children with severe disease) should be hospitalized. A quiet environment may decrease the stimulation that can trigger paroxysmal episodes. Use of β-adrenergic agonists and/or glucocorticoids has been advocated by some authorities but has not been proven to be effective. Cough suppressants are not effective and play no role in the management of pertussis.

TABLE 53-2

ANTIMICROBIAL THERAPY FOR PERTUSSIS

DRUG	ADULT DAILY DOSE	FREQUENCY	DURATION (DAYS)	COMMENTS
Erythromycin estolate	1–2 g	3 divided doses	7–14	Frequent gastrointestinal side effects
Clarithromycin	500 mg	2 divided doses	7	
Azithromycin	500 mg on day 1, 250 mg subsequently	1 daily dose	5	
Trimethoprim-sulfamethoxazole	160 mg of trimethoprim, 800 mg of sulfamethoxazole	2 divided doses	14	For patients allergic to macrolides; data on effectiveness limited

INFECTION CONTROL MEASURES Hospitalized patients with pertussis should be placed in respiratory isolation, with the use of precautions appropriate for pathogens spread by large respiratory droplets. Isolation should continue for 5 days after initiation of erythromycin therapy or for 3 weeks (i.e., until nasopharyngeal cultures are consistently negative) when the patient cannot tolerate antimicrobial therapy.

PREVENTION

Chemoprophylaxis

Because the risk of transmission of *B. pertussis* within households is high, chemoprophylaxis is widely recommended for household contacts of pertussis cases. The effectiveness of chemoprophylaxis, although unproven, is supported by several epidemiologic studies of institutional and community outbreaks. In the only randomized placebo-controlled study, erythromycin estolate (50 mg/kg per day in three divided doses; maximum dose, 1 g/d) was effective in reducing the incidence of bacteriologically confirmed pertussis by 67%; however, there was no decrease in the incidence of clinical disease. Despite these disappointing results, many authorities continue to recommend chemoprophylaxis, particularly in households with members at high risk of severe disease (children <1 year of age, pregnant women). Data are not available on use of the newer macrolides for chemoprophylaxis, but these drugs are commonly used because of their increased tolerability and their effectiveness.

Immunization

(See also Chap. 4) The mainstay of pertussis prevention is active immunization. Pertussis vaccine, now available for >80 years, became widely used in North America after 1940; the reported number of pertussis cases has since fallen by >90%. Whole-cell pertussis vaccines are prepared through the heating, chemical inactivation, and purification of whole *B. pertussis* organisms. Although effective (average efficacy estimate, 85%; range for different products, 30–100%), whole-cell pertussis vaccines are associated with adverse events—both common (fever; injection-site pain, erythema, and swelling; irritability) and uncommon (febrile seizures, hypotonic hyporesponsive episodes). Alleged associations of whole-cell pertussis vaccine with encephalopathy, sudden infant death syndrome, and autism, although not substantiated, have spawned an active anti-immunization lobby. The development of acellular pertussis vaccines, which are effective but less reactogenic, has greatly alleviated concerns about the inclusion of pertussis vaccine in the combined infant immunization series.

Although whole-cell vaccines are still used extensively in developing regions of the world, acellular pertussis vaccines are used exclusively for childhood immunization in much of the developed world. In North America, acellular pertussis vaccines for children are given as a three-dose primary series at 2, 4, and 6 months of age, with a reinforcing dose at 15–18 months of age and a booster dose at 4–6 years of age.

Although a wide variety of acellular pertussis vaccines were developed, only a few are still widely marketed; all contain pertussis toxoid and filamentous hemagglutinin. One acellular pertussis vaccine also contains pertactin, and another contains pertactin and two types of fimbriae. In light of phase 3 efficacy studies, most experts have concluded that two-component acellular pertussis vaccines are more effective than monocomponent vaccines and that the addition of pertactin increases efficacy still more. The further addition of fimbriae appears to enhance protective efficacy against milder disease. In two studies, protection conferred by pertussis vaccines correlated best with the production of antibody to pertactin, fimbriae, and pertussis toxin.

Adult formulations of acellular pertussis vaccines have been shown to be safe, immunogenic, and efficacious in clinical trials in adolescents and adults and are now recommended for routine immunization of these groups in several countries, including the United States. In this country, adolescents should receive a dose of the adult-formulation diphtheria–tetanus–acellular pertussis vaccine at the preadolescence physician's visit, and all unvaccinated adults should receive a single dose of this combined vaccine. In addition, it is recommended that all health care workers in the United States be vaccinated against pertussis. Pertussis vaccine coverage among U.S. adolescents rose from 10.8% to 30.4% from 2006 to 2007. Further improvements in adolescent and adult vaccine coverage may permit better control of pertussis across the age spectrum, with collateral protection of infants too young to be immunized.

CHAPTER 54

DISEASES CAUSED BY GRAM-NEGATIVE ENTERIC BACILLI

Thomas A. Russo ■ James R. Johnson

GENERAL FEATURES AND PRINCIPLES

The gram-negative enteric bacilli are common causes of a wide variety of infections involving diverse anatomic sites in both healthy and compromised hosts. Some members of this group have become increasingly resistant to antimicrobial treatment, and new infectious syndromes have emerged. Therefore, a thorough knowledge of clinical presentations and appropriate therapeutic choices is necessary for optimal outcomes.

EPIDEMIOLOGY

Escherichia coli, *Klebsiella*, *Proteus*, *Enterobacter*, *Serratia*, *Citrobacter*, *Morganella*, *Providencia*, and *Edwardsiella* are components of the normal animal and human colonic flora and/or of the flora of a variety of environmental habitats, including long-term-care facilities (LTCFs) and hospitals. As a result, except for certain pathotypes of intestinal pathogenic *E. coli*, these genera are global pathogens. In healthy humans, *E. coli* is the predominant species of gram-negative bacilli (GNB) in the colonic flora. GNB (primarily *E. coli*, *Klebsiella*, and *Proteus*) only transiently colonize the oropharynx and skin of healthy individuals. In contrast, in LTCF and hospital settings, a variety of GNB emerge as the dominant flora of both mucosal and skin surfaces, particularly in association with antimicrobial use, severe illness, and extended length of stay. This colonization may lead to subsequent infection; for example, oropharyngeal colonization may lead to pneumonia. In general, among adults, the incidence of infection due to these agents increases with age. Thus, as the mean age of the population increases, so will the number of these infections.

STRUCTURE AND FUNCTION

GNB possess an extracytoplasmic outer membrane, a feature shared generally among gram-negative bacteria. This outer membrane consists of a lipid bilayer with associated proteins, lipoproteins, and polysaccharides (capsule, lipopolysaccharide [LPS]). The outer membrane interfaces with the bacterial environment, including the human host. A variety of components of the outer membrane are critical determinants in pathogenesis and antimicrobial resistance.

PATHOGENESIS

Multiple bacterial virulence factors are required for the pathogenesis of infections caused by GNB. Possession of specialized virulence genes defines pathogens and enables them to infect the host efficiently. Hosts and their cognate pathogens have been co-adapting throughout evolutionary history, and it has been speculated that infection is just one point on the spectrum of evolved relationships between microbes and hosts. At one end of this spectrum is a commensal/symbiotic interaction (e.g., mitochondria—formerly bacteria—within eukaryotic cells); at the other end is a lethal outcome, producing a dead-end relationship (e.g., Ebola virus). During the host-pathogen "chess match" over time, various and redundant strategies have emerged in both the pathogens and their hosts that enable these partners to maintain their coexistence **(Table 54-1)**.

Extraintestinal pathogenic *E. coli* (ExPEC) strains and the other genera discussed in this chapter cause infection outside the bowel. All are primarily extracellular pathogens and therefore share certain pathogenic features. Innate immunity (including the activities of complement, antimicrobial peptides, and professional phagocytes) and humoral immunity are the principal host defense components. Both susceptibility to and severity of infection are increased with dysfunction or deficiencies of these components (Chap. 1). In contrast, the virulence traits of intestinal pathogenic *E. coli*—i.e., the distinctive strains that can cause diarrheal disease—are for the most part different from those of ExPEC and other GNB that cause extraintestinal infections. This distinction reflects

TABLE 54-1

INTERACTIONS OF EXTRAINTESTINAL PATHOGENIC *E. COLI* WITH THE HUMAN HOST: A PARADIGM FOR EXTRACELLULAR, EXTRAINTESTINAL GRAM-NEGATIVE BACTERIAL PATHOGENS

BACTERIAL GOAL	HOST OBSTACLE	BACTERIAL SOLUTION
Extraintestinal attachment	Flow of urine, mucociliary blanket	Multiple adhesins (e.g., type I, S, and F1C fimbriae; P pili)
Nutrient acquisition for growth	Nutrient sequestration (e.g., iron via intracellular storage and extracellular scavenging via lactoferrin and transferrin)	Cellular lysis (e.g., hemolysin), multiple mechanisms for competing for iron (e.g., siderophores) and other nutrients
Initial avoidance of host bactericidal activity	Complement, phagocytic cells, antimicrobial peptides	Capsular polysaccharide, lipopolysaccharide
Transmission	?	Irritant tissue damage resulting in increased excretion (e.g., toxins such as hemolysin)
Late avoidance of host bactericidal activity	Acquired immunity (e.g., specific antibodies), treatment with antibiotics	?Cell entry, acquisition of antimicrobial resistance

site-specific differences in host environments and defense mechanisms.

The virulence factors of extraintestinal pathogenic GNB subserve diverse functions. A given strain usually possesses multiple adhesins for binding to a variety of host cells (e.g., in *E. coli*: type 1, S, and F1C fimbriae; P pili). Nutrient acquisition (e.g., of iron via siderophores) requires many genes that are necessary, but not sufficient for pathogenesis. The ability to resist the bactericidal activity of complement and phagocytes in the absence of antibody (e.g., as conferred by capsule or O antigen of LPS) is one of the defining traits of an extracellular pathogen. Tissue damage (e.g., as mediated by hemolysin in the case of *E. coli*) may facilitate spread within the host. Without doubt, many important virulence genes await identification, and our understanding of many aspects of the pathogenesis of infections due to GNB is in its infancy (Chap. 2).

The ability to induce septic shock is another defining feature of these genera. GNB are the most common causes of this potentially lethal syndrome. The lipid A moiety of LPS (via interaction with host Toll-like receptor 4) and probably also other bacterial factors stimulate a proinflammatory host response that, if overly exuberant, results in shock (Chap. 16).

Many antigenic variants (serotypes) exist in most genera of GNB. For example, there are >150 O-specific antigens and >80 capsular antigens in *E. coli*. This antigenic variability, which permits immune evasion and allows recurrent infection by different strains of the same species, has impeded vaccine development (Chap. 4).

INFECTIOUS SYNDROMES

Although certain strains of *E. coli* have evolved to be strictly intestinal pathogens, causing gastroenteritis by a variety of unique pathogenic mechanisms, extraintestinal infections are the predominant disease presentation caused by enteric GNB generally. Depending on both the host and the pathogen, nearly every organ or body cavity can be infected with GNB. *E. coli* and—to a lesser degree—*Klebsiella* and *Proteus* account for most extraintestinal infections due to GNB and are the most virulent pathogens within this group. However, the other genera are becoming increasingly important, particularly among LTCF residents and hospitalized patients. This expanding spectrum of disease-causing genera is due in large part to the intrinsic or acquired antimicrobial resistance of these organisms and the increasing number of individuals with alterations or disruptions of host defenses. The mortality rate is substantial in many GNB infections and correlates with the severity of illness. Especially problematic are pneumonia and bacteremia (arising from any source) when complicated by organ failure (severe sepsis) and/or shock, for which the associated mortality rates are 20–50%.

DIAGNOSIS

Isolation of GNB from ordinarily sterile anatomic sites almost always implies infection, whereas their isolation from nonsterile sites, particularly from open soft-tissue wounds and the respiratory tract, requires clinical correlation to differentiate colonization from infection. Tentative laboratory identification based on lactose fermentation and indole production (described for each of the following genus), which usually is possible before final identification of the organism and determination of its antimicrobial susceptibilities, may guide empirical antimicrobial therapy.

TREATMENT Infections Caused by Gram-Negative Enteric Bacilli

(See also Chap. 36) In this chapter, the Clinical Laboratory Standards Institute (CLSI) classification of cephalosporins will be used, according to which the previously designated first-, second-, third-, and fourth-generation cephalosporins will be designated cephalosporins I, II,

III, and IV, respectively. Likewise, the terms *extended* or *expanded spectrum*, which have been used to describe third- and fourth-generation cephalosporins, will be avoided. Accumulating evidence indicates that initiation of appropriate empirical antimicrobial therapy early in the course of GNB infections (particularly serious infections) leads to improved outcomes. Familiarity with evolving patterns of antimicrobial resistance in enteric GNB is necessary in the selection of appropriate empirical therapy, particularly given the lag between published and real-time resistance rates and the ever-increasing prevalence of multidrug-resistant (MDR) GNB. However, if broad-spectrum treatment has been initiated and information on antimicrobial susceptibilities becomes available, it is just as important to use the most appropriate narrower-spectrum agent. Such responsible antimicrobial stewardship will avoid unnecessary selection of and potential superinfection with resistant bacteria, may decrease costs, and will maximize the useful longevity of available antimicrobial agents. Likewise, it is important not to treat patients who are colonized but not infected. The antimicrobial resistance profiles of GNB vary by species, geographic location, regional antimicrobial use, and hospital site (e.g., intensive care units [ICUs] versus wards). At present, the most reliably active agents against enteric GNB are the carbapenems (e.g., imipenem), the aminoglycoside amikacin, the cephalosporin IV cefepime, and piperacillin-tazobactam.

β-Lactamases, which inactivate β-lactam agents, are the most important mediators of resistance to these drugs in GNB. Decreased permeability and/or active efflux of β-lactam agents, although less common, may occur alone or in combination with β-lactamase-mediated resistance. *Broad-spectrum* β-lactamases, which mediate resistance to many penicillins and cephalosporins I, are frequently expressed in enteric GNB. These enzymes are inhibited by agents such as clavulanate. *Extended-spectrum* β-lactamases (ESBLs) confer resistance to the same drugs as broad-spectrum β-lactamases as well as to cephalosporins III, aztreonam, and (in some instances) cephalosporins IV. The prevalence of acquired ESBL-encoding genes via transferable plasmids is increasing in GNB worldwide, with rates varying greatly even among hospitals in a given region. To date, ESBLs are most prevalent in *Klebsiella pneumoniae*, *K. oxytoca*, and *E. coli*, but also occur (and are probably underrecognized) in *Enterobacter*, *Citrobacter*, *Proteus*, *Serratia*, and other enteric GNB. At present, the regional prevalence of ESBL-producing GNB declines in rank order as follows: Latin America > Western Pacific > Europe > United States and Canada. ESBL-producing GNB were initially described in hospitals (ICUs > wards) and LTCFs. However, over the last decade, CTX-M ESBLs have been increasingly described in community-acquired strains. Hospital outbreaks due to ESBL-producing strains have been associated with extensive use of cephalosporins III, particularly ceftazidime. The carbapenems are the most reliably active β-lactam agents against ESBL-expressing strains. GNB that express ESBLs may also possess porin mutations that result in decreased uptake of cephalosporins and β-lactam/β-lactamase inhibitor combinations. Thus, ESBL-producing isolates should be considered resistant to all penicillins, cephalosporins, and aztreonam. Ceftobiprole, which is currently under review by the U.S. Food and Drug Administration (FDA), is a first-in-class cephalosporin with activity against methicillin-resistant *Staphylococcus aureus* and most Enterobacteriaceae; however, it has poor activity in vitro against ESBL-producing GNB. Oral options for the treatment of strains expressing CTX-M ESBLs are limited (see "Treatment of Extraintestinal *E. coli* Infections," later).

AmpC β-lactamases confer resistance to the same substrates as ESBLs plus the cephamycins (e.g., cefoxitin and cefotetan). AmpC enzymes resist inhibition by β-lactamase inhibitors. The presence of constitutive chromosomal AmpC β-lactamases in nearly all strains of *Enterobacter*, *Serratia*, *Citrobacter*, *Proteus vulgaris*, *Providencia*, and *Morganella* results in resistance to aminopenicillins, cefazolin, and cefoxitin. In addition, some strains of *E. coli*, *K. pneumoniae*, and other Enterobacteriaceae have acquired plasmids containing AmpC β-lactamase genes. The cephalosporin IV cefepime is stable to AmpC β-lactamases and is an appropriate treatment option if the concomitant presence of an ESBL can be excluded.

Carbapenemases (e.g., the IMP, VIM, and KPC families) confer resistance to the same drugs as ESBLs plus cephamycins and carbapenems. Linked resistance to fluoroquinolones and aminoglycosides is common. Occasionally, resistance to carbapenems is due to the possession of a β-lactamase plus decreased permeability. Unfortunately, carbapenemase-producing enteric GNB are becoming increasingly common, and infection with these strains is associated with elevated mortality rates. Automated susceptibility systems may be unreliable for detection of carbapenemases, particularly those conferring resistance to imipenem and meropenem. Resistance to ertapenem is the most sensitive marker for carbapenem resistance in automated systems. An elevated carbapenem minimal inhibitory concentration should prompt additional polymerase chain reaction (PCR) testing for resistance genes or a modified Hodge test; these methods are more reliable for detection of carbapenemase-producing strains. Tigecycline and the polymyxins exhibit the greatest in vitro activity against such strains. However, tigecycline reaches only low concentrations in serum and urine, a characteristic that warrants concern about its use in the treatment of bacteremia and urinary tract infection (UTI). Furthermore, emerging resistance to both of these agents poses the risk of onset of a post-antimicrobial era with respect to GNB.

Resistance to fluoroquinolones usually is due to alterations of the target site (DNA gyrase and/or topoisomerase IV), with or without decreased permeability, active efflux, or protection of the target site. Resistance to

fluoroquinolones is increasingly prevalent among GNB and is associated with resistance to other antimicrobial classes; for example, 20–80% of ESBL-producing enteric GNB are also resistant to fluoroquinolones. At present, fluoroquinolones should be considered unreliable as empirical therapy for infections due to GNB in critically ill patients.

Given the increasing prevalence of MDR GNB, it is reasonable—pending susceptibility results—to combine agents for empirical treatment of GNB infections in critically ill patients. Antimicrobial resistance may not always be identified by in vitro testing; therefore, it is important to assess the clinical response to treatment. Moreover, resistance may evolve during therapy (e.g., through stable derepression of AmpC β-lactamases). In addition, drainage of abscesses and removal of infected foreign bodies are often required for cure. GNB are commonly involved in polymicrobial infections, in which the role of each individual pathogen is uncertain (Chap. 69). Although some GNB are more pathogenic than others, it is usually prudent, if possible, to design an antimicrobial regimen active against all of the GNB identified, since each is capable of pathogenicity in its own right. Finally, the possibility of a superinfection (e.g., *Clostridium difficile* colitis) must always be kept in mind.

PREVENTION

(See also Chap. 14) Diligent adherence to hand-hygiene protocols by health care personnel and avoidance of inappropriate antimicrobial use are key measures in preventing infection and the further development of antimicrobial resistance. Contact precautions should be implemented for patients colonized or infected with carbapenem-resistant (and perhaps other MDR) GNB. Likewise, avoidance of the use of indwelling devices (e.g., urinary and intravascular catheters, endotracheal tubes) and, when they are necessary, placement according to an appropriate protocol decrease infection risk. Positioning (e.g., head of bed at ≥30°) and good oral hygiene decrease the incidence of pneumonia in ventilated patients.

ESCHERICHIA COLI INFECTIONS

COMMENSAL STRAINS

For the most part, commensal *E. coli* variants, which constitute the bulk of the normal facultative intestinal flora in most humans, confer benefits to the host (e.g., resistance to colonization with pathogenic organisms). These strains generally lack the specialized virulence traits that enable extraintestinal and intestinal pathogenic *E. coli* strains to cause disease outside and within the gastrointestinal tract, respectively. However, even commensal *E. coli* strains can be involved in extraintestinal infections in the presence of an aggravating factor, such as a foreign body (e.g., a urinary catheter), host compromise (e.g., local anatomic or functional abnormalities such as urinary or biliary tract obstruction or systemic immunocompromise), or an inoculum that is large or contains a mixture of bacterial species (e.g., fecal contamination of the peritoneal cavity).

EXTRAINTESTINAL PATHOGENIC (ExPEC) STRAINS

The majority of *E. coli* isolates from symptomatic infections of the urinary tract, bloodstream, cerebrospinal fluid, respiratory tract, and peritoneum (spontaneous bacterial peritonitis) can be differentiated from commensal and intestinal pathogenic strains of *E. coli* by virtue of their distinctive virulence factor profiles (Table 54-1) and phylogenetic background. ExPEC strains can also cause surgical wound infection, osteomyelitis, and myositis, but the number of cases evaluated to date is too small for a reliable assessment of proportions.

Like commensal *E. coli* (but in contrast to intestinal pathogenic *E. coli*), ExPEC strains are often found in the intestinal flora of healthy individuals and do not cause gastroenteritis in humans. Although acquisition of an ExPEC strain by the host is a prerequisite for ExPEC infection, it is not the rate-limiting step, which instead is entry of an ExPEC strain from its site of colonization (e.g., the colon, vagina, or oropharynx) into a normally sterile extraintestinal site (e.g., the urinary tract, peritoneal cavity, or lungs). ExPEC strains have acquired genes encoding diverse extraintestinal virulence factors that enable the bacteria to cause infections outside the gastrointestinal tract in both normal and compromised hosts (Table 54–1). These virulence genes are, for the most part, distinct from those that enable intestinal pathogenic strains to cause diarrheal disease. All age groups, all types of hosts, and nearly all organs and anatomic sites are susceptible to infection by ExPEC. Even previously healthy hosts can become severely ill or die when infected with ExPEC; however, adverse outcomes are more common among hosts with comorbid illnesses and host defense abnormalities. *E. coli* is the most common enteric GNB to cause extraintestinal infection in ambulatory, LTCF, and hospital settings. The diversity and the medical and economic impact of ExPEC infections are evident from consideration of the following specific syndromes.

Extraintestinal infectious syndromes

Urinary tract infection

The urinary tract is the site most frequently infected by ExPEC. An exceedingly common infection among ambulatory patients, UTI accounts for 1% of ambulatory care visits in the United States and is second only to lower respiratory tract infection among infections responsible for hospitalization. UTIs are best considered by clinical syndrome (e.g., uncomplicated cystitis, pyelonephritis, and catheter-associated UTIs) and within the context of specific hosts (e.g., premenopausal women, compromised hosts; Chap. 28). *E. coli* is the single most common

pathogen for all UTI syndrome/host group combinations. Each year in the United States, *E. coli* causes 85–95% of an estimated 6–8 million episodes of uncomplicated cystitis in premenopausal women, with an estimated $1.6 billion in direct health care costs. Furthermore, 20% of women with an initial cystitis episode develop frequent recurrences (from 0.3 to >20 per year).

Uncomplicated cystitis, the most common acute UTI syndrome, is characterized by dysuria, urinary frequency, and suprapubic pain. Fever and/or back pain suggests progression to pyelonephritis. Even with appropriate treatment of pyelonephritis, fever may take 5–7 days to resolve completely. Persistently elevated or increasing fever and neutrophil counts should prompt evaluation for intrarenal or perinephric abscess and/or obstruction. Renal parenchymal damage and loss of renal function during pyelonephritis occur primarily with urinary obstruction. Pregnant women are at unusually high risk for developing pyelonephritis, which can adversely affect the outcome of pregnancy. As a result, prenatal screening for and treatment of asymptomatic bacteriuria are standard. Prostatic infection is a potential complication of UTI in men. The diagnosis and treatment of UTI, as detailed in Chap. 28, should be tailored to the individual host, the nature and site of infection, and local patterns of antimicrobial susceptibility.

Abdominal and pelvic infection

The abdomen/pelvis is the second most common site of extraintestinal infection due to *E. coli*. A wide variety of clinical syndromes occur in this location, including acute peritonitis secondary to fecal contamination, spontaneous bacterial peritonitis, dialysis-associated peritonitis, diverticulitis, appendicitis, intraperitoneal or visceral abscesses (hepatic, pancreatic, splenic), infected pancreatic pseudocysts, and septic cholangitis and/or cholecystitis. In intraabdominal infections, *E. coli* can be isolated either alone or (as often occurs) in combination with other facultative and/or anaerobic members of the intestinal flora (Chap. 25).

Pneumonia

E. coli is not usually considered a cause of pneumonia (Chap. 18). Indeed, enteric GNB account for only 2–5% of cases of community-acquired pneumonia (CAP), in part because these organisms only transiently colonize the oropharynx in a minority of healthy individuals. However, rates of oral colonization with *E. coli* and other GNB increase with severity of illness and antibiotic use. Consequently, GNB are a common cause of pneumonia among residents of LTCFs and are the most common cause (60–70% of cases) of hospital-acquired pneumonia (HAP) (Chap. 25), particularly among postoperative and ICU patients (e.g., ventilator-associated pneumonia). Pulmonary infection is usually acquired by small-volume aspiration but occasionally occurs via hematogenous spread, in which case multifocal nodular infiltrates can be seen. Tissue necrosis, probably due to cytotoxins produced by GNB, is common. Despite significant institutional variation, *E. coli* is generally the third or fourth most commonly isolated GNB in hospital-acquired pneumonia, accounting for 5–8% of episodes in both U.S.-based and European-based studies. Regardless of the host, pneumonia due to enteric GNB is a serious disease, with high crude and attributable mortality rates (20–60% and 10–20%, respectively).

Meningitis

(See also Chap. 31) *E. coli* is one of the two leading causes of neonatal meningitis, the other being group B *Streptococcus*. Most *E. coli* strains that cause neonatal meningitis possess the K1 capsular antigen and derive from a limited number of familiar meningitis-associated clonal groups. After the first month of life, *E. coli* meningitis is uncommon, occurring predominantly in the setting of disruption of the meninges from craniotomy or trauma or in the presence of cirrhosis. In patients with cirrhosis who develop meningitis, the meninges are presumably seeded as a result of poor hepatic clearance of portal vein bacteremia.

Cellulitis/musculoskeletal infection

E. coli contributes frequently to infection of decubitus ulcers and occasionally to infection of ulcers and wounds of the lower extremity in diabetic patients and other hosts with neurovascular compromise. Osteomyelitis secondary to contiguous spread can occur in these settings. *E. coli* also causes cellulitis or infections of burn sites or surgical wounds (accounting, in fact, for 10% of surgical site infections), particularly when the infection originates close to the perineum. Hematogenously acquired osteomyelitis, especially of vertebral bodies, is more commonly caused by *E. coli* than is generally appreciated; this organism accounts for up to 10% of cases in some series (Chap. 23). *E. coli* occasionally causes orthopedic device–associated infection or septic arthritis and rarely causes hematogenous myositis. Upper-leg myositis or fasciitis due to *E. coli* should prompt an evaluation for an abdominal source with contiguous spread.

Endovascular infection

Despite being one of the most common causes of bacteremia, *E. coli* rarely seeds native heart valves. When the organism does seed native valves, it usually does so in the setting of prior valvular disease. *E. coli* infections of aneurysms and vascular grafts are quite uncommon.

Miscellaneous infections

E. coli can cause infection in nearly every organ and anatomic site. It occasionally causes postoperative mediastinitis or complicated sinusitis and uncommonly causes endophthalmitis or brain abscess.

Bacteremia

E. coli bacteremia can arise from primary infection at any extraintestinal site. In addition, primary *E. coli* bacteremia can arise from percutaneous intravascular devices or transrectal prostate biopsy or from the increased intestinal mucosal permeability seen in neonates and in the settings of neutropenia and chemotherapy-induced mucositis, trauma, and burns. Roughly equal proportions

of *E. coli* bacteremia cases originate in the community and in the hospital. In most studies, *E. coli* and *S. aureus* are the two most common blood isolates of clinical significance. *E. coli*, which accounts for 17–37% of cases, is the most frequent GNB blood isolate in the ambulatory setting and in most LTCF and hospital settings. Isolation of *E. coli* from the blood is almost always clinically significant and is typically accompanied by the sepsis syndrome, severe sepsis (sepsis-induced dysfunction of at least one organ or system), or septic shock (Chap. 16). Calculations based on conservative estimates for the incidence of severe sepsis (0.76/1000), the proportional contribution of *E. coli* to severe sepsis (17%), and a sepsis-associated mortality rate of 30% translate into an estimated 265,000 deaths annually in the world (2009 census data).

The urinary tract is the most common source of *E. coli* bacteremia, accounting for one-half to two-thirds of episodes. Bacteremia from a urinary tract source is particularly common in patients with pyelonephritis, urinary tract obstruction, or urinary instrumentation in the presence of infected urine. The abdomen is the second most common source, accounting for 25% of episodes. Although biliary obstruction (stones, tumor) and overt bowel disruption, which typically are readily apparent, are responsible for many of these cases, some abdominal sources (e.g., abscesses) are remarkably silent clinically and require identification via imaging studies (e.g., CT). Therefore, the physician should be cautious in designating the urinary tract as the source of *E. coli* bacteremia in the absence of characteristic signs and symptoms of UTI. Soft tissue, bone, pulmonary, and intravascular catheter infections are other sources of *E. coli* bacteremia.

Diagnosis

Strains of *E. coli* that cause extraintestinal infections usually grow both aerobically and anaerobically within 24 h on standard diagnostic media and are easily identified by the clinical microbiology laboratory according to routine biochemical criteria. More than 90% of ExPEC strains are rapid lactose fermenters and are indole positive.

TREATMENT **Extraintestinal *E. coli* Infections**

In the past, most *E. coli* isolates were highly susceptible to a broad range of antimicrobial agents. Unfortunately, this situation has changed, and, of the Enterobacteriaceae, *E. coli* is the species in which resistance is evolving most rapidly. In general, the high prevalence of resistance precludes empirical use of ampicillin and amoxicillin-clavulanate, even for community-acquired infections. The prevalence of resistance to cephalosporins I and trimethoprim-sulfamethoxazole (TMP-SMX) is increasing among community-acquired strains in the United States (with current rates of 10–40%) and is even higher outside North America. Until recently, TMP-SMX was the drug of choice for the treatment of uncomplicated cystitis in many locales. Although continued empirical use of TMP-SMX will predictably result in ever-diminishing cure rates, a wholesale switch to alternative agents (e.g., fluoroquinolones) will just as predictably accelerate the widespread emergence of resistance to these antimicrobial classes, as has already occurred in some areas. More than 90% of isolates that cause uncomplicated cystitis remain susceptible to nitrofurantoin and fosfomycin. The prevalence of resistance to fluoroquinolones has increased steadily over the last decade (e.g., from 5% to 20% in North America between 2002 and 2005 and from 8% to 25% among bacteremia isolates from the United Kingdom and Ireland between 2001 and 2006) and is even higher in other regions (Mexico, India). Prevalence figures are higher in settings where fluoroquinolone prophylaxis is used extensively (e.g., in patients with leukemia, transplant recipients, and patients with cirrhosis) and among isolates from LTCFs and hospitals. As for cephalosporin resistance, data from the U.S. National Healthcare Safety Network (NHSN) indicated that just 6% of *E. coli* device-associated/surgical site infections were due to strains resistant to cephalosporins III in 2006–2007. However, significantly higher rates have been reported outside North America; 54% of isolates assessed by the International Nosocomial Infection Control Consortium (INICC) in 2002–2007 were resistant. ESBL-containing strains are increasingly prevalent among both health care–associated (5–10%) and ambulatory isolates (region-dependent figures). An increasing number of reports describe *E. coli* strains causing community-acquired UTIs that contain CTX-M ESBLs. Data suggest that acquisition of CTX-M-containing and fluoroquinolone-resistant strains may result from consumption of meat products from food animals treated with cephalosporins III and IV and fluoroquinolones. Oral treatment options are limited with these strains; however, in vitro and limited clinical data indicate that fosfomycin and—for cystitis—nitrofurantoin appear to be viable options. Carbapenems (e.g., imipenem) and amikacin are the most predictably active agents overall, but carbapenemase-producing strains are on the rise (1–5% among health care–associated isolates). Tigecycline and polymyxin B have been used most frequently for these nearly panresistant isolates. Although this evolving antimicrobial resistance is a source of serious concern, of equal importance is the need to use the most appropriate narrower-spectrum agent whenever possible and to avoid treating colonized but uninfected patients so that the ever-escalating selection of increasingly resistant bacteria is not unnecessarily fueled.

INTESTINAL PATHOGENIC STRAINS

Certain strains of *E. coli* are capable of causing diarrheal disease. Other important intestinal pathogens are discussed in Chaps. 26, 46, 58 and 61. At least in the industrialized world, intestinal pathogenic strains of

E. coli are rarely encountered in the fecal flora of healthy persons and instead appear to be essentially obligate pathogens. These strains have evolved a special ability to cause enteritis, enterocolitis, and colitis when ingested in sufficient quantities by a naive host. At least five distinct pathotypes of intestinal pathogenic *E. coli* exist: (1) Shiga toxin–producing *E. coli* (STEC)/enterohemorrhagic *E. coli* (EHEC), (2) enterotoxigenic *E. coli* (ETEC), (3) enteropathogenic *E. coli* (EPEC), (4) enteroinvasive *E. coli* (EIEC), and (5) enteroaggregative *E. coli* (EAEC). Diffusely adherent *E. coli* (DAEC) and cytodetaching *E. coli* are additional putative pathotypes. Transmission occurs predominantly via contaminated food and water for ETEC, STEC/EHEC, EIEC, and EAEC and by person-to-person spread for EPEC (and occasionally STEC/EHEC). Gastric acidity confers some protection against infection; therefore, persons with decreased stomach acid levels are especially susceptible. Humans are the major reservoir (except for STEC/EHEC, with regard to which bovines are the main concern); host range appears to be dictated by species-specific attachment factors. Although there is some overlap, each pathotype possesses a unique combination of virulence traits that results in a distinctive intestinal pathogenic mechanism **(Table 54-2)**. These strains are largely incapable of causing disease outside the intestinal tract. Except in the cases of STEC/EHEC and EAEC, disease due to this group of pathogens occurs primarily in developing countries.

Shiga toxin–producing and enterohemorrhagic E. coli

STEC/EHEC strains constitute an emerging group of pathogens that can cause hemorrhagic colitis and the hemolytic-uremic syndrome (HUS). Several large outbreaks resulting from the consumption of fresh produce (e.g., lettuce, spinach, sprouts) and of undercooked ground beef have received significant attention in the media. O157:H7 is the most prominent serotype, but serogroups O6, O26, O55, O91, O103, O111, O113, and OX3 have also been associated with these syndromes. The ability of STEC/EHEC to produce Shiga toxin (Stx2 and/or Stx1) or related toxins is a critical factor in the expression of clinical disease. *Shigella dysenteriae* strains that produce the closely related Shiga toxin Stx can cause the same syndrome. Stx2 and its Stx2C variant (which may be variably present in combination with Stx2 and/or Stx1) appear to be more important than Stx1 in the development of HUS. All Shiga toxins studied to date are multimers composing one enzymatically active A subunit and five identical B subunits that mediate binding to globosyl ceramides, which are membrane-associated glycolipids expressed on certain host cells. The Stx1 A subunit cleaves an adenine from the host cell's 28S rRNA, thereby irreversibly inhibiting ribosomal function, whereas the Stx2 A subunit inactivates *Bcl2*, inducing apoptosis.

TABLE 54-2

INTESTINAL PATHOGENIC *E. COLI*

PATHOTYPE[a]	EPIDEMIOLOGY	CLINICAL SYNDROME[b]	DEFINING MOLECULAR TRAIT	RESPONSIBLE GENETIC ELEMENT[c]
STEC/EHEC	Food, water, person-to-person; all ages, industrialized countries	Hemorrhagic colitis, hemolytic-uremic syndrome	Shiga toxin	Lambda-like Stx1- or Stx2-encoding bacteriophage
ETEC	Food, water; young children in and travelers to developing countries	Traveler's diarrhea	Heat-stable and -labile enterotoxins, colonization factors	Virulence plasmid(s)
EPEC	Person-to-person; young children and neonates in developing countries	Watery diarrhea, persistent diarrhea	Localized adherence, attaching and effacing lesion on intestinal epithelium	EPEC adherence factor plasmid pathogenicity island (locus for enterocyte effacement [LEE])
EIEC	Food, water; children in and travelers to developing countries	Dysentery	Invasion of colonic epithelial cells, intracellular multiplication, cell-to-cell spread	Multiple genes contained primarily in a large virulence plasmid
EAEC	?Food, water; children in and travelers to developing countries; all ages, industrialized countries	Traveler's diarrhea, acute diarrhea, persistent diarrhea	Aggregative/diffuse adherence, virulence factors regulated by AggR	Chromosomal or plasmid-associated adherence and toxin genes

[a]EAEC, enteroadherent *E. coli*; EHEC, enterohemorrhagic *E. coli*; EIEC, enteroinvasive *E. coli*; EPEC, enteropathogenic *E. coli*; ETEC, enterotoxigenic *E. coli*; STEC, Shiga toxin–producing *E. coli*.

[b]Classic syndromes; see text for details on disease spectrum.

[c]Pathogenesis involves multiple genes, including genes in addition to those listed.

Additional properties, such as acid tolerance and adherence, are necessary for full pathogenicity among STEC strains. Most disease-causing isolates possess the chromosomal locus for enterocyte effacement (LEE). This pathogenicity island was first described in EPEC strains and contains genes that mediate adherence to intestinal epithelial cells. EHEC strains make up the subgroup of STEC strains that possess stx_1 and/or stx_2 as well as LEE.

Domesticated ruminant animals, particularly cattle and young calves, serve as the major reservoir for STEC/EHEC. Ground beef—the most common food source of STEC/EHEC strains—is often contaminated during processing. Furthermore, manure from cattle or other animals (including that in the form of fertilizer) can contaminate produce (potatoes, lettuce, spinach, sprouts, fallen apples), and fecal runoff from this source can contaminate water systems. Petting zoos are another source of infection. It is estimated that $<10^2$ CFU of STEC/EHEC can cause disease. Therefore, not only can low levels of food or environmental contamination (e.g., in water swallowed while swimming) result in disease, but person-to-person transmission (e.g., at day-care centers and in institutions) is an important route for secondary spread. Laboratory-associated infections also take place. Illness due to this group of pathogens occurs both as outbreaks and as sporadic cases, with a peak incidence in the summer months.

In contrast to other intestinal pathotypes, STEC/EHEC causes infections more frequently in industrialized countries than in developing regions. O157:H7 strains are the fourth most commonly reported cause of bacterial diarrhea in the United States (after *Campylobacter*, *Salmonella*, and *Shigella*). Colonization of the colon and perhaps the ileum results in symptoms after an incubation period of 3 or 4 days. Colonic edema and an initial nonbloody secretory diarrhea may develop into the STEC/EHEC hallmark syndrome of grossly bloody diarrhea (as detected by history or examination) in >90% of cases. Significant abdominal pain and fecal leukocytes are common (70% of cases), whereas fever is not; absence of fever can incorrectly lead to consideration of noninfectious conditions (e.g., intussusception and inflammatory or ischemic bowel disease). Occasionally, infections caused by *C. difficile*, *K. oxytoca* (see "*Klebsiella* Infections," later in the chapter), *Campylobacter*, and *Salmonella* present in a similar fashion. STEC/EHEC disease is usually self-limited, lasting 5–10 days. An uncommon but feared complication of this infection is HUS, which occurs 2–14 days after diarrhea in 2–8% of cases, most often affecting very young or elderly patients. It is estimated that >50% of all cases of HUS in the United States and 90% of HUS cases in children are caused by STEC/EHEC. This complication is probably mediated by the systemic translocation of Shiga toxins. Erythrocytes may serve as carriers of Stx to endothelial cells located in the small vessels of the kidney and brain. The subsequent development of thrombotic microangiopathy (perhaps with direct toxin-mediated effects on various non-endothelial cells) commonly produces some combination of fever, thrombocytopenia, renal failure, and encephalopathy. Although the mortality rate with dialysis support is <10%, residual renal and neurologic dysfunction may persist.

Enterotoxigenic E. coli

In tropical or developing countries, ETEC is a major cause of endemic diarrhea. After weaning, children in these locales commonly experience several episodes of ETEC infection during the first 3 years of life. The incidence of disease diminishes with age, a pattern that correlates with the development of mucosal immunity to colonization factors (i.e., adhesins). In industrialized countries, infection usually follows travel to endemic areas, although occasional foodborne outbreaks occur. ETEC is the most common agent of traveler's diarrhea, causing 25–75% of cases. The incidence of infection may be decreased by prudent avoidance of potentially contaminated fluids and foods (Chap. 5). ETEC infection is uncommon in the United States, but outbreaks secondary to consumption of food products imported from endemic areas have occurred. A large inoculum (10^6–10^{10} CFU) is needed to produce disease. After ingestion of contaminated water or food (particularly items that are poorly cooked, unpeeled, or unrefrigerated), colonization factor–mediated intestinal adherence occurs over 12–72 h.

Disease is mediated primarily by a heat-labile toxin (LT-1) and/or a heat-stable toxin (STa) that causes net fluid secretion via activation of adenylate cyclase (LT-1) and/or guanylate cyclase (STa) in the jejunum and ileum. The result is watery diarrhea accompanied by cramps. LT-1 consists of an A and a B subunit and is structurally and functionally similar to cholera toxin. Strong binding of the B subunit to the GM_1 ganglioside on intestinal epithelial cells leads to the intracellular translocation of the A subunit, which functions as an ADP-ribosyltransferase. Mature STa is an 18- or 19-amino-acid secreted peptide whose biologic activity is mediated by binding to the guanylate cyclase C found in the brush-border membrane of enterocytes; this binding results in increased intracellular concentrations of cyclic GMP. Characteristically absent in ETEC-mediated disease are histopathologic changes within the small bowel; mucus, blood, and inflammatory cells in stool; and fever. The disease spectrum ranges from a mild illness to a life-threatening cholera-like syndrome. Although symptoms are usually self-limited (typically lasting for 3 days), infection may result in significant morbidity and mortality (mostly from profound volume depletion) when access to health care or suitable rehydration fluids is limited and when small and/or undernourished children are affected.

Enteropathogenic E. coli

EPEC causes disease primarily in young children, including neonates. The first *E. coli* pathotype recognized as an agent of diarrheal disease, EPEC was responsible for outbreaks of infantile diarrhea

(including some outbreaks in hospital nurseries) in industrialized countries in the 1940s and 1950s. At present, EPEC infection is an uncommon cause of diarrhea in developed countries, but is an important cause of diarrhea (both sporadic and epidemic) among infants in developing countries. Breast-feeding diminishes the incidence of EPEC infection. Rapid person-to-person spread may occur. Upon colonization of the small bowel, symptoms develop after a brief incubation period (1 or 2 days). Initial localized adherence leads to a characteristic effacement of microvilli, with the formation of cuplike, actin-rich pedestals. The actual mechanisms of diarrhea production are an area of ongoing investigation. Diarrheal stool often contains mucus but not blood. Although usually self-limited (lasting 5–15 days), EPEC diarrhea may persist for weeks.

Enteroinvasive E. coli

EIEC, a relatively uncommon cause of diarrhea, is rarely identified in the United States, although a few food-related outbreaks have been described. In developing countries, sporadic disease is infrequently recognized in children and travelers. EIEC shares many genetic and clinical features with *Shigella*; however, unlike *Shigella*, EIEC produces disease only at a large inoculum (10^8–10^{10} CFU), with onset generally following an incubation period of 1–3 days. Initially, enterotoxins are believed to induce secretory small-bowel diarrhea. Subsequently, colonization and invasion of the colonic mucosa, followed by replication therein and cell-to-cell spread, result in the development of inflammatory colitis characterized by fever, abdominal pain, tenesmus, and scant stool containing mucus, blood, and inflammatory cells. Symptoms are usually self-limited (7–10 days).

Enteroaggregative and diffusely adherent E. coli

EAEC has been described primarily in developing countries and in young children. However, recent studies indicate that it may be a relatively common cause of diarrhea in all age groups in industrialized countries. EAEC has also been recognized increasingly as an important cause of traveler's diarrhea. A large inoculum is required for infection, which manifests as watery and sometimes persistent diarrhea in both healthy and HIV-infected hosts. In vitro, the organisms exhibit a diffuse or "stacked-brick" pattern of adherence to epithelial cells. Virulence factors that probably are necessary for disease are regulated in part by the transcriptional activator AggR and include the aggregative adherence fimbriae (AAF/I-III); the Hda adhesin; surface protein dispersion; and the enterotoxins Pet, EAST-1, ShET1, and ShET2. Some strains of DAEC are capable of causing diarrheal disease, primarily in children 2–6 years of age in some developing countries, and may perhaps cause traveler's diarrhea. The Afa/Dr adhesins may contribute to the pathogenesis of infection.

Diagnosis

A practical approach to the evaluation of diarrhea is to distinguish noninflammatory from inflammatory cases (Chap. 26). ETEC, EPEC, and DAEC are uncommon causes of noninflammatory diarrhea in the United States; the incidence of EAEC infection in this country may be underrecognized. The diagnosis of these infections requires specialized assays (e.g., PCR-based tests for pathotype-specific genes) that are not routinely available and are rarely needed since the diseases are self-limited. ETEC causes the majority and EAEC a minority of cases of noninflammatory traveler's diarrhea. Definitive diagnosis generally is not necessary. Empirical antimicrobial (or symptom-based) treatment, along with rehydration therapy, is a reasonable approach. If diarrhea persists despite treatment, *Giardia* or *Cryptosporidium* (or, in immunocompromised hosts, certain other microbial agents) should be sought. The diagnosis of infection with EIEC, a rare cause of inflammatory diarrhea in the United States, also requires specialized assays. However, evaluation for STEC/EHEC infection, particularly when bloody diarrhea is reported or observed, is appropriate. Although the most common method currently used to detect STEC/EHEC is to screen for *E. coli* strains that do not ferment sorbitol, with subsequent serotyping for O157, testing for Shiga toxins or toxin genes is more sensitive, specific, and rapid. The latter approach offers the added advantage of detecting both non-O157 STEC/EHEC strains and sorbitol-fermenting strains of O157:H7, which otherwise are difficult to identify. DNA-based, enzyme-linked immunosorbent, and cytotoxicity assays are in various stages of development and are emerging as the diagnostic methods of choice.

TREATMENT **Intestinal *E. coli* Infections**

(See also Chap. 26) The mainstay of treatment for all diarrheal syndromes is replacement of water and electrolytes. The use of prophylactic antibiotics to prevent traveler's diarrhea generally should be discouraged, especially in light of high rates of antimicrobial resistance. However, in selected patients (e.g., those who cannot afford a brief illness or have an increased susceptibility to infection), the use of rifaximin, which is nonabsorbable and is well tolerated, is reasonable. When stools are free of mucus and blood, early patient-initiated treatment of traveler's diarrhea with a fluoroquinolone or azithromycin decreases the duration of illness, and the use of loperamide may halt symptoms within a few hours. Although dysentery caused by EIEC is self-limited, treatment hastens the resolution of symptoms, particularly in severe cases. In contrast, antimicrobial therapy for STEC/EHEC infection (the presence of which is suggested by grossly bloody diarrhea without fever) should be avoided, since antibiotics may increase the incidence of HUS (possibly via increased production/release of Stx).

KLEBSIELLA INFECTIONS

K. pneumoniae is the most important *Klebsiella* species from a medical standpoint, causing community-acquired, LTCF-acquired, and nosocomial infections. *K. oxytoca* is primarily a pathogen in LTCF and hospital settings. *Klebsiella* species are broadly prevalent in the environment and colonize mucosal surfaces of mammals. In healthy humans, the prevalence of *K. pneumoniae* colonization is 5–35% in the colon and 1–5% in the oropharynx; the skin is usually colonized only transiently. In LTCFs and hospitals, colonization with *K. oxytoca* also occurs, and carriage rates are substantial among both staff and patients. Person-to-person spread is the predominant mode of acquisition. Most *Klebsiella* infections due to "classic" *K. pneumoniae* (cKP) now occur in hospitals and LTCFs. The most common clinical syndromes due to cKP are pneumonia, UTI, abdominal infection, intravascular device infection, surgical site infection, soft tissue infection, and subsequent bacteremia. A critical feature of cKP as a successful health care–associated pathogen has been its evolution into an MDR gram-negative bacillus. MDR strains of cKP have caused a number of nosocomial infection outbreaks in ICUs and neonatal nurseries. Historically, cKP caused severe community-acquired pneumonia, primarily in alcoholics; this syndrome is still observed with some frequency in Africa and Asia, but has become increasingly uncommon in the United States and Europe. cKP strains appear to be genomically distinct from hypervirulent *K. pneumoniae* (hvKP), an emerging pathogen that has been recognized increasingly over the past two decades (see "Abdominal Infection," later in the chapter); it is possible, however, that cKP and hvKP strains have virulence factors in common. *K. pneumoniae* subspecies *rhinoscleromatis* is the causative agent of rhinoscleroma, a granulomatous mucosal upper respiratory infection that progresses slowly (over months or years) and causes necrosis and occasionally obstruction of the nasal passages. *K. pneumoniae* subspecies *ozaenae* has been implicated as a cause of chronic atrophic rhinitis and rarely of invasive disease in compromised hosts. These two *K. pneumoniae* subspecies are usually isolated from patients in tropical climates and are genomically distinct from both cKP and hvKP.

INFECTIOUS SYNDROMES

Pneumonia

K. pneumoniae accounts for only a small proportion of cases of CAP (Chap. 18); however, CAP due to *K. pneumoniae* is more common in Africa and Asia than in Europe and the United States. This infection occurs primarily in hosts with underlying conditions (e.g., alcoholism, diabetes, or chronic lung disease). Pulmonary infection is especially common among residents of LTCFs and hospitalized patients because of increased rates of oropharyngeal colonization. Mechanical ventilation is an important risk factor. As in all pneumonias due to enteric GNB, production of purulent sputum and evidence of airspace disease are typical. Presentation with earlier, less extensive infection is more common than the classically described lobar infiltrate with a bulging fissure. Pulmonary necrosis, pleural effusion, and empyema can occur with disease progression.

UTI

K. pneumoniae accounts for only 1–2% of UTI episodes among otherwise healthy adults but for 5–17% of episodes of complicated UTI, including infections associated with indwelling urinary catheters.

Abdominal infection

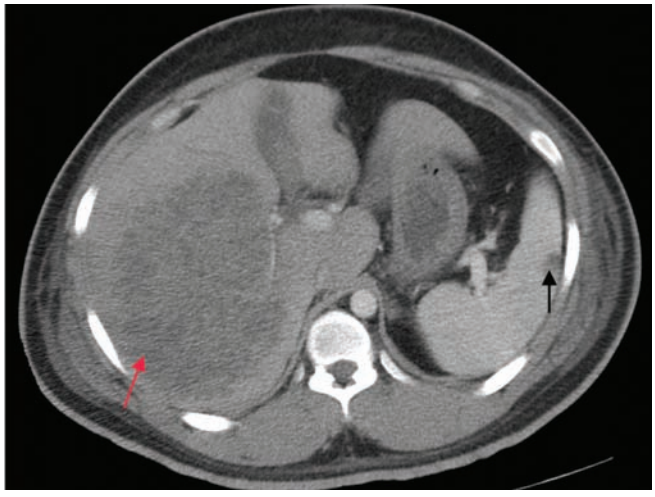
Klebsiella causes a spectrum of abdominal infections similar to that caused by *E. coli* but is less frequently isolated from these infections. The new hypervirulent variant of *K. pneumoniae* (hvKP) that has emerged over the past decade was initially reported from the Pacific Rim, but was later described in the United States, Canada, Europe, and elsewhere. At first, hvKP infection was characterized and distinguished from traditional infections due to cKP by (1) presentation as community-acquired hepatic abscess, (2) occurrence in patients lacking a history of hepatobiliary disease, and (3) a propensity for metastatic spread to distant sites (e.g., eyes, central nervous system, lungs) in 11–80% of cases **(Fig. 54-1, left)**. More recently, this variant has been identified as the cause of a variety of serious extrahepatic abscesses/infections as well. The affected individuals often have diabetes mellitus and are of Asian extraction; however, nondiabetics and all ethnic groups can be affected. Not uncommonly, hosts are young and healthy. Survivors with metastatic spread often suffer catastrophic morbidity, such as loss of vision and neurologic sequelae.

Other infections

Klebsiella cellulitis or soft tissue infection most frequently affects devitalized tissue (e.g., decubitus and diabetic ulcers, burn sites) and immunocompromised hosts. *Klebsiella* causes some cases of surgical site infection, hematogenously derived endophthalmitis (especially in association with hepatic abscess), and nosocomial sinusitis in addition to occasional cases of osteomyelitis contiguous to soft tissue infection, nontropical myositis, and meningitis (both during the neonatal period and after neurosurgery). Cytotoxin-producing strains of *K. oxytoca* have been implicated as a cause of hemorrhagic (but *not* nonhemorrhagic) antibiotic-associated non–*C. difficile* colitis.

Bacteremia

Klebsiella infection at any site can produce bacteremia. Infections of the urinary tract, respiratory tract, and abdomen (especially hepatic abscess) each account for 15–30% of episodes of *Klebsiella* bacteremia. Intravascular device–related infections account for another 5–15%



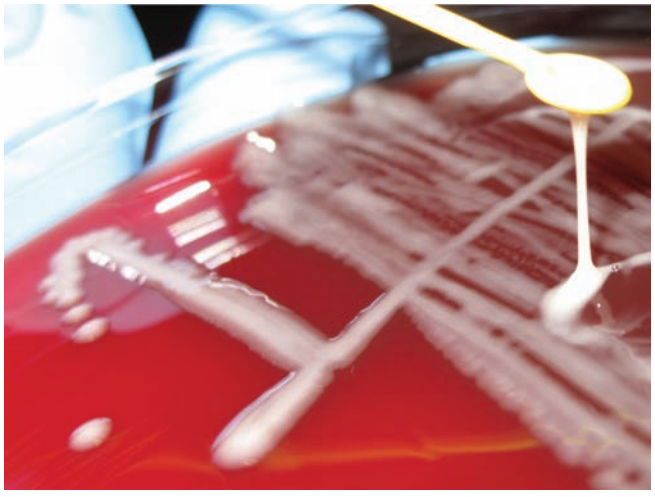


FIGURE 54-1
New hypervirulent variant of *K. pneumoniae* (hvKP). *Left*: An image from an abdominal CT scan of a previously healthy 24-year-old Vietnamese man shows a primary liver abscess (*red arrow*) with metastatic spread to the spleen (*black arrow*). *(Courtesy of Drs. Chiu-Bin Hsaio and Diana Pomakova.) Right*: A culture of the responsible hvKP strain was grown from the patient's blood and the abscess. A hypermucoviscous phenotype has been associated with hvKP strains that cause community-acquired primary liver abscess. This phenotype has been semiquantitatively defined by a positive "string test" (formation of a viscous string >5 mm long when bacterial colonies on an agar plate are stretched by an inoculation loop).

of episodes, and surgical site and miscellaneous infections account for the rest. *Klebsiella* is a cause of sepsis in neonates and of bacteremia in neutropenic patients. Like enteric GNB in general, *Klebsiella* rarely causes endocarditis or endovascular infection.

DIAGNOSIS

Klebsiellae are readily isolated and identified in the laboratory. These organisms usually ferment lactose, although the subspecies *rhinoscleromatis* and *ozaenae* are nonfermenters and are indole negative. The new hypervirulent clinical variant most commonly is capsular serotype K1 or K2 and possesses a hypermucoviscous phenotype (Fig. 54-1, right).

TREATMENT *Klebsiella* Infections

K. pneumoniae and *K. oxytoca* have largely similar antibiotic resistance profiles. These species are intrinsically resistant to ampicillin and ticarcillin, and nitrofurantoin is only poorly active against them. Data from the NHSN indicated that 24% of *K. pneumoniae* device-associated infections were due to strains resistant to cephalosporins III in 2006–2007. Even higher rates have been reported outside North America, with 68% of isolates from the INICC resistant in 2002–2007. This increasing resistance is mediated primarily by plasmid-encoded ESBLs. In addition, such plasmids usually encode resistance to aminoglycosides, tetracyclines, and TMP-SMX. Furthermore, isolates of *K. pneumoniae* that contain CTX-M ESBLs have been obtained from ambulatory patients with no recent health care contact (see *E. coli* for treatment options). Resistance to β-lactam/β-lactamase inhibitor combinations and cephamycins independent of ESBL-encoding plasmids has also been described with increasing frequency, particularly in Latin America. The prevalence of fluoroquinolone resistance is 15–20% overall and is 50% among ESBL-containing strains. Given both the undesirability of treating the latter strains with penicillins or cephalosporins and the fluoroquinolone resistance often associated with ESBLs, empirical treatment of serious or health care–associated *Klebsiella* infections with amikacin or carbapenems is prudent. Predictably, however, the ESBL-driven use of carba-penems has selected for strains of *Klebsiella* that possess carba-penemases, which confer resistance to the substrates of ESBLs as well as to cephamycins and carbapenems. In the United States, some strains of *Klebsiella* possess KPC-family carbapenemases on transferable plasmids and also exhibit resistance to fluoroquinolones and aminoglycosides. Treatment of infections due to strains that possess carbapenemases is highly challenging, and these strains are increasingly nearly panresistant. The optimal choice for therapy is unclear. Tigecycline, polymyxin B, and polymyxin E (colistin) are the most active agents in vitro and are used most frequently. However, resistance to these agents is already emerging, and strains of *Klebsiella* resistant to all known antimicrobial agents have been described in the United States and globally. At present, there are no treatment options for these strains. In treating isolates that are more "antimicrobial friendly," it is critical to use the most appropriate narrower-spectrum agent whenever possible.

PROTEUS INFECTIONS

P. mirabilis causes 90% of *Proteus* infections, which occur in the community, LTCFs, and hospitals. *P. vulgaris* and *P. penneri* are associated primarily with infections acquired in LTCFs or hospitals. *Proteus* species are part of the colonic flora of a wide variety of mammals, birds, fish, and reptiles. The ability of these GNB to generate histamine from contaminated fish has implicated them in the pathogenesis of scombroid (fish) poisoning (Chap. 131). *P. mirabilis* colonizes healthy humans (prevalence, 50%), whereas *P. vulgaris* and *P. penneri* are isolated primarily from individuals with underlying disease. The urinary tract is by far the most common site of *Proteus* infection, with adhesins, flagella, IgA protease, and urease representing the principal known urovirulence factors. *Proteus* less commonly causes infection at a variety of other extraintestinal sites.

INFECTIOUS SYNDROMES

UTI

Most *Proteus* infections arise from the urinary tract. *P. mirabilis* causes only 1–2% of cases of UTI in healthy women, and *Proteus* species collectively cause only 5% of cases of hospital-acquired UTI. However, *Proteus* is responsible for 10–15% of cases of complicated UTI, primarily those associated with catheterization; indeed, among UTI isolates from chronically catheterized patients, the prevalence of *Proteus* is 20–45%. This high prevalence is due in part to bacterial production of urease, which hydrolyzes urea to ammonia and results in alkalization of the urine. Alkalization of urine, in turn, leads to precipitation of organic and inorganic compounds, which contributes to formation of struvite and carbonate-apatite crystals, formation of biofilms on catheters, and/or development of frank calculi. *Proteus* becomes associated with the stones and biofilms; thereafter, it usually can be eradicated only by removal of the stones or the catheter. Over time, staghorn calculi may form within the renal pelvis and lead to obstruction and renal failure. Thus, urine samples with unexplained alkalinity should be cultured for *Proteus*, and identification of a *Proteus* species in urine should prompt consideration of an evaluation for urolithiasis.

Other infections

Proteus occasionally causes pneumonia (primarily in LTCF residents or hospitalized patients), nosocomial sinusitis, intraabdominal abscesses, biliary tract infection, surgical site infection, soft tissue infection (especially decubitus and diabetic ulcers), and osteomyelitis (primarily contiguous); in rare cases, it causes nontropical myositis. In addition, *Proteus* uncommonly causes neonatal meningitis, with the umbilicus commonly implicated as the source; this disease is often complicated by development of a cerebral abscess. Otogenic brain abscess also occurs.

Bacteremia

The majority of *Proteus* bacteremia episodes originate from the urinary tract; however, any of the less common sites of infection as well as intravascular devices are also potential sources. Endovascular infection is rare. *Proteus* species are occasional agents of sepsis in neonates and of bacteremia in neutropenic patients.

DIAGNOSIS

Proteus is readily isolated and identified in the laboratory. Most strains are lactose negative, produce H_2S, and demonstrate characteristic swarming motility on agar plates. *P. mirabilis* is indole negative, whereas *P. vulgaris* and *P. penneri* are indole positive.

TREATMENT ***Proteus*** **Infections**

P. mirabilis is usually susceptible to most antimicrobial agents except tetracycline, nitrofurantoin, polymyxin B, and tigecycline. Resistance to ampicillin and cephalosporins I has been acquired by 10–50% of strains. Overall, 10–15% of *P. mirabilis* isolates are resistant to fluoroquinolones; 5% of isolates in the United States now produce ESBLs. Furthermore, isolates of *P. mirabilis* that contain CTX-M ESBLs have been obtained from ambulatory patients with no recent health care contact (see *E. coli* section for treatment options). *P. vulgaris* and *P. penneri* exhibit more extensive drug resistance than does *P. mirabilis*. Resistance to ampicillin and cephalosporins I is the rule, and 30–40% of isolates are resistant to fluoroquinolones. Derepression of an inducible chromosomal mpC β-lactamase (not present in *P. mirabilis*) occurs in up to 30% of *P. vulgaris* isolates. Imipenem, cephalosporins IV (e.g., cefepime), amikacin, and TMP-SMX display excellent activity against *Proteus* species (90–100% of isolates susceptible).

ENTEROBACTER INFECTIONS

E. cloacae and *E. aerogenes* are responsible for most *Enterobacter* infections (65–75% and 15–25%, respectively); *E. sakazakii* (recently renamed *Cronobacter sakazakii*) and *E. gergoviae* are less commonly isolated (1% and <1% of *Enterobacter* isolates, respectively). *Enterobacter* species cause primarily hospital-acquired and other health care–related infections. The organisms are widely prevalent in foods, environmental sources (including equipment at health care facilities), and a variety of animals. Few healthy humans are colonized, but the percentage increases significantly with LTCF residence or hospitalization. Although colonization is an important prelude to infection, direct introduction via IV lines (e.g., contaminated IV fluids or pressure monitors) also occurs. Extensive antibiotic resistance has developed in *Enterobacter* species and probably has contributed to the emergence of the

organisms as prominent nosocomial pathogens. Individuals who have previously received antibiotic treatment, have comorbid disease, and are being treated in ICUs are at greatest risk for infection. *Enterobacter* causes a spectrum of extraintestinal infections similar to that described for other GNB.

INFECTIOUS SYNDROMES

Pneumonia, UTI (particularly catheter-related), intravascular device–related infection, surgical site infection, and abdominal infection (primarily postoperative or related to devices such as biliary stents) are the most common syndromes encountered. Nosocomial sinusitis, meningitis related to neurosurgical procedures (including use of intracranial pressure monitors), osteomyelitis, and endophthalmitis after eye surgery are less frequent. *E.* (*C.*) *sakazakii* is associated with neonatal meningitis/sepsis (particularly in premature infants); contaminated formula has been implicated as a source of this infection, which is often complicated by brain abscess or ventriculitis. Bacteremia can result from infection at any anatomic site. In *Enterobacter* bacteremia of unclear origin, the contamination of IV fluids or medications, blood components or plasma derivatives, catheter-flushing fluids, pressure monitors, and dialysis equipment should be considered, particularly in an outbreak setting. *Enterobacter* can also cause bacteremia in neutropenic patients. *Enterobacter* endocarditis is rare, occurring primarily in association with illicit IV drug use or prosthetic valves.

DIAGNOSIS

Enterobacter is readily isolated and identified in the laboratory. Most strains are lactose positive and indole negative.

TREATMENT *Enterobacter* Infections

Significant antimicrobial resistance exists among *Enterobacter* strains. Ampicillin and cephalosporins I and II have little or no activity. The extensive use of cephalosporins III has resulted in the selection of strains that are derepressed for production of AmpC β-lactamase, which confers resistance to cephalosporins III, monobactams (e.g., aztreonam), and—in many cases—β-lactam/β-lactamase inhibitor combinations. Resistance may emerge during therapy; in one study, emergence of resistance was documented in 20% of patients. De novo resistance should be considered when clinical deterioration follows initial improvement, and cephalosporins III should be avoided in the treatment of serious *Enterobacter* infections. National Nosocomial Infections Surveillance System data for 2003 identified resistance to cephalosporins III in 31% of ICU isolates, and INICC data for 2002–2007 reported such resistance in 57% of isolates. Cefepime is stable in the presence of AmpC β-lactamases; thus, it is a suitable option for treatment of *Enterobacter* infections so long as no coexistent ESBL is present. However, the prevalence of ESBL production in *Enterobacter* species (particularly *E. cloacae*) has been increasing and is now 5–30%. Such strains, which are also resistant to cefepime, can be challenging to treat. Fortunately, in the United States, carbapenems, amikacin, and fluoroquinolones have generally retained excellent activity (90–99% of isolates susceptible). Although clinical experience is limited, tigecycline is highly active in vitro. Once again, it is critical to use the most appropriate narrower-spectrum agent whenever possible.

SERRATIA INFECTIONS

S. marcescens causes the majority (>90%) of *Serratia* infections; *S. liquefaciens, S. rubidaea, S. fonticola,* and *S. odorifera* are isolated occasionally. Serratiae are found primarily in the environment (including in health care institutions), particularly in moist settings. Although serratiae have been isolated from a variety of animals, healthy humans are rarely colonized. In LTCFs or hospitals, reservoirs for the organisms include the hands and fingernails of health care personnel, food, milk (on neonatal units), sinks, respiratory equipment, pressure monitors, IV solutions or parenteral medications (particularly those generated by compounding pharmacies), multiply accessed medication vials, blood products (e.g., platelets), hand soaps and lotions, irrigation solutions, and even disinfectants. Infection results from either direct inoculation (e.g., via IV fluid) or colonization (primarily of the respiratory tract) and subsequent infection. Sporadic infection is most common, but epidemics (often involving MDR strains in adult and neonatal ICUs) and common-source outbreaks occasionally occur. The spectrum of extraintestinal infections caused by *Serratia* is similar to that for other GNB. *Serratia* species are usually considered as causative agents of health care–associated infection and account for 1–3% of hospital-acquired infections. However, population-based laboratory surveillance studies in Canada and Australia demonstrated that community-acquired infections occur more commonly than was previously appreciated.

INFECTIOUS SYNDROMES

The respiratory tract, the genitourinary tract, intravascular devices, and surgical wounds are the most common sites of *Serratia* infection and sources of *Serratia* bacteremia. Soft tissue infections (including myositis), osteomyelitis, abdominal and biliary tract infection (postprocedural), contact lens–associated keratitis, endophthalmitis, septic arthritis (primarily from intraarticular injections), and infusion-related bacteremias occur less commonly. Serratiae are uncommon causes of neonatal or postsurgical meningitis and of bacteremia in neutropenic patients. Endocarditis is rare.

DIAGNOSIS

Serratiae are readily cultured and identified by the laboratory and are usually lactose and indole negative. Some *S. marcescens* strains and *S. rubidaea* are red-pigmented.

TREATMENT *Serratia* Infections

Most *Serratia* strains (>80%) are resistant to ampicillin, cephalosporins I, nitrofurantoin, and polymyxin B. In general, >90% of *Serratia* isolates are susceptible to other antibiotics appropriate for use against GNB. Stable derepression of inducible chromosomal AmpC β-lactamases may be preexistent or may develop during therapy. Both in the United States and globally, the prevalence of ESBL-producing isolates is <5%.

CITROBACTER INFECTIONS

C. freundii and *C. koseri* cause most human *Citrobacter* infections, which are epidemiologically and clinically similar to *Enterobacter* infections. *Citrobacter* species are commonly present in water, food, soil, and certain animals. *Citrobacter* is part of the normal fecal flora in a minority of healthy humans, but colonization rates increase in LTCFs and hospitals—the settings in which nearly all *Citrobacter* infections occur. *Citrobacter* species account for 1–2% of nosocomial infections. The affected hosts are usually immunocompromised or have comorbid disease. *Citrobacter* causes extraintestinal infections similar to those described for other GNB.

INFECTIOUS SYNDROMES

The urinary tract accounts for 40–50% of *Citrobacter* infections. Less commonly involved sites include the biliary tree (particularly with stones or obstruction), the respiratory tract, surgical sites, soft tissue (e.g., decubitus ulcers), the peritoneum, and intravascular devices. Osteomyelitis (usually from a contiguous focus), neurosurgery-related infection, and myositis occur rarely. *Citrobacter* (particularly *C. koseri*) also uncommonly causes neonatal meningitis, with brain abscess complicating 50–80% of cases. Bacteremia is most often due to UTI, biliary or abdominal infection, or intravascular device infection. *Citrobacter* occasionally causes bacteremia in neutropenic patients. Endocarditis and endovascular infections are rare.

DIAGNOSIS

Citrobacter species are readily isolated and identified; 35–50% of isolates are lactose positive, and 100% are oxidase negative. *C. freundii* is indole negative, whereas *C. koseri* is indole positive.

TREATMENT *Citrobacter* Infections

C. freundii is more extensively resistant to antibiotics than is *C. koseri*. Ampicillin and the cephalosporins I and II display poor activity. *Citrobacter* species possess inducible AmpC β-lactamases; stable derepression may be preexistent or may develop during therapy. Resistance to antipseudomonal penicillins, aztreonam, fluoroquinolones, gentamicin, and cephalosporins III is variable but increasing. The prevalence of ESBL-producing isolates is <5%. Carbapenems, amikacin, cefepime, tigecycline (with which there is limited clinical experience), ceftobiprole (FDA approval pending), fosfomycin (available in the United States only as an oral formulation), and polymyxins (the agents of last resort because of potential toxicities) are most active, with >90% of strains susceptible.

MORGANELLA AND *PROVIDENCIA* INFECTIONS

M. morganii, *P. stuartii*, and (less frequently) *P. rettgeri* are the members of their respective genera that cause human infections. In terms of epidemiologic associations, pathogenic properties, and clinical manifestations, these organisms are largely similar to *Proteus* species; however, *Morganella* and *Providencia* occur more commonly among LTCF residents; to a lesser degree, they affect hospitalized patients.

INFECTIOUS SYNDROMES

These species are primarily urinary tract pathogens, causing UTIs that are most often associated with long-term (>30-day) catheterization. Such infections commonly lead to biofilm formation and catheter encrustation (sometimes causing catheter obstruction) or the development of struvite bladder or renal stones (sometimes causing renal obstruction and serving as foci for relapse). Other, less common infectious syndromes include surgical site infection, soft tissue infection (primarily involving decubitus and diabetic ulcers), burn site infection, pneumonia (particularly ventilator-associated), intravascular device infection, and intraabdominal infection. Rarely, the other extraintestinal infections described for GNB also occur. Bacteremia is uncommon; although any infected site can serve as the source, the urinary tract accounts for most cases, and the next most common sources are surgical, soft tissue, and hepatobiliary sites.

DIAGNOSIS

M. morganii and *Providencia* are readily isolated and identified. Nearly all isolates are lactose negative and indole positive.

TREATMENT *Morganella* and *Providencia* Infections

Morganella and *Providencia* may be extensively resistant to antibiotics. Most isolates are resistant to ampicillin, cephalosporins I, nitrofurantoin, fosfomycin, tigecycline, and polymyxin B; 40% are resistant to quinolones. *Morganella* and *Providencia* possess inducible AmpC β-lactamases; stable derepression may be preexistent or may develop during therapy. Resistance to antipseudomonal penicillins, aztreonam, gentamicin, TMP-SMX, and cephalosporins II and III is emerging but still variably prevalent. The β-lactamase inhibitor tazobactam increases susceptibility to β-lactam agents, but sulbactam and clavulanic acid do not. Imipenem, amikacin, and cefepime are the most active agents (>90% of isolates susceptible). Removal of a colonized catheter or stone is critical for eradication of UTI.

EDWARDSIELLA INFECTIONS

E. tarda is the only member of the genus *Edwardsiella* that is associated with human disease. This organism is found predominantly in freshwater and marine environments and the associated animal species. Human acquisition occurs primarily during interaction with these reservoirs. *E. tarda* infection is rare in the United States; recently reported cases are mostly from Southeast Asia. This pathogen shares clinical features with both *Salmonella* species (as a diarrheal pathogen; Chap. 58) and *Vibrio vulnificus* (as an extraintestinal pathogen; Chap. 61).

INFECTIOUS SYNDROMES

Gastroenteritis is the predominant infectious syndrome (50–80% of infections). Self-limiting watery diarrhea is most common, but severe colitis also occurs. The most common extraintestinal infection is wound infection due to direct inoculation, which is often associated with freshwater-, marine-, or snake-related injuries. Other infectious syndromes result from invasion of the gastrointestinal tract and subsequent bacteremia. Most afflicted hosts have comorbidities (e.g., hepatobiliary disease, iron overload, cancer, or diabetes mellitus). A primary bacteremic syndrome, sometimes complicated by meningitis, has a 40% case-fatality rate. Visceral (primarily hepatic) and intraperitoneal abscesses also occur.

DIAGNOSIS

Although *E. tarda* can readily be isolated and identified, most laboratories do not routinely seek to identify it in stool samples. Production of hydrogen sulfide is a characteristic biochemical property.

TREATMENT *Edwardsiella* Infections

E. tarda is susceptible to most antimicrobial agents appropriate for use against GNB. Gastroenteritis is generally self-limiting, but treatment with a fluoroquinolone may hasten resolution. In the setting of severe sepsis, fluoroquinolones, cephalosporins III and IV, carbapenems, and amikacin—either alone or in combination—are the safest choices pending susceptibility information.

INFECTIONS CAUSED BY MISCELLANEOUS GENERA

Species of *Hafnia*, *Kluyvera*, *Cedecea*, *Pantoea*, *Ewingella*, *Leclercia*, and *Photorhabdus* are occasionally isolated from diverse clinical specimens, including blood, sputum, cerebrospinal fluid, joint fluid, bile, and wounds. These organisms are rare and usually cause infection in a compromised host or in the setting of an invasive procedure or a foreign body.

CHAPTER 55

ACINETOBACTER INFECTIONS

David L. Paterson ■ Anton Y. Peleg

Infections with bacteria of the genus *Acinetobacter* have become a significant problem worldwide. *Acinetobacter baumannii* is particularly formidable because of its propensity to acquire antibiotic resistance determinants. Outbreaks of infection caused by strains of *A. baumannii* resistant to multiple antibiotic classes, including carbapenems, are a serious concern in many specialized hospital units, including intensive care units (ICUs). The foremost implication of infection with carbapenem-resistant *A. baumannii* is the need to use "last-line" antibiotics such as colistin, polymyxin B, or tigecycline; these options have the potential to render these bacteria resistant to all available antibiotics.

DEFINITION

Acinetobacter species are oxidase-negative, nonmotile, nonfermenting, short gram-negative bacilli that grow well at 37° C in aerobic conditions on a range of laboratory media (e.g., blood agar). Some species may not grow on MacConkey agar. Differentiation of *Acinetobacter* species is difficult with the means typically available to most clinical microbiology laboratories, including commercial semiautomated identification systems. DNA-DNA hybridization is a method used for speciation in reference laboratories. Identification of the most clinically relevant species, *A. baumannii*, by detection of the bla_{OXA-51}-like carbapenemase gene intrinsic to this species has been described.

ETIOLOGY

Widely distributed in nature, *Acinetobacter* species can be found in water, in soil, and on vegetables. *Acinetobacter* is a component of the human skin flora and is sometimes identified as a contaminant in blood samples collected for culture. Fecal carriage can be detected in both healthy and hospitalized individuals. Despite the ubiquity of some *Acinetobacter* species, the natural habitat of *A. baumannii* remains to be fully defined.

EPIDEMIOLOGY

A. baumannii infections have been diagnosed in patients on all inhabited continents. The vast majority of infections occur in hospitalized patients and other patients with significant health care contact. Outbreaks of carbapenem-resistant *A. baumannii* are particularly problematic. A significant issue is the introduction of carbapenem-resistant *A. baumannii* into hospitals as a result of medical transfers, especially from hospitals where the organism is highly endemic.

The Americas

In 1991 and 1992, outbreaks of carbapenem-resistant *A. baumannii* infection occurred in a hospital in New York City. Subsequently, numerous other hospitals in the United States and South America have had outbreaks of carbapenem-resistant *A. baumannii*. The incidence of infections with *A. baumannii* among military personnel from the United States and Canada has increased since 2002; 102 patients had bloodstream infections at facilities treating U.S. military personnel injured in Iraq or Afghanistan from January 1, 2002, through August 31, 2004. An epidemiologic investigation revealed that *A. baumannii* could be grown from environmental sites in field hospitals and that the environmental strains were closely related genotypically to clinical isolates. *A. baumannii* strains from injured military personnel from the United States and the United Kingdom were also genotypically related; this finding provided further evidence that *A. baumannii* was being acquired in field hospitals.

Europe

A. baumannii infections have posed a substantial clinical challenge in many parts of Europe since the early 1980s. Three clones (European clones I, II, and III) have been the predominant causes of *A. baumannii* infection in hospitals in Europe. Carbapenem resistance in *A. baumannii* is a significant issue in many European

countries, most notably the United Kingdom, Greece, Italy, Spain, and Turkey.

Asia, Australia, the Middle East, and Africa

Although surveillance data are sparse from many countries in these regions, problems with carbapenem-resistant *A. baumannii* abound. Community-acquired infections are well described in northern Australia and some parts of Asia. These infections may be more likely in men >45 years of age who have histories of cigarette smoking, alcoholism, diabetes mellitus, or chronic obstructive airway disease. Community-acquired strains are more susceptible to antimicrobial agents than are hospital-acquired strains.

PATHOGENESIS

A. baumannii colonizes patients exposed to heavily contaminated hospital environments or to the hands of health care workers in these locations. Colonization of the upper airways in mechanically ventilated patients may lead to nosocomial pneumonia. Colonization of the skin may lead to central line–associated bloodstream infection, catheter-associated urinary tract infection (UTI), wound infection, or postneurosurgical meningitis. Throat carriage and microaspiration may be involved in the pathogenesis of community-acquired pneumonia due to *A. baumannii*.

Much less is known about the virulence mechanisms of and host responses to *A. baumannii* than about these aspects of other pathogenic gram-negative bacteria. Because of the emergence of multidrug-resistant strains, including those resistant to all available antibiotics, the impetus to study *A. baumannii* pathogenesis has grown. Novel targets for antibacterial drug development are desperately required, and drugs that have antivirulence mechanisms may provide new therapeutic options. Specific virulence mechanisms in *A. baumannii* include iron acquisition and transport systems; outer-membrane protein A (OmpA), which mediates mammalian cell adhesion, invasion, and cytotoxicity through mitochondrial damage and initiation of caspase-dependent apoptosis; lipopolysaccharide (LPS); and the ability to form biofilm on abiotic and biotic surfaces. Biofilm formation on abiotic surfaces is dependent on a pilus assembly system, which in turn is controlled by a traditional two-component regulatory system mediated by *bfmR*. Also important in biofilm formation are biofilm-associated protein; OmpA; the quorum-sensing gene *abaI*, which controls the secretion of 3-hydroxy-C_{12}-homoserine lactone; and the *pga* locus, which is essential for the production of the polysaccharide poly-β-1,6-*N*-acetylglucosamine.

New model systems for the study of *A. baumannii* infection, including both nonmammalian (invertebrate) and mammalian models, have been described. Furthermore, the use of *A. baumannii* transposon-generated mutant libraries to screen for mutants with attenuated growth in human biological fluids (serum and ascites fluid) has allowed the identification of new virulence mechanisms. These include phospholipase D; capsule production mediated by *ptk* and *epsA*; penicillin-binding protein 7/8 encoded by the *pbpG* gene; and a glycosyltransferase important for LPS biosynthesis encoded by the *lpsB* gene.

The LPS of *A. baumannii* appears to play a significant role in eliciting host responses. In studies with knockout mice, Toll-like receptor 4 and CD14 were shown to be important in host recognition, signaling, and cytokine production in response to *A. baumannii*. Humoral responses targeting iron-regulated outer-membrane proteins and the O-polysaccharide component of LPS have also been described.

APPROACH TO THE PATIENT ***Acinetobacter* Infection**

Acinetobacter must be considered in the differential diagnosis of hospital-acquired pneumonia, central line–associated bloodstream infection, posttraumatic wound infection in military personnel returning from Iraq and Afghanistan, and postneurosurgical meningitis.

CLINICAL MANIFESTATIONS

Pneumonia

It may be difficult to distinguish between upper-airway colonization with *A. baumannii* and hospital-acquired pneumonia. An estimated 5–10% of cases of ventilator-associated pneumonia are due to *A. baumannii*, although much regional variation exists. Typically, patients with *A. baumannii* ventilator-associated pneumonia have had a prolonged stay in ICUs; in outbreak situations, however, patients may acquire the infection within days of arrival in an ICU.

Community-acquired pneumonia due to *A. baumannii* has been described in tropical regions of Australia and Asia. The disease typically occurs during the "wet" season among people with a history of alcohol abuse. Infection may result in fulminant pneumonia requiring admission to an ICU, with a mortality rate of ~50%.

Bloodstream infection

Although *A. baumannii* accounts for only ~1–2% of nosocomial bloodstream infections, crude mortality rates from these infections may be as high as 40%. Sources of bloodstream infection are typically a central line or underlying pneumonia, UTI, or wound infection.

Traumatic battlefield and other wounds

A. baumannii is a well-known pathogen in burn units. This organism is commonly isolated from wounds of

combat casualties from Iraq or Afghanistan; it was the most commonly isolated organism in one assessment of combat victims with open tibial fractures but did not appear to contribute directly to persistent nonunion or the need for amputation.

Meningitis

A. baumannii may cause meningitis following neurosurgical procedures. Patients typically have an external ventricular drain in situ.

Urinary tract infection

A. baumannii is an occasional cause of catheter-associated UTI. It is highly unusual for this organism to cause uncomplicated UTI in healthy women.

Other clinical manifestations

A small number of case reports describe *Acinetobacter* prosthetic-valve endocarditis and endophthalmitis/keratitis. The latter is sometimes related to contact lens use or eye surgery.

DIAGNOSIS

Acinetobacter infection should be suspected when plump coccobacilli are seen in Gram's-stained respiratory tract secretions, blood cultures, or cerebrospinal fluid. Sometimes the organisms are difficult to de-stain. Given their small size, they may be misidentified as either gram-negative or gram-positive cocci.

TREATMENT *Acinetobacter* Infection (Table 55-1)

Treatment is hampered by the remarkable ability of *A. baumannii* to upregulate or acquire antibiotic resistance determinants. The most prominent example is that of β-lactamases, including those capable of inactivating carbapenems, cephalosporins, and penicillins. These enzymes, which include the OXA-type β-lactamases (e.g., OXA-23) and the metallo-β-lactamases, are typically resistant to β-lactamase inhibitors such as clavulanate or tazobactam. Plasmids harboring genes encoding these β-lactamases may also harbor genes encoding resistance to aminoglycosides and sulfur antibiotics. The end result is that carbapenem-resistant *A. baumannii* may become truly multidrug resistant.

Selection of empirical antibiotic therapy when *A. baumannii* is suspected is challenging and must rely on a knowledge of local epidemiology. The interval from onset of infection to initiation of effective empirical therapy clearly influences outcome. Given the diversity of resistance mechanisms in *A. baumannii*, definitive therapy should be based on the results of antimicrobial susceptibility testing. Carbapenems (imipenem, meropenem, and doripenem but not ertapenem) have long been thought of as the agents of choice for serious *A. baumannii* infections. However, the clinical utility of carbapenems is increasingly jeopardized by the production of carbapenemases, as described above. Sulbactam may be an alternative to carbapenems. Unlike other β-lactamase inhibitors (e.g., clavulanic acid and tazobactam), sulbactam has intrinsic activity against *Acinetobacter*; this activity is mediated by the drug's binding to penicillin-binding protein 2 rather than its ability to inhibit β-lactamases. Sulbactam is commercially available in a combined formulation with either ampicillin or cefoperazone and may also be available as a single agent in some countries. Despite the absence of randomized clinical trials, sulbactam seems to be equivalent to carbapenems in clinical effectiveness against susceptible strains.

Therapy for carbapenem-resistant *A. baumannii* is particularly problematic. The only currently available choices are polymyxins (colistin and polymyxin B) or tigecycline. Neither option is perfect. Polymyxins may be nephrotoxic and neurotoxic. The optimal dose and schedule for administration of polymyxins to patients in vulnerable groups (e.g., those requiring renal replacement therapy) are unknown. Conventional doses of tigecycline may not result in serum concentrations adequate to treat bloodstream infections. Resistance of *A. baumannii* to tigecycline may develop during treatment with this drug. Clearly, new treatment options are needed for serious *A. baumannii* infections.

TABLE 55-1

TREATMENT OPTIONS FOR *ACINETOBACTER* INFECTIONS

ANTIBIOTIC	COMMENTS
Sulbactam	Intrinsic activity against *Acinetobacter*, not linked to β-lactamase inhibition
Trimethoprim-sulfamethoxazole	May be an option for urinary tract infection or wound infection
Meropenem	Widely used in ventilator-associated pneumonia, but carbapenem resistance is widespread
Amikacin	May be an option for carbapenem-resistant strains
Tigecycline	May be an option for carbapenem-resistant strains but inappropriate for urinary tract infection, bloodstream infection, or meningitis
Colistin or polymyxin B	May be an option for carbapenem-resistant strains, but pharmacokinetics not yet well understood

COMPLICATIONS AND PROGNOSIS

Given the propensity of *A. baumannii* to cause infections in seriously ill patients in ICUs, it is not surprising that *A. baumannii* infections are associated with high mortality rates. Thus a pertinent question is whether *A. baumannii* infections are associated with high attributable mortality rates after the severity of illness is controlled for. A number of studies have addressed this issue but have had disparate results. Whether the discrepant results can be explained purely by methodologic differences is unknown at present.

PREVENTION

Multidrug-resistant *A. baumannii* clearly causes outbreaks of infection. In many outbreaks, just one or two strain types are found by molecular epidemiologic analysis. Even in endemic situations, a small number of strain types predominate. In the outbreaks in New York City, for example, two strain types accounted for >80% of carbapenem-resistant isolates. This "oligoclonality" plainly demonstrates the potential importance of infection control interventions in response to outbreaks of multidrug-resistant *A. baumannii* infection.

The hospital environment is an important reservoir of organisms capable of colonizing patients and causing infection. Environmental sources of *A. baumannii* include computer keyboards, glucometers, multidose medication vials, IV nutrition, inadequately sterilized reusable arterial pressure transducers, ventilator tubing, suction catheters, humidifiers, containers of distilled water, urine collection jugs, and moist bedding articles. Pulsatile-lavage wound treatment—a high-pressure irrigation system used to debride wounds—has been associated with an outbreak of *A. baumannii* infection.

Contaminated inanimate objects should be removed from the patient-care environment or subjected to enhanced environmental cleaning. Although contact-isolation procedures (use of gloves and gowns when dealing with colonized patients or their environment), accommodation of patients in single rooms, and improved hand hygiene are critical, attention to the patient-care environment may be the only measure that leads to control of outbreaks of *A. baumannii* infection.

CHAPTER 56

HELICOBACTER PYLORI INFECTIONS

John C. Atherton ■ Martin J. Blaser

DEFINITION

Helicobacter pylori colonizes the stomachs of ~50% of the world's human population throughout their lifetimes. Colonization with this organism is the main risk factor for peptic ulceration as well as for gastric adenocarcinoma and gastric MALT (mucosa-associated lymphoid tissue) lymphoma. Treatment for *H. pylori* has revolutionized the management of peptic ulcer disease, providing a permanent cure in most cases. Such treatment also represents first-line therapy for patients with low-grade gastric MALT lymphoma. Treatment of *H. pylori* is of no benefit in the treatment of gastric adenocarcinoma, but prevention of *H. pylori* colonization could potentially prevent gastric malignancy and peptic ulceration. In contrast, increasing evidence indicates that lifelong *H. pylori* colonization may offer some protection against complications of gastroesophageal reflux disease (GERD), including esophageal adenocarcinoma. Recent research has focused on whether *H. pylori* colonization is a risk factor for some extragastric diseases and whether it is protective against some recently emergent medical problems, such as asthma and obesity.

ETIOLOGIC AGENT

H. pylori is a gram-negative bacillus that has naturally colonized humans for at least 50,000 years—and probably throughout human evolution. It lives in gastric mucus, with a small proportion of the bacteria adherent to the mucosa and possibly a very small number of the organisms entering cells or penetrating the mucosa;

its distribution is never systemic. Its spiral shape and flagella render *H. pylori* motile in the mucus environment. The organism has several acid-resistance mechanisms, most notably a highly expressed urease that catalyzes urea hydrolysis to produce buffering ammonia. *H. pylori* is microaerophilic (requiring low levels of oxygen), is slow-growing, and requires complex growth media in vitro. Publication of several complete genomic sequences of *H. pylori* since 1997 has led to significant advances in the understanding of the organism's biology.

A very small proportion of gastric *Helicobacter* infections are due to species other than *H. pylori*, possibly acquired as zoonoses. Whether these non-*pylori* gastric helicobacters cause disease remains controversial. In immunocompromised hosts, several nongastric (intestinal) *Helicobacter* species can cause disease with clinical features resembling those of *Campylobacter* infections; these species are covered in Chap. 60.

EPIDEMIOLOGY

The prevalence of *H. pylori* among adults is ~30% in the United States and other developed countries as opposed to >80% in most developing countries. In the United States, prevalence varies with age: ~50% of 60-year-old persons, ~20% of 30-year-old persons, and <10% of children are colonized. *H. pylori* is usually acquired in childhood. The age association is due mostly to a birth-cohort effect whereby current 60-year-olds were more commonly colonized as children than are current children. Spontaneous acquisition or loss of *H. pylori* in adulthood is uncommon. Other strong risk factors for *H. pylori* colonization are markers of crowding and maternal colonization. The low incidence among children in developed countries at present is due, at least in part, to decreased maternal colonization and increased use of antibiotics.

Humans are the only important reservoir of *H. pylori*. Children may acquire the organism from their parents (more often from the mother) or from other children. Whether transmission takes place more often by the fecal-oral or the oral-oral route is unknown, but *H. pylori* is easily cultured from vomitus and gastroesophageal refluxate and is less easily cultured from stool.

PATHOLOGY AND PATHOGENESIS

H. pylori colonization induces a tissue response in the stomach, *chronic superficial gastritis*, which includes infiltration of the mucosa by both mononuclear and polymorphonuclear cells. (The term *gastritis* should be used specifically to describe histologic features; it has also been used to describe endoscopic appearances and even symptoms, which do not correlate with microscopic findings or even with the presence of *H. pylori*.) Although *H. pylori* is capable of numerous adaptations that prevent excessive stimulation of the immune system, colonization is accompanied by a considerable persistent immune response, including the production of both local and systemic antibodies as well as cell-mediated responses. However, these responses are ineffective in clearing the bacterium. This inefficient clearing appears to be due in part to *H. pylori*'s downregulation of the immune system, which fosters its own persistence.

Most *H. pylori*–colonized persons do not develop clinical sequelae. That some persons develop overt disease whereas others do not is related to a combination of factors: bacterial strain differences, host susceptibility to disease, and environmental factors.

Several *H. pylori* virulence factors are more common among strains that are associated with disease than among those that are not. The *cag* island is a group of genes that encodes a bacterial secretion system through which a specific protein, CagA, is translocated into epithelial cells. CagA affects host cell signal transduction, inducing proliferative, cytoskeletal, and inflammatory changes; a proportion of transgenic mice expressing CagA in the stomach develop gastric adenocarcinoma. The secretion system also translocates soluble components of the peptidoglycan cell wall into the gastric epithelial cell; these components are recognized by the intracellular emergency bacterial receptor Nod1, which stimulates a proinflammatory cytokine response resulting in enhanced gastric inflammation. Patients with peptic ulcer disease or gastric adenocarcinoma are more likely than persons without these conditions to be colonized by *cag*-positive strains. The secreted *H. pylori* protein VacA occurs in several forms. Strains with the more active forms are more commonly isolated from patients with peptic ulcer disease or gastric carcinoma than from persons without these conditions. Other bacterial factors that are associated with increased disease risk include adhesins, such as BabA and SabA, and incompletely characterized genes, such as *dupA*.

The best-characterized host determinants of disease are genetic polymorphisms leading to enhanced activation of the innate immune response, such as polymorphisms in cytokine genes or genes encoding bacterial recognition proteins such as Toll-like receptors (TLRs). For example, colonized people with polymorphisms in the interleukin (IL) 1 gene that cause the production of large quantities of this cytokine in response to *H. pylori* infection are at increased risk of gastric adenocarcinoma. In addition, environmental cofactors are important in pathogenesis. Smoking increases the risks of ulcers and cancer in *H. pylori*–positive individuals. Diets high in salt and preserved foods increase cancer risk, whereas diets high in antioxidants and vitamin C are protective.

The pattern of gastric inflammation is associated with disease risk: antral-predominant gastritis is most closely linked with duodenal ulceration, whereas pangastritis is linked with gastric ulceration and adenocarcinoma. This difference probably explains why patients with duodenal ulceration are not at high risk of developing gastric adenocarcinoma later in life, despite being colonized by *H. pylori*.

How gastric colonization causes duodenal ulceration is now becoming clearer. *H. pylori*–induced inflammation

diminishes the number of somatostatin-producing D cells. Since somatostatin inhibits gastrin release, gastrin levels are higher than in *H. pylori*–negative persons, and these higher levels lead to increased meal-stimulated acid secretion in the gastric corpus, which is only mildly inflamed in antral-predominant gastritis. How this increases duodenal ulcer risk remains controversial, but the increased acid secretion may contribute to the formation of the potentially protective gastric metaplasia found in the duodenum of duodenal ulcer patients. Gastric metaplasia in the duodenum may become colonized by *H. pylori* and subsequently inflamed and ulcerated.

The pathogenesis of gastric ulceration and that of gastric adenocarcinoma are less well understood, although both conditions arise in association with pan- or corpus-predominant gastritis. The hormonal changes described earlier still occur, but the inflammation in the gastric corpus means that it produces less acid (hypochlorhydria) despite hypergastrinemia. Gastric ulcers usually occur at the junction of antral and corpus-type mucosa, and this region is particularly inflamed. Gastric cancer probably stems from progressive DNA damage and the survival of abnormal epithelial cell clones. The DNA damage is thought to be due principally to reactive oxygen and nitrogen species arising from inflammatory cells and perhaps in relation to other bacteria that survive in a hypochlorhydric stomach. Longitudinal analyses of gastric biopsy specimens taken years apart from the same patient show that the common *intestinal* type of gastric adenocarcinoma follows stepwise changes from simple gastritis to gastric atrophy, intestinal metaplasia, and dysplasia. A second, *diffuse* type of gastric adenocarcinoma may arise directly from chronic gastritis alone.

CLINICAL MANIFESTATIONS

Essentially all *H. pylori*–colonized persons have gastric tissue responses, but fewer than 15% develop associated illnesses such as peptic ulceration, gastric adenocarcinoma, or gastric lymphoma **(Fig. 56-1)**.

Worldwide, >80% of duodenal ulcers and >60% of gastric ulcers are related to *H. pylori* colonization, although the proportion of ulcers due to aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) is increasing, especially in developed countries. The main lines of evidence for an ulcer-promoting role for *H. pylori* are that (1) the presence of the organism is a risk factor for the development of ulcers, (2) non-NSAID-induced ulcers rarely develop in the absence of *H. pylori*, (3) eradication of *H. pylori* markedly reduces rates of ulcer relapse, and (4) experimental *H. pylori* infection of gerbils causes gastric ulceration.

Prospective nested case-control studies have shown that *H. pylori* colonization is a risk factor for adenocarcinomas of the distal (noncardia) stomach. Long-term experimental infection of gerbils also may result in gastric adenocarcinoma. Moreover, the presence of *H. pylori* is strongly associated with primary gastric lymphoma, although this condition is much less common. Many low-grade gastric B cell lymphomas arising from MALT are driven by T cell proliferation, which in turn is

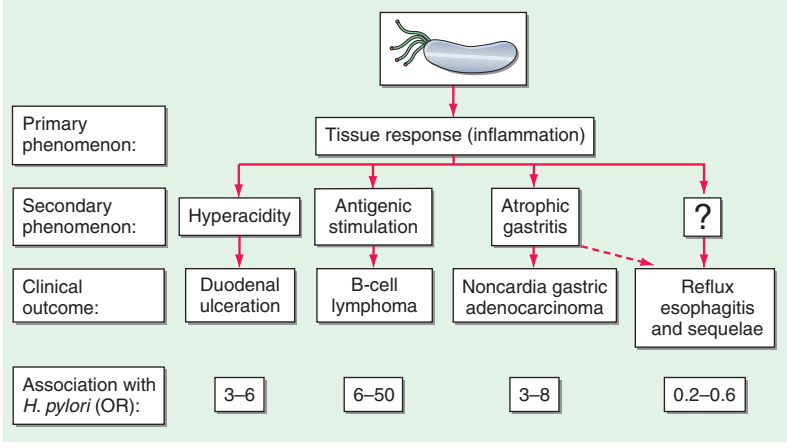


FIGURE 56-1
Schematic of the relationships between colonization with *Helicobacter pylori* and diseases of the upper gastrointestinal tract among persons in developed countries. Essentially all persons colonized with *H. pylori* develop a host response, which is generally termed chronic gastritis. The nature of the interaction of the host with the particular bacterial population determines the clinical outcome. *H. pylori* colonization increases the lifetime risk of peptic ulcer disease, noncardia gastric cancer, and B cell non-Hodgkin's gastric lymphoma (odds ratios [ORs] for all, >3). In contrast, a growing body of evidence indicates that *H. pylori* colonization (especially with *cagA*$^+$ strains) protects against adenocarcinoma of the esophagus (and the sometimes related gastric cardia) and premalignant lesions such as Barrett's esophagus (OR, <1). While the incidences of peptic ulcer disease (cases not due to nonsteroidal anti-inflammatory drugs) and noncardia gastric cancer are declining in developed countries, the incidence of adenocarcinoma of the esophagus is rapidly increasing. (*Adapted from MJ Blaser: Hypothesis: The changing relationships of Helicobacter pylori and humans: Implications for health and disease. J Infect Dis 179:1523, 1999, with permission.*)

driven by *H. pylori* antigen stimulation; *H. pylori* antigen–driven tumors may regress either fully or partially after *H. pylori* eradication but require careful long-term monitoring.

Many patients have upper gastrointestinal symptoms but have normal results in upper gastrointestinal endoscopy (so-called functional or nonulcer dyspepsia. Because *H. pylori* is common, some of these patients will be colonized with the organism. *H. pylori* eradication leads to symptom resolution a little (7%) more commonly than does placebo treatment. Whether such patients have peptic ulcers in remission at the time of endoscopy or whether a small subgroup of patients with true functional dyspepsia respond to *H. pylori* treatment is unclear.

Much interest has focused on a possible protective role for *H. pylori* against GERD, Barrett's esophagus, and adenocarcinoma of the esophagus and gastric cardia. The main lines of evidence for this role are (1) that there is a temporal relationship between a falling prevalence of gastric *H. pylori* colonization and a rising incidence of these conditions and (2) that, in most studies, the prevalence of *H. pylori* colonization (especially with proinflammatory *cagA*$^+$ strains) is significantly lower among patients with these esophageal diseases than among control subjects. The mechanism underlying this protective effect appears to include *H. pylori*–induced hypochlorhydria. Since, at the individual level, GERD symptoms may decrease, worsen, or remain unchanged after treatment targeting *H. pylori*, concerns about GERD should not affect decisions about *H. pylori* treatment when an indication exists.

H. pylori has an increasingly recognized role in other gastric pathologies. It may be one initial precipitant of autoimmune gastritis and pernicious anemia and also may predispose some patients to iron deficiency through occult blood loss and/or hypochlorhydria and reduced iron absorption. In addition, several extragastrointestinal pathologies have been linked with *H. pylori* colonization, although evidence of causality is less strong. Several small studies of *H. pylori* treatment in idiopathic thrombocytopenic purpura have described improvement in or even normalization of platelet counts. Potentially important but even more controversial associations are with ischemic heart disease and cerebrovascular disease. However, the strength of these latter associations is reduced if confounding factors are taken into account, and most authorities consider the associations to be noncausal. Recent studies have shown an inverse association of *cagA*$^+$ *H. pylori* with childhood-onset asthma, hay fever, and atopic disorders. Whether *H. pylori* status is merely a marker or is causally associated with protection against these diseases remains to be determined.

DIAGNOSIS

Tests for the presence of *H. pylori* can be divided into two groups: invasive tests, which require upper gastrointestinal endoscopy and are based on the analysis of gastric biopsy specimens, and noninvasive tests **(Table 56-1)**. Endoscopy often is not performed in the initial management of young dyspeptic patients without "alarm" symptoms but is commonly used to exclude malignancy in older patients. If endoscopy is performed, the most convenient biopsy-based test is the biopsy urease test, in which one large or two small antral biopsy specimens are placed into a gel containing urea and an indicator. The presence of *H. pylori* urease leads to a pH alteration and therefore to a color change, which often occurs within minutes but can require up to 24 h. Histologic examination of biopsy specimens for *H. pylori* also is accurate, provided that a special stain (e.g., a modified Giemsa or silver stain) permitting optimal visualization of the organism is used. If biopsy specimens are obtained from

TABLE 56-1

TESTS COMMONLY USED TO DETECT *HELICOBACTER PYLORI*

TEST	ADVANTAGES	DISADVANTAGES
Invasive (Based on Endoscopic Biopsy)		
Biopsy urease test	Quick, simple	Some commercial tests not fully sensitive before 24 h
Histology	May give additional histologic information	Sensitivity dependent on experience and use of special stains
Culture	Permits determination of antibiotic susceptibility	Sensitivity dependent on experience
Noninvasive		
Serology	Inexpensive and convenient; not affected by recent antibiotics or proton pump inhibitors to the same extent as breath and stool tests	Cannot be used for early follow-up after treatment; some commercial kits inaccurate, and all less accurate than breath test
^{13}C urea breath test	Inexpensive and simpler than endoscopy; useful for follow-up after treatment	Requires fasting; not as convenient as blood or stool tests
Stool antigen test	Inexpensive and convenient; useful for follow-up after treatment; may be useful in children	May be disliked by people from some cultures; may be slightly less accurate than urea breath test, particularly when used to assess treatment success

both antrum and corpus, histologic study yields additional information, including the degree and pattern of inflammation, atrophy, metaplasia, and dysplasia. Microbiologic culture is most specific but may be insensitive because of difficulty with *H. pylori* isolation. Once the organism is cultured, its identity as *H. pylori* can be confirmed by its typical appearance on Gram's stain and its positive reactions in oxidase, catalase, and urease tests. Moreover, the organism's susceptibility to antibiotics can be determined, and this information can be clinically useful in difficult cases. The occasional biopsy specimens containing the less common non-*pylori* gastric helicobacters give only weakly positive results in the biopsy urease test. Positive identification of these bacteria requires visualization of the characteristic long, tight spirals in histologic sections.

Noninvasive *H. pylori* testing is the norm if gastric cancer does not need to be excluded by endoscopy. The most consistently accurate test is the urea breath test. In this simple test, the patient drinks a solution of urea labeled with the nonradioactive isotope ^{13}C and then blows into a tube. If *H. pylori* urease is present, the urea is hydrolyzed and labeled carbon dioxide is detected in breath samples. The stool antigen test, another simple assay, is more convenient and potentially less expensive than the urea breath test but has been slightly less accurate in some comparative studies. The simplest tests for ascertaining *H. pylori* status are serologic assays measuring specific IgG levels in serum by enzyme-linked immunosorbent assay or immunoblot. The best of these tests are as accurate as other diagnostic methods, but many commercial tests—especially rapid office tests—do not perform well.

The urea breath test, the stool antigen test, and biopsy-based tests can all be used to assess the success of treatment **(Fig. 56-2)**. However, because these tests are dependent on *H. pylori* load, their use <4 weeks after treatment may yield false-negative results. Furthermore, these tests are unreliable if performed within 4 weeks of intercurrent treatment with antibiotics or bismuth compounds or within 2 weeks of the discontinuation of proton pump inhibitor (PPI) treatment. In the assessment of treatment success, noninvasive tests are normally preferred; however, after gastric ulceration, endoscopy should be repeated to ensure healing and to exclude gastric carcinoma by further histologic sampling.

Serologic tests are not used to monitor treatment success, as the gradual drop in titer of *H. pylori*–specific antibodies is too slow to be of practical use.

TREATMENT *H. pylori* Infections

The most clear-cut indications for treatment are *H. pylori*–related duodenal or gastric ulceration or low-grade gastric B cell lymphoma. *H. pylori* should be eradicated in patients with documented ulcer disease, whether or not the ulcers are currently active, to reduce the likelihood of relapse (Fig. 56-2). Many guidelines now recommend *H. pylori* eradication in uninvestigated simple dyspepsia following noninvasive diagnosis; others also recommend treatment in functional dyspepsia, in case the patient is one of the perhaps 7% (beyond placebo effects) to benefit from such treatment. Individuals with

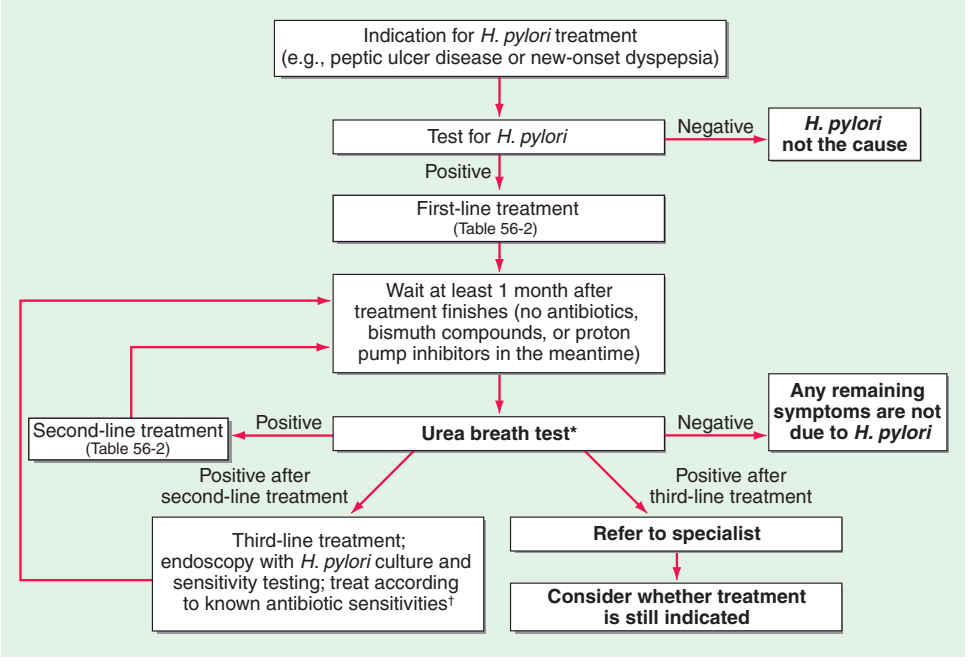


FIGURE 56-2
Algorithm for the management of *Helicobacter pylori* infection. *Occasionally, an endoscopy and a biopsy-based test are used instead of a urea breath test in follow-up after treatment. The main indication for these invasive tests is gastric ulceration; in this condition, as opposed to duodenal ulceration, it is important to check healing and to exclude underlying gastric adenocarcinoma. †Some authorities now use empirical third-line regimens, several of which have been described.

a strong family history of gastric cancer should be treated to eradicate *H. pylori* in the hope that their cancer risk will be reduced. Currently, widespread community screening for and treatment of *H. pylori* as primary prophylaxis for gastric cancer and peptic ulcers are not recommended, mainly because it is unclear whether treatment for *H. pylori* reduces the risk of cancer to that in persons who have never acquired the organism. The largest randomized controlled study to date (performed in China) showed no cancer risk reduction during the 7 years of follow-up, although a post hoc subgroup analysis documented improvement in the group of participants who did not already have gastric atrophy or intestinal metaplasia. Other studies have found a reduced cancer risk after treatment, but the size of this effect in different populations remains unclear, and the results of further large-scale prospective interventional studies must be awaited. Other reasons for not treating *H. pylori* in asymptomatic populations at present include (1) the adverse side effects of the multiple-antibiotic regimens used (which are common and can be severe in rare cases); (2) antibiotic resistance, which may arise in *H. pylori* or other incidentally carried bacteria; (3) the anxiety that may arise in otherwise healthy people, especially if treatment is unsuccessful; and (4) the apparent existence of a subset of people who will develop GERD symptoms after treatment, although on average *H. pylori* treatment does not affect GERD symptoms or severity.

Although *H. pylori* is susceptible to a wide range of antibiotics in vitro, monotherapy is not usually successful, probably because of inadequate antibiotic delivery to the colonization niche. Failure of monotherapy has prompted the development of multidrug regimens, the most successful of which are triple and quadruple combinations. Initially these regimens produced *H. pylori* eradication rates of >90% in many trials; in recent years, however, resistance to key antibiotics has become more common, a trend leading to *H. pylori* eradication rates of only 75–80% for the most commonly used regimens. Current regimens consist of a PPI or ranitidine bismuth citrate and two or three antimicrobial agents given for 7–14 days (Table 56-2). Research on optimizing drug combinations to increase efficacy continues, and it is likely that guidelines will change as the field develops and as countries increasingly individualize treatment to suit local antibiotic resistance patterns and economic needs.

The two most important factors in successful *H. pylori* treatment are the patient's close compliance with the regimen and the use of drugs to which the patient's strain of *H. pylori* has not acquired resistance. Treatment failure following minor lapses in compliance is common and often leads to acquired resistance to metronidazole or clarithromycin. To stress the importance of compliance, written instructions should be given to the patient, and minor side effects of the regimen should be explained. Resistance to clarithromycin and, to a lesser extent, to metronidazole are of growing concern. Clarithromycin resistance is less prevalent but, if present, usually results in treatment failure. Strains of

TABLE 56-2

RECOMMENDED TREATMENT REGIMENS FOR *HELICOBACTER PYLORI*

REGIMEN (DURATION)	DRUG 1	DRUG 2	DRUG 3	DRUG 4
Regimen 1: OCM (7–14 days)[a]	Omeprazole[b] (20 mg bid)	Clarithromycin (500 mg bid)	Metronidazole (500 mg bid)	—
Regimen 2: OCA (7–14 days)[a]	Omeprazole[b] (20 mg bid)	Clarithromycin (500 mg bid)	Amoxicillin (1 g bid)	—
Regimen 3: OBTM (14 days)[c]	Omeprazole[b] (20 mg bid)	Bismuth subsalicylate (2 tabs qid)	Tetracycline HCl (500 mg qid)	Metronidazole (500 mg tid)
Regimen 4[d]: sequential (5 days + 5 days)	Omeprazole[b] (20 mg bid)	Amoxicillin (1 g bid)		
	Omeprazole[b] (20 mg bid)	Clarithromycin (500 mg bid)	Tinidazole (500 mg bid)	
Regimen 5[e]: OAL (10 days)	Omeprazole[b] (20 mg bid)	Amoxicillin (1 g bid)	Levofloxacin (500 mg bid)	

[a]Meta-analyses show that a 14-day course of therapy is slightly superior to a 7-day course. However, in populations where 7-day treatment is known to have very high success rates, this shorter course is still often used.
[b]Omeprazole may be replaced with any proton pump inhibitor at an equivalent dosage or, in regimens 1 and 2, with ranitidine bismuth citrate (400 mg).
[c]Data supporting this regimen come mainly from Europe and are based on the use of bismuth subcitrate and metronidazole (400 mg tid). This is the most commonly used second-line regimen.
[d]Data supporting this regimen come from Europe. Although the two 5-day courses of different drugs have usually been given sequentially, recent evidence suggests no added benefit from this approach. Thus 10 days of the four drugs combined may be as good and may aid compliance.
[e]Data supporting this second- or third-line regimen come from Europe. This regimen may be less effective where rates of quinolone use are high. Theoretically, it may also be wise to avoid it in populations where *Clostridium difficile* infection is common after broad-spectrum antibiotic use.

H. pylori that are apparently resistant to metronidazole are more common but still may be cleared by metronidazole-containing regimens, which have only slightly reduced efficacy. Assessment of antibiotic susceptibilities before treatment would be optimal but is not usually undertaken because endoscopy and mucosal biopsy are necessary to obtain *H. pylori* for culture and because most microbiology laboratories are inexperienced in *H. pylori* culture. In the absence of susceptibility information, a history of the patient's (even distant) antibiotic use for other conditions should be obtained; use of the agent should then be avoided if possible, particularly in the case of clarithromycin (e.g., previous use for upper respiratory infection). If initial *H. pylori* treatment fails, one of two strategies may be used (Fig. 56-2). The more common approach is empirical re-treatment with another drug regimen, usually quadruple therapy (Table 56-2). The second approach is endoscopy, biopsy, and culture plus treatment based on documented antibiotic sensitivities. If re-treatment fails, susceptibility testing should ideally be performed, although empirical third-line therapies are often used.

Clearance of non-*pylori* gastric helicobacters can follow the use of bismuth compounds alone or of triple-drug regimens. However, in the absence of trials, it is unclear whether this outcome represents successful treatment or natural clearance of the bacterium.

PREVENTION

Carriage of *H. pylori* has considerable public health significance in developed countries, where it is associated with peptic ulcer disease and gastric adenocarcinoma, and in developing countries, where gastric adenocarcinoma may be an even more common cause of cancer death late in life. If mass prevention were contemplated, vaccination would be the most obvious method, and experimental immunization of animals has given promising results. However, given that *H. pylori* has co-evolved with its human host over millennia, preventing or eliminating colonization on a population basis may have distinct disadvantages. For example, lifelong absence of *H. pylori* is a risk factor for GERD complications, including esophageal adenocarcinoma. We have speculated that the disappearance of *H. pylori* may be associated with an increased risk of other emerging diseases reflecting aspects of the current Western lifestyle, such as asthma, obesity, and conceivably even type 2 diabetes mellitus.

CHAPTER 57

INFECTIONS DUE TO *PSEUDOMONAS* SPECIES AND RELATED ORGANISMS

Reuben Ramphal

The pseudomonads are a heterogeneous group of gram-negative bacteria that have in common an inability to ferment lactose. Formerly classified in the genus *Pseudomonas*, the members of this group are now assigned to three medically important genera—*Pseudomonas, Burkholderia*, and *Stenotrophomonas*—whose biologic behaviors encompass both similarities and marked differences and whose genetic repertoires differ in many respects. The pathogenicity of most pseudomonads is based on opportunism; the exceptions are the organisms that cause melioidosis (*B. pseudomallei*) and glanders (*B. mallei*), which can be considered primary pathogens.

P. aeruginosa, the major pathogen of the group, is a significant cause of infections in hospitalized patients and in patients with cystic fibrosis (CF). Cytotoxic chemotherapy, mechanical ventilation, and broad-spectrum antibiotic therapy probably paved the way for increasing numbers of patients colonized and infected by this organism. Since the implementation of these advances in medical therapy, most conditions

predisposing to *P. aeruginosa* infections have involved host compromise and/or broad-spectrum antibiotic use. The other members of the genus *Pseudomonas*—*P. putida, P. fluorescens*, and *P. stutzeri*—infect humans infrequently.

The genus *Burkholderia* comprises >40 species, of which *B. cepacia* is most frequently encountered in Western countries. Like *P. aeruginosa, B. cepacia* is both a nosocomial pathogen and a cause of infection in CF. The other medically important members of this genus are *B. pseudomallei* and *B. mallei,* which, as stated earlier, cause melioidosis and glanders, respectively.

The genus *Stenotrophomonas* contains one species of medical significance, *S. maltophilia* (previously classified in the genera *Pseudomonas* and *Xanthomonas*). This organism is strictly an opportunist that "overgrows" in the setting of potent broad-spectrum antibiotic use.

PSEUDOMONAS AERUGINOSA

EPIDEMIOLOGY

P. aeruginosa is found in most moist environments. Soil, plants, vegetables, tap water, and countertops can all be reservoirs for this microbe, as it has simple nutritional needs. Given the ubiquity of *P. aeruginosa*, contact with the organism obviously is not sufficient for colonization or infection. Clinical and experimental observations suggest that *P. aeruginosa* infection often occurs concomitantly with host defense compromise, mucosal trauma, physiologic derangement, and antibiotic-mediated suppression of normal flora. Thus, it comes as no surprise that the majority of *P. aeruginosa* infections occur in intensive care units (ICUs), where these factors frequently converge. It is believed that the organism is initially acquired from environmental sources, but patient-to-patient spread also occurs in clinics and families.

Burn patients once appeared to be unusually susceptible to *P. aeruginosa*. For example, in 1959–1963, *Pseudomonas* burn-wound sepsis was the principal cause of death in 60% of burned patients dying at the U.S. Army Institute of Surgical Research. For reasons that are unclear, *P. aeruginosa* infection in burns is no longer the major problem that it was during the 1950s and 1960s. Similarly, in the 1960s, *P. aeruginosa* appeared as a common pathogen in patients receiving cytotoxic chemotherapy at many institutions in the United States, but it subsequently diminished in importance. Despite this subsidence, *P. aeruginosa* remains one of the most feared pathogens in this population because of its high attributable mortality rate.

In some parts of Asia and Latin America, *P. aeruginosa* continues to be the most common cause of gram-negative bacteremia in neutropenic patients.

In contrast to the trends for burn patients and neutropenic patients in the United States, the incidence of *P. aeruginosa* infections among patients with CF has not changed. *P. aeruginosa* remains the most common contributing factor to respiratory failure in CF and is responsible for the majority of deaths among CF patients.

LABORATORY FEATURES

P. aeruginosa is a nonfastidious, motile, gram-negative rod that grows on most common laboratory media, including blood and MacConkey agars. It is easily identified in the laboratory on primary-isolation agar plates by pigment production that confers a yellow to dark green or even bluish appearance. Colonies have a shiny "gun-metal" appearance and a characteristic fruity odor. Two of the identifying biochemical characteristics of *P. aeruginosa* are an inability to ferment lactose on MacConkey agar and a positive reaction in the oxidase test. Most strains are identified on the basis of these readily detectable laboratory features even before extensive biochemical testing is done. Some isolates from CF patients are easily identified by their mucoid appearance, which is due to the production of large amounts of the mucoid exopolysaccharide or alginate.

PATHOGENESIS

Unraveling the mechanisms underlying disease caused by *P. aeruginosa* has proved challenging. Of the common gram-negative bacteria, no other species produces such a large number of putative virulence factors **(Table 57-1)**. Yet *P. aeruginosa* rarely initiates an infectious process in the absence of host injury or compromise, and few of its putative virulence factors have been shown definitively to be involved in disease in humans. Despite its metabolic versatility and possession of multiple colonizing factors, *P. aeruginosa* exhibits no competitive advantage over enteric bacteria in the human gut; neither is it a normal

TABLE 57-1

MAIN PUTATIVE VIRULENCE FACTORS OF *PSEUDOMONAS AERUGINOSA*

SUBSTANCE/ ORGANELLE	FUNCTION	VIRULENCE IN ANIMAL DISEASE
Pili	Adhesion to cells	?
Flagella	Adhesion, motility, inflammation	Yes
Lipopolysaccharide	Antiphagocytic activity, inflammation	Yes
Type III secretion system	Cytotoxic activity (ExoU)	Yes
Proteases	Proteolytic activity, cytotoxicity	?
Phospholipases	Cytotoxicity	?
Exotoxin A	Cytotoxicity	?

inhabitant of the human gastrointestinal tract, despite the host's continuous environmental exposure to the organism.

Virulence attributes involved in acute P. aeruginosa infections

Motility and colonization

A general tenet of bacterial pathogenesis is that most bacteria must adhere to surfaces or colonize a host niche in order to initiate disease. Most pathogens examined thus far possess adherence factors called *adhesins*. *P. aeruginosa* is no exception. Among its many adhesins are its pili, which demonstrate adhesive properties for a variety of cells and adhere best to injured cell surfaces. In the organism's flagellum, the flagellin molecule binds to cells, and the flagellar cap attaches to mucins through the recognition of glycan chains. Nonflagellated *P. aeruginosa* mutants are less virulent or avirulent in some but not all animal models; however, it is unclear whether this decreased virulence is due to the loss of adhesion or to the loss of other flagellar functions. Other *P. aeruginosa* adhesins include the outer core of the lipopolysaccharide (LPS) molecule, which binds to the cystic fibrosis transmembrane conductance regulator (CFTR) and aids in internalization of the organism, and the alginate coat of mucoid strains, which enhances adhesion to cells and mucins. In addition, membrane proteins and lectins have been proposed as colonization factors. It appears that the deletion of any given adhesin is not sufficient to abrogate the ability of *P. aeruginosa* to colonize surfaces.

Evasion of host defenses

The transition from bacterial colonization to disease requires the evasion of host defenses by a substantial number of bacteria. *P. aeruginosa* appears to be well equipped for evasion. Attached bacteria inject four known toxins (ExoS, ExoU, ExoT, and ExoY) via a type III secretion system that allows the bacteria to evade phagocytic cells either by cytotoxicity or by inhibition of phagocytosis. Mutants with defects in this system fail to disseminate in some animal models of infection. Secreted toxins such as exotoxin A and leukocidin have the potential to kill phagocytic cells, and multiple secreted proteases may degrade host effector molecules such as cytokines and chemokines that are released in response to infection.

Tissue injury

Among gram-negative bacteria, *P. aeruginosa* probably produces the largest number of substances that are toxic to cells and thus may injure tissues. The toxins secreted by its type III secretion system are capable of tissue injury. However, their delivery requires the adherence of the organism to cells. Thus, the effects of these toxins are likely to be local or to depend on the presence of vast numbers of bacteria. On the other hand, diffusible toxins, secreted by the organism's type II secretion system, can act freely wherever they come into contact with cells. Exotoxin A, four different proteases, at least two phospholipases, rhamnolipids, pyocyanin, and hydrocyanic acid are all produced by *P. aeruginosa* and are all capable of inducing host injury.

Inflammatory components

The inflammatory components of *P. aeruginosa* (e.g., the inflammatory responses to the lipid A component of LPSs and to flagellin, mediated through the Toll-like receptor [TLR] system [principally TLR4 and TLR5]) have been thought to represent the most important factor in disease causation. Although these inflammatory responses are required for successful defense against *P. aeruginosa* (i.e., in their absence, animals are defenseless against *P. aeruginosa* infection), florid responses are likely to result in disease. When the sepsis syndrome and septic shock develop in *P. aeruginosa* infection, they are probably the result of the host response to one or both of these substances, but injury to the lung by *Pseudomonas* toxins may also result in sepsis syndromes, possibly by causing cell death and the release of cellular components (e.g., heat-shock proteins) that may activate the TLR or another proinflammatory system.

Chronic P. aeruginosa infections

Chronic infection due to *P. aeruginosa* occurs mainly in the lungs in the setting of structural pulmonary diseases. The classic example is CF; others include bronchiectasis and chronic relapsing panbronchiolitis, a disease seen in Japan and some Pacific Islands. Hallmarks of these illnesses are altered mucociliary clearance leading to mucus stasis and mucus accumulation in the lungs. There is probably a common factor that selects for *P. aeruginosa* colonization in these lung diseases—perhaps the adhesiveness of *P. aeruginosa* for mucus, a phenomenon that is not noted for most other common gram-negative bacteria, and/or the ability of *P. aeruginosa* to evade host defenses in mucus. Furthermore, *P. aeruginosa* seems to evolve in ways that allow its prolonged survival in the lung without an early fatal outcome for the host. The strains found in CF patients exhibit minimal production of virulence factors. Some strains even lose the ability to produce pili and flagella, and most become complement-sensitive because of the loss of the O side chain of their LPS molecules. An example of the impact of these changes is found in the organism's discontinuation of the production of flagellin (probably its most strongly proinflammatory molecule) when it encounters purulent mucus. This response probably dampens the host's response, allowing the organism to survive in mucus. *P. aeruginosa* is also believed to lose the ability to secrete many of its injectable toxins during growth in mucus. Although the alginate coat is thought to play a role in the organism's survival, alginate is not essential, as nonmucoid strains may also predominate for long periods. In short, virulence in chronic infections may be mediated mainly by the attenuated host inflammatory response, which injures the lungs over decades.

CLINICAL MANIFESTATIONS

P. aeruginosa causes infections at almost all sites in the body but shows a rather strong predilection for the lungs. The infections encountered most commonly in hospitalized patients are described next.

Bacteremia

Crude mortality rates exceeding 50% have been reported among patients with *P. aeruginosa* bacteremia. Consequently, this clinical entity has been much feared, and its management has been attempted with the use of multiple antibiotics. Recent publications report attributable mortality rates of 28–44%, with the precise figure depending on the adequacy of treatment and the seriousness of the underlying disease. In the past, the patient with *P. aeruginosa* bacteremia classically was neutropenic or had a burn injury. Today, however, a minority of such patients have bacteremic *P. aeruginosa* infections. Rather, *P. aeruginosa* bacteremia is seen most often in patients on ICUs.

The clinical presentation of *P. aeruginosa* bacteremia rarely differs from that of sepsis in general. Patients are usually febrile, but those who are most severely ill may be in shock or even hypothermic. The only point differentiating this entity from gram-negative sepsis of other causes may be the distinctive skin lesions (ecthyma gangrenosum) of *Pseudomonas* infection, which occur almost exclusively in markedly neutropenic patients and patients with AIDS. These small or large, painful, reddish, maculopapular lesions have a geographic margin; they are initially pink, then darken to purple, and finally become black and necrotic **(Fig. 57-1)**. Histopathologic studies indicate that the lesions are due to vascular invasion and are teeming with bacteria. Although similar lesions may occur in aspergillosis and mucormycosis, their presence suggests *P. aeruginosa* bacteremia as the most likely diagnosis.

TREATMENT **Bacteremia**

(Table 57-2) Antimicrobial treatment of *P. aeruginosa* bacteremia has been controversial. Before 1971, the outcome of *Pseudomonas* bacteremia in febrile neutropenic patients treated with the available agents—gentamicin and the polymyxins—was dismal. Studies published around that time indicated that treatment with carbenicillin, with or without an aminoglycoside, significantly improved outcomes. Concurrently, several retrospective analyses suggested that the use of two agents that were synergistic against gram-negative pathogens in vitro resulted in better outcomes in neutropenic patients. Thus, combination therapy became the standard of care—first for *P. aeruginosa* bacteremia in febrile neutropenic patients and then for all *P. aeruginosa* infections in neutropenic or nonneutropenic patients.

With the introduction of newer antipseudomonal drugs, a number of studies have revisited the choice between combination treatment and monotherapy for *Pseudomonas* bacteremia. Although the majority of experts still favor combination therapy, most of these observational studies indicate that a single modern antipseudomonal β-lactam agent to which the isolate is sensitive is as efficacious as a combination. Even in patients at greatest risk of early death from *P. aeruginosa* bacteremia (i.e., those with fever and neutropenia), empirical antipseudomonal monotherapy is deemed to be as efficacious as empirical combination therapy by the practice guidelines of the Infectious Diseases Society of America. One firm conclusion is that monotherapy with an aminoglycoside is not optimal.

There are, of course, institutions and countries where rates of susceptibility of *P. aeruginosa* to first-line antibiotics are <80%. Thus, when a septic patient with a high probability of *P. aeruginosa* infection is encountered in such settings, empirical combination therapy should be administered until the pathogen is identified and susceptibility data become available. Thereafter, whether one or two agents should be continued remains a matter of individual preference.

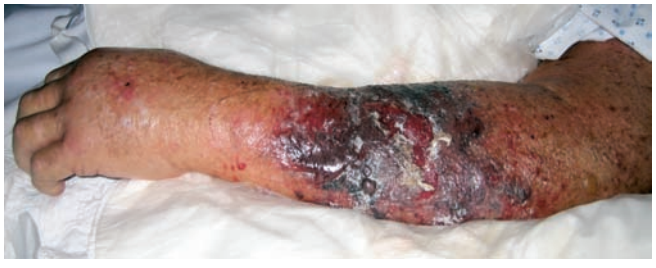


FIGURE 57-1
Ecthyma gangrenosum in a neutropenic patient 3 days after onset.

Acute pneumonia

Respiratory infections are the most common of all infections caused by *P. aeruginosa*. This organism appears first or second on most lists of the causes of ventilator-associated pneumonia (VAP). However, much debate centers on the actual role of *P. aeruginosa* in VAP. Many of the relevant data are based on cultures of sputum or endotracheal tube aspirates and may represent nonpathogenic colonization of the tracheobronchial tree, biofilms on the endotracheal tube, or simple tracheobronchitis.

Older reports of *P. aeruginosa* pneumonia described patients with an acute clinical syndrome of fever, chills, cough, and necrotizing pneumonia indistinguishable from other gram-negative bacterial pneumonias. The traditional accounts described a fulminant infection, with cyanosis, tachypnea, copious sputum, and systemic toxicity. Chest radiographs demonstrated bilateral pneumonia, often with nodular densities with or without cavities. This picture is now remarkably rare. Today, the typical patient is using a ventilator, has a slowly progressive infiltrate, and has been colonized with *P. aeruginosa* for days. While some cases may progress rapidly over 48–72 h, they are the exceptions. Nodular densities are not commonly seen. However, infiltrates may go on to necrosis. Necrotizing pneumonia has also been seen in the community (e.g., after inhalation of hot-tub water contaminated with *P. aeruginosa*). The typical patient has fever, leukocytosis, and purulent sputum, and

TABLE 57-2

ANTIBIOTIC TREATMENT OF INFECTIONS DUE TO *PSEUDOMONAS AERUGINOSA* AND RELATED SPECIES

INFECTION	ANTIBIOTICS AND DOSAGES	OTHER CONSIDERATIONS
Bacteremia		
Nonneutropenic host	Monotherapy: Ceftazidime (2 g q8h IV) or cefepime (2 g q12h IV) Combination therapy: Piperacillin/tazobactam (3.375 g q4h IV) or imipenem (500 mg q6h IV) or meropenem (1 g q8h IV) or doripenem (500 mg q8h IV) *plus* Amikacin (7.5 mg/kg q12h or 15 mg/kg q24h IV)	Add an aminoglycoside for patients in shock and in regions or hospitals where rates of resistance to the primary β-lactam agents are high. Tobramycin may be used instead of amikacin (susceptibility permitting).
Neutropenic host	Cefepime (2 g q8h IV) or all other agents (except doripenem) in above dosages	
Endocarditis	Antibiotic regimens as for bacteremia for 6–8 weeks	Resistance during therapy is common. Surgery is required for relapse.
Pneumonia	Drugs and dosages as for bacteremia, except that the available carbapenems should not be the sole primary drugs because of high rates of resistance during therapy	IDSA guidelines recommend the addition of an aminoglycoside or ciprofloxacin. The duration of therapy is 10–14 days.
Bone infection, malignant otitis externa	Cefepime or ceftazidime at the same dosages as for bacteremia; aminoglycosides not a necessary component of therapy; ciprofloxacin (500–750 mg q12h PO) may be used	Duration of therapy varies with the drug used (e.g., 6 weeks for a β-lactam agent; at least 3 months for oral therapy except in puncture-wound osteomyelitis, for which the duration should be 2–4 weeks).
Central nervous system infection	Ceftazidime or cefepime (2 g q8h IV) or meropenem (1 g q8h IV)	Abscesses or other closed-space infections may require drainage. The duration of therapy is ≥2 weeks.
Eye infection		
Keratitis/ulcer	Topical therapy with tobramycin/ciprofloxacin/levofloxacin eyedrops	Use maximal strengths available or compounded by pharmacy.
Endophthalmitis	Ceftazidime or cefepime as for central nervous system infection *plus* Topical therapy	
Urinary tract infection	Ciprofloxacin (500 mg q12h PO) or levofloxacin (750 mg q24h) or any aminoglycoside (total daily dose given once daily)	Relapse may occur if an obstruction or a foreign body is present.
Multidrug-resistant *P. aeruginosa* infection	Colistin (100 mg q12h IV) for the shortest possible period to obtain a clinical response	Doses used have varied. Dosage adjustment is required in renal failure. Inhaled colistin may be added for pneumonia (100 mg q12h).
Stenotrophomonas maltophilia infection	TMP-SMX (1600/320 mg q12h IV for 14 days) Ticarcillin/clavulanate (3.1 g q4h IV for 14 days)	Resistance to all agents is increasing. Levofloxacin may be an alternative, but there is little published clinical experience with this agent.
Burkholderia cepacia infection	Meropenem (1 g q8h IV for 14 days) TMP-SMX (1600/320 mg q12h IV for 14 days)	Resistance to both agents is increasing. Do not use them in combination because of possible antagonism.
Melioidosis, glanders	Ceftazidime (2 g q6h for 2 weeks) or meropenem (1 g q8h for 2 weeks) or imipenem (500 mg q6h for 2 weeks) *followed by* TMP-SMX (1600/320 mg q12h PO for 3 months)	

Abbreviations: IDSA, Infectious Diseases Society of America; TMP-SMX, trimethoprim-sulfamethoxazole.

the chest radiograph shows a new infiltrate or the expansion of a preexisting infiltrate. Chest examination generally detects rales or dullness. Of course, such findings are quite common among ventilated patients in the ICU. A sputum Gram's stain showing mainly polymorphonuclear leukocytes (PMNs) in conjunction with a culture positive for *P. aeruginosa* in this setting suggests a diagnosis of acute *P. aeruginosa* pneumonia. There is no consensus about whether an invasive procedure (e.g., bronchoalveolar lavage or protected-brush sampling of the distal airways) is superior to tracheal aspiration to obtain samples for lung cultures in order to substantiate the occurrence of *P. aeruginosa* pneumonia and prevent antibiotic overuse.

TREATMENT **Acute Pneumonia**

(Table 57-2) The results of therapy for *P. aeruginosa* pneumonia have been unsatisfactory. Reports suggest mortality rates of 40–80%, but how many of these deaths are attributable to underlying disease remains unknown. The drugs of choice for *P. aeruginosa* pneumonia are similar to those given for bacteremia. A potent antipseudomonal β-lactam drug is the mainstay of therapy. Failure rates were high when aminoglycosides were used as single agents, possibly because of their poor penetration into the airways and their binding to airway secretions. Thus a strong case cannot be made for the inclusion of the aminoglycoside component in regimens used against fully susceptible organisms, especially given the evidence that aminoglycosides are not optimally active in the lungs at concentrations normally reached after IV administration. Nonetheless, aminoglycosides are commonly used in clinical practice. Some experts suggest the combination of a β-lactam agent and an antipseudomonal fluoroquinolone instead when combination therapy is desired.

Chronic respiratory tract infections

P. aeruginosa is responsible for chronic infections of the airways associated with a number of underlying or predisposing conditions—most commonly CF in Caucasian populations. A state of chronic colonization beginning early in childhood is seen in some Asian populations with chronic or diffuse panbronchiolitis, a disease of unknown etiology. *P. aeruginosa* is one of the organisms that colonizes damaged bronchi in bronchiectasis, a disease secondary to multiple causes in which profound structural abnormalities of the airways result in mucus stasis.

TREATMENT **Chronic Respiratory Tract Infections**

Optimal management of chronic *P. aeruginosa* lung infection has not been determined. Patients respond clinically to antipseudomonal therapy, but the organism is rarely eradicated. Since eradication is unlikely, the aim of treatment for chronic infection is to quell exacerbations of inflammation. The regimens used are similar to those used for pneumonia, but an aminoglycoside is almost always added because resistance is common in chronic disease. However, it may be appropriate to use an inhaled aminoglycoside preparation in order to maximize airway drug levels.

Endovascular infections

Infective endocarditis due to *P. aeruginosa* is a disease of IV drug users whose native valves are involved. This organism has also been reported to cause prosthetic valve endocarditis. Sites of prior native-valve injury due to the injection of foreign material such as talc or fibers probably serve as niduses for bacterial attachment to the heart valve. The manifestations of *P. aeruginosa* endocarditis resemble those of other forms of acute endocarditis in IV drug users except that the disease is more indolent than *Staphylococcus aureus* endocarditis. While most disease involves the right side of the heart, left-sided involvement is not rare and multivalvular disease is common. Fever is a common manifestation, as is pulmonary involvement (due to septic emboli to the lungs). Hence, patients may also experience chest pain and hemoptysis. Involvement of the left side of the heart may lead to signs of cardiac failure, systemic emboli, and local cardiac involvement with sinus of Valsalva abscesses and conduction defects. Skin manifestations are rare in this disease, and ecthyma gangrenosum is not seen. The diagnosis is based on positive blood cultures along with clinical signs of endocarditis.

TREATMENT **Endovascular Infections**

(Table 57-2) It has been customary to use synergistic antibiotic combinations in treating *P. aeruginosa* endocarditis because of the development of resistance during therapy with a single antipseudomonal β-lactam agent. Which combination therapy is preferable is unclear, as all combinations have failed. Cases of *P. aeruginosa* endocarditis that relapse during or fail to respond to therapy are often caused by resistant organisms and may require surgical therapy. Other considerations for valve replacement are similar to those in other forms of endocarditis (Chap. 20).

Bone and joint infections

Although *P. aeruginosa* is an infrequent cause of bone and joint infections, *Pseudomonas* bacteremia or infective endocarditis caused by the injection of contaminated illicit drugs has been well documented to result in vertebral osteomyelitis and sternoclavicular joint arthritis. The clinical presentation of vertebral *P. aeruginosa* osteomyelitis is more indolent than that of staphylococcal osteomyelitis. The duration of symptoms in IV drug users with vertebral osteomyelitis due to *P. aeruginosa* varies from weeks to months. Fever is not uniformly present; when present, it tends to be low grade. There may be

mild tenderness at the site of involvement. Blood cultures are usually negative unless there is concomitant endocarditis. The erythrocyte sedimentation rate (ESR) is generally elevated. Vertebral osteomyelitis due to *P. aeruginosa* has also been reported in the elderly, in whom it originates from urinary tract infections (UTIs). The infection generally involves the lumbosacral area because of a shared venous drainage (Batson's plexus) between the lumbosacral spine and the pelvis. Sternoclavicular septic arthritis due to *P. aeruginosa* is seen almost exclusively in IV drug users. This disease may occur with or without endocarditis, and a primary site of infection often is not found. Plain radiographs show joint or bone involvement. Treatment of these forms of disease is generally successful.

Pseudomonas osteomyelitis of the foot most often follows puncture wounds through sneakers and mostly affects children. The main manifestation is pain in the foot, sometimes with superficial cellulitis around the puncture wound and tenderness on deep palpation of the wound. Multiple joints or bones of the foot may be involved. Systemic symptoms are generally absent, and blood cultures are usually negative. Radiographs may or may not be abnormal, but the bone scan is usually positive, as are MRI studies. Needle aspiration usually yields a diagnosis. Prompt surgery, with exploration of the nail puncture tract and debridement of the involved bones and cartilage, is generally recommended in addition to antibiotic therapy.

Central nervous system (CNS) infections

CNS infections due to *P. aeruginosa* are relatively rare. Involvement of the CNS is almost always secondary to a surgical procedure or head trauma. The entity seen most often is postoperative or posttraumatic meningitis. Subdural or epidural infection occasionally results from contamination of these areas. Embolic disease arising from endocarditis in IV drug users and leading to brain abscesses has also been described. The cerebrospinal fluid (CSF) profile of *P. aeruginosa* meningitis is no different from that of pyogenic meningitis of any other etiology.

TREATMENT **Central Nervous System Infections**

(Table 57-2) Treatment of *Pseudomonas* meningitis is difficult; little information has been published, and no controlled trials in humans have been undertaken. However, the general principles involved in the treatment of meningitis apply, including the need for high doses of bactericidal antibiotics to attain high drug levels in the CSF. The agent with which there is the most published experience in *P. aeruginosa* meningitis is ceftazidime, but other antipseudomonal β-lactam drugs that reach high CSF concentrations, such as cefepime and meropenem, have also been used successfully. Other forms of *P. aeruginosa* CNS infection, such as brain abscesses and epidural and subdural empyema, generally require surgical drainage in addition to antibiotic therapy.

Eye infections

Eye infections due to *P. aeruginosa* occur mainly as a result of direct inoculation into the tissue during trauma or surface injury by contact lenses. Keratitis and corneal ulcers are the most common types of eye disease and are often associated with contact lenses (especially the extended-wear variety). Keratitis can be slowly or rapidly progressive, but the classic description is disease progressing over 48 h to involve the entire cornea, with opacification and sometimes perforation. *P. aeruginosa* keratitis should be considered a medical emergency because of the rapidity with which it can progress to loss of sight. *P. aeruginosa* endophthalmitis secondary to bacteremia is the most devastating of *P. aeruginosa* eye infections. The disease is fulminant, with severe pain, chemosis, decreased visual acuity, anterior uveitis, vitreous involvement, and panophthalmitis.

TREATMENT **Eye Infections**

(Table 57-2) The usual therapy for keratitis is the administration of topical antibiotics. Therapy for endophthalmitis includes the use of high-dose local and systemic antibiotics (to achieve higher drug concentrations in the eye) and vitrectomy.

Ear infections

P. aeruginosa infections of the ears vary from mild swimmer's ear to serious life-threatening infections with neurologic sequelae. Swimmer's ear is common among children and results from infection of moist macerated skin of the external ear canal. Most cases resolve with treatment, but some patients develop chronic drainage. Swimmer's ear is managed with topical antibiotic agents (otic solutions). The most serious form of *Pseudomonas* infection involving the ear has been given various names: two of these designations, malignant otitis externa and necrotizing otitis externa, are now used for the same entity. This disease was originally described in elderly diabetic patients, in whom the majority of cases still occur. However, it has also been described in patients with AIDS and in elderly patients without underlying diabetes or immunocompromise. The usual presenting symptoms are decreased hearing and ear pain, which may be severe and lancinating. The pinna is usually painful, and the external canal may be tender. The ear canal almost always shows signs of inflammation, with granulation tissue and exudate. Tenderness anterior to the tragus may extend as far as the temporomandibular joint and mastoid process. A small minority of patients have systemic symptoms. Patients in whom the diagnosis is made late may present with cranial nerve palsies or even with cavernous venous sinus thrombosis. The ESR is invariably elevated (≥100 mm/h). The diagnosis is made on clinical grounds in severe cases; however, the "gold standard" is a positive technetium-99 bone scan in a patient with otitis externa due to *P. aeruginosa*. In diabetic patients, a positive bone

scan constitutes presumptive evidence for this diagnosis and should prompt biopsy or empirical therapy.

TREATMENT **Ear Infections**

(Table 57-2) Given the infection of the ear cartilage, sometimes with mastoid or petrous ridge involvement, patients with malignant (necrotizing) otitis externa are treated as for osteomyelitis.

Urinary tract infections

UTIs due to *P. aeruginosa* generally occur as a complication of a foreign body in the urinary tract, an obstruction in the genitourinary system, or urinary tract instrumentation or surgery. However, UTIs caused by *P. aeruginosa* have been described in pediatric outpatients without stones or evident obstruction.

TREATMENT **Urinary Tract Infections**

(Table 57-2) Most *P. aeruginosa* UTIs are considered complicated infections that must be treated longer than uncomplicated cystitis. In general, a 7- to 10-day course of treatment suffices, with up to 2 weeks of therapy in cases of pyelonephritis. Urinary catheters, stents, or stones should be removed to prevent relapse, which is common and may be due not to resistance but rather to factors such as a foreign body that has been left in place or an ongoing obstruction.

Skin and soft tissue infections

Besides pyoderma gangrenosum in neutropenic patients, folliculitis and other papular or vesicular lesions due to *P. aeruginosa* have been extensively described and are collectively referred to as *dermatitis*. Multiple outbreaks have been linked to whirlpools, spas, and swimming pools. To prevent such outbreaks, the growth of *P. aeruginosa* in the home and in recreational environments must be controlled by proper chlorination of water. Most cases of hot-tub folliculitis are self-limited, requiring only the avoidance of exposure to the contaminated source of water.

Toe-web infections occur especially often in the tropics, and the "green nail syndrome" is caused by *P. aeruginosa* paronychia, which results from frequent submersion of the hands in water. In the latter entity, the green discoloration results from diffusion of pyocyanin into the nail bed. *P. aeruginosa* remains a prominent cause of burn wound infections in some parts of the world. The management of these infections is best left to specialists in burn wound care.

Infections in febrile neutropenic patients

In febrile neutropenia, *P. aeruginosa* has historically been the organism against which empirical coverage is always essential. In the 1960s and early 1970s, *P. aeruginosa* infection occurred commonly in febrile neutropenic patients, with high associated mortality rates. Although in Western countries these infections are now less common, their importance has not diminished because of persistently high mortality rates. In other parts of the world as well, *P. aeruginosa* continues to be a significant problem in febrile neutropenia, causing a larger proportion of infections in febrile neutropenic patients than any other single organism. For example, *P. aeruginosa* was responsible for 28% of documented infections in 499 febrile neutropenic patients in one study from the Indian subcontinent and for 31% of such infections in another. In a large study of infections in leukemia patients from Japan, *P. aeruginosa* was the most frequently documented cause of bacterial infection. In studies performed in North America, northern Europe, and Australia, the incidence of *P. aeruginosa* bacteremia in febrile neutropenia was quite variable. In a review of 97 reports published in 1987–1994, the incidence was reported to be 1–2.5% among febrile neutropenic patients given empirical therapy and 5–12% among microbiologically documented infections. The most common clinical syndromes encountered were bacteremia, pneumonia, and soft tissue infections manifesting mainly as ecthyma gangrenosum.

TREATMENT **Infections in Febrile Neutropenic Patients**

(Table 57-2) Compared with rates three decades ago, improved rates of response to antibiotic therapy have been reported in many studies. A study of 127 patients demonstrated a reduction in the mortality rate from 71% to 25% with the introduction of ceftazidime and imipenem. Since neutrophils—the normal host defenses against this organism—are absent in febrile neutropenic patients, maximal doses of antipseudomonal β-lactam antibiotics should be used for the management of *P. aeruginosa* bacteremia in this setting.

Infections in patients with AIDS

Both community- and hospital-acquired *P. aeruginosa* infections were documented in patients with AIDS before the advent of antiretroviral therapy. Since the introduction of protease inhibitors, *P. aeruginosa* infections in AIDS patients have been seen less frequently but still occur, particularly in the form of sinusitis. The clinical presentation of *Pseudomonas* infection (especially pneumonia and bacteremia) in AIDS patients is remarkable in that, although the illness may appear not to be severe, the infection may nonetheless be fatal. Patients with bacteremia may have only a low-grade fever and may present with ecthyma gangrenosum. Bacteremia may herald underlying disease at another site (often pneumonia or sinusitis). Pneumonia, with or without bacteremia, is perhaps the most common type of *P. aeruginosa* infection in AIDS patients. Patients with AIDS and *P. aeruginosa* pneumonia exhibit the

classic clinical signs and symptoms of pneumonia, such as fever, productive cough, and chest pain. The infection may be lobar or multilobar and shows no predisposition for any particular location. The most striking feature is the high frequency of cavitary disease.

TREATMENT **Infections in Patients with AIDS**

Therapy for any of these conditions in AIDS patients is no different from that in other patients. However, relapse is the rule unless the patient's CD4+ T cell count rises to >50/μL or suppressive antibiotic therapy is given. In attempts to achieve cures and prevent relapses, therapy tends to be more prolonged than in the case of an immunocompetent patient.

Multidrug-resistant infections

(Table 57-2) *P. aeruginosa* is notorious for antibiotic resistance. During three decades, the impact of resistance was minimized by the rapid development of potent antipseudomonal agents. However, the situation has recently changed, with the worldwide selection of strains carrying determinants that mediate resistance to β-lactams, fluoroquinolones, and aminoglycosides. This situation has been compounded by the lack of development of new classes of antipseudomonal drugs for nearly two decades. Physicians now resort to drugs such as colistin and polymyxin, which were discarded decades ago. These alternative approaches to the management of multiresistant *P. aeruginosa* infections were first used some time ago in CF patients, who receive colistin (polymyxin E) IV and by aerosol despite its renal toxicity. Colistin is rapidly becoming the last-resort agent of choice, even in non-CF patients infected with multiresistant *P. aeruginosa*.

The clinical outcome of multidrug-resistant *P. aeruginosa* infections treated with colistin is difficult to judge from case reports, especially given the many drugs used in the complicated management of these patients. Although earlier reports described marginal efficacy and serious nephrotoxicity and neurotoxicity, recent reports have been more encouraging. Because colistin shows synergy with other antimicrobial agents in vitro, it may be possible to reduce the dosage—and thus the toxicity—of this drug when it is combined with drugs such as rifampin and β-lactams; however, no studies in humans or animals support this approach at this time.

OTHER PSEUDOMONADS

STENOTROPHOMONAS MALTOPHILIA

S. maltophilia is the only potential human pathogen among a genus of ubiquitous organisms found in the rhizosphere (i.e., the soil that surrounds the roots of plants). The organism is an opportunist that is acquired from the environment but is even more limited than *P. aeruginosa* in its ability to colonize patients or cause infections. Immunocompromise is not sufficient to permit these events; rather, major perturbations of the human flora are usually necessary for the establishment of *S. maltophilia*. Accordingly, most cases of human infection occur in the setting of very broad-spectrum antibiotic therapy with agents such as advanced cephalosporins and carbapenems, which eradicate the normal flora and other pathogens. The remarkable ability of *S. maltophilia* to resist virtually all classes of antibiotics is attributable to the possession of antibiotic efflux pumps and of two β-lactamases (L1 and L2) that mediate β-lactam resistance, including that to carbapenems. It is fortunate that the virulence of *S. maltophilia* appears to be limited. Although a serine protease is present in some strains, virulence is probably a result of the host's inflammatory response to components of the organism such as LPS and flagellin. *S. maltophilia* is most commonly found in the respiratory tract of ventilated patients, where the distinction between its roles as a colonizer and as a pathogen is often difficult to make. However, *S. maltophilia* does cause pneumonia and bacteremia in such patients, and these infections have led to septic shock. Also common is central venous line–associated infection (with or without bacteremia), which has been reported most often in patients with cancer. *S. maltophilia* is a rare cause of ecthyma gangrenosum in neutropenic patients. It has been isolated from ~5% of CF patients but is not believed to be a significant pathogen in this setting.

TREATMENT ***S. maltophilia* Infections**

The intrinsic resistance of *S. maltophilia* to most antibiotics renders infection difficult to treat. The antibiotics to which it is most often (although not uniformly) susceptible are trimethoprim-sulfamethoxazole (TMP-SMX), ticarcillin/clavulanate, and levofloxacin (Table 57-2). Consequently, a combination of TMP-SMX and ticarcillin/clavulanate is recommended for initial therapy. Catheters must be removed in the treatment of bacteremia to hasten cure and prevent relapses. The treatment of VAP due to *S. maltophilia* is much more difficult than that of bacteremia, with the frequent development of resistance during therapy.

BURKHOLDERIA CEPACIA

B. cepacia gained notoriety as the cause of a rapidly fatal syndrome of respiratory distress and septicemia (the "cepacia syndrome") in CF patients. Previously, it had been recognized as an antibiotic-resistant nosocomial pathogen (then designated *P. cepacia*) in ICU patients. Patients with chronic granulomatous disease are also predisposed to *B. cepacia* lung disease. The organism has been reclassified into nine subgroups, only some of which are common in CF. *B. cepacia* is an environmental organism that inhabits moist environments and is found in the rhizosphere.

This organism possesses multiple virulence factors that may play roles in disease as well as colonizing factors that are capable of binding to lung mucus—an ability that may explain the predilection of *B. cepacia* for the lungs in CF. *B. cepacia* secretes elastase and possesses components of an injectable toxin-secretion system like that of *P. aeruginosa*; its LPS is among the most potent of all LPSs in stimulating an inflammatory response in the lungs. Inflammation may be the major cause of the lung disease seen in the cepacia syndrome. The organism can penetrate epithelial surfaces by virtue of motility and inhibition of host innate immune defenses. Besides infecting the lungs in CF, *B. cepacia* appears as an airway colonizer during broad-spectrum antibiotic therapy and is a cause of VAP, catheter-associated infections, and wound infections.

TREATMENT ***B. cepacia* Infections**

B. cepacia is intrinsically resistant to many antibiotics. Therefore, treatment must be tailored according to sensitivities. TMP-SMX, meropenem, and doxycycline are the most effective agents in vitro and may be started as first-line agents (Table 57-2). Some strains are susceptible to third-generation cephalosporins and fluoroquinolones, and these agents may be used against isolates known to be susceptible. Combination therapy for serious pulmonary infection (e.g., in CF) is suggested for multidrug-resistant strains; the combination of meropenem and TMP-SMX may be antagonistic, however. Resistance to all agents used has been reported during therapy.

BURKHOLDERIA PSEUDOMALLEI

B. pseudomallei is the causative agent of melioidosis, a disease of humans and animals that is geographically restricted to Southeast Asia and northern Australia, with occasional cases in countries such as India and China. This organism may be isolated from individuals returning directly from these endemic regions and from military personnel who have served in endemic regions and then returned home after stops in Europe. Symptoms of this illness may develop only at a later date because of the organism's ability to cause latent infections. *B. pseudomallei* is found in soil and water. Humans and animals are infected by inoculation, inhalation, or ingestion; only rarely is the organism transmitted from person to person. Humans are not colonized without being infected. Among the pseudomonads, *B. pseudomallei* is perhaps the most virulent. Host compromise is not an essential prerequisite for disease, although many patients have common underlying medical diseases (e.g., diabetes or renal failure). *B. pseudomallei* is a facultative intracellular organism whose replication in PMNs and macrophages may be aided by the possession of a polysaccharide capsule. The organism also possesses elements of a type III secretion system that plays a role in its intracellular survival. During infection, there is a florid inflammatory response whose role in disease is unclear.

B. pseudomallei causes a wide spectrum of disease, ranging from asymptomatic infection to abscesses, pneumonia, and disseminated disease. It is a significant cause of fatal community-acquired pneumonia and septicemia in endemic areas, with mortality rates as high as 44% reported in Thailand. Acute pulmonary infections are the most commonly diagnosed form of melioidosis. Pneumonia may be asymptomatic (with routine chest radiographs showing mainly upper-lobe infiltrates) or may present as severe necrotizing disease. *B. pseudomallei* also causes chronic pulmonary infections with systemic manifestations that mimic those of tuberculosis, including chronic cough, fever, hemoptysis, night sweats, and cavitary lung disease. Besides pneumonia, the other principal form of *B. pseudomallei* disease is skin ulceration with associated lymphangitis and regional lymphadenopathy. Spread from the lungs or skin, which is most often documented in debilitated individuals, gives rise to septicemic forms of melioidosis that carry a high mortality rate.

TREATMENT ***B. pseudomallei* Infections**

B. pseudomallei is susceptible to advanced penicillins and cephalosporins and to carbapenems (Table 57-2). Treatment is divided into two stages: an intensive 2-week phase of therapy with ceftazidime or a carbapenem followed by at least 12 weeks of oral TMP-SMX to eradicate the organism and prevent relapse. The recognition of this bacterium as a potential agent of biologic warfare has stimulated interest in the development of a vaccine.

BURKHOLDERIA MALLEI

B. mallei causes the equine disease glanders in Africa, Asia, and South America. The organism was eradicated from Europe and North America decades ago. The last case seen in the United States occurred in 2001 in a laboratory worker; before that, *B. mallei* had last been seen in this country in 1949. In contrast to the other organisms discussed in this chapter, *B. mallei* is not an environmental organism and does not persist outside its equine hosts. Consequently, *B. mallei* infection is an occupational risk for handlers of horses, equine butchers, and veterinarians in areas of the world where it still exists. The polysaccharide capsule is a critical virulence determinant; diabetics are thought to be more susceptible to infection by this organism. The organism is transmitted from animals to humans by inoculation into the skin, where it causes local infection with nodules and lymphadenitis. Regional lymphadenopathy is common. Respiratory secretions from infected horses are extremely infectious. Inhalation results in clinical signs of typical pneumonia but may also cause an acute febrile illness with ulceration of the trachea.

The organism may disseminate from the skin or lungs to cause septicemia with signs of sepsis. The septicemic form is frequently associated with shock and a high mortality rate. The infection may also enter a chronic phase and present as disseminated abscesses. *B. mallei* infection may present as early as 1–2 days after inhalation or (in cutaneous disease) may not become evident for months.

TREATMENT ***B. mallei* Infections**

The antibiotic susceptibility pattern of *B. mallei* is similar to that of *B. pseudomallei*; in addition, the organism is susceptible to the newer macrolides azithromycin and clarithromycin. *B. mallei* infection should be treated with the same drugs and for the same duration as melioidosis.

CHAPTER 58

SALMONELLOSIS

David A. Pegues ■ Samuel I. Miller

Bacteria of the genus *Salmonella* are highly adapted for growth in both humans and animals and cause a wide spectrum of disease. The growth of serotypes *S. typhi* and *S. paratyphi* is restricted to human hosts, in whom these organisms cause enteric (typhoid) fever. The remaining serotypes (nontyphoidal *Salmonella*, or NTS) can colonize the gastrointestinal tracts of a broad range of animals, including mammals, reptiles, birds, and insects. More than 200 serotypes are pathogenic to humans, in whom they often cause gastroenteritis and can be associated with localized infections and/or bacteremia.

ETIOLOGY

This large genus of gram-negative bacilli within the family Enterobacteriaceae consists of two species: *S. enterica*, which contains six subspecies, and *S. bongori*. *S. enterica* subspecies I includes almost all the serotypes pathogenic for humans. According to the current *Salmonella* nomenclature system, the full taxonomic designation *S. enterica* subspecies *enterica* serotype *typhimurium* can be shortened to *Salmonella* serotype *typhimurium* or simply *S. typhimurium*.

Members of the seven *Salmonella* subspecies are classified into >2500 serotypes (serovars) according to the somatic O antigen (lipopolysaccharide [LPS] cell-wall components), the surface Vi antigen (restricted to *S. typhi* and *S. paratyphi* C), and the flagellar H antigen. For simplicity, most *Salmonella* serotypes are named for the city where they were identified, and the serotype is often used as the species designation.

Salmonellae are gram-negative, non-spore-forming, facultatively anaerobic bacilli that measure 2–3 by 0.4–0.6 μm. The initial identification of salmonellae in the clinical microbiology laboratory is based on growth characteristics. Salmonellae, like other Enterobacteriaceae, produce acid on glucose fermentation, reduce nitrates, and do not produce cytochrome oxidase. In addition, all salmonellae except *S. gallinarum-pullorum* are motile by means of peritrichous flagella, and all but *S. typhi* produce gas (H_2S) on sugar fermentation. Notably, only 1% of clinical isolates ferment lactose; a high level of suspicion must be maintained to detect these rare clinical lactose-fermenting isolates.

Although serotyping of all surface antigens can be used for formal identification, most laboratories perform a few simple agglutination reactions that define specific O-antigen serogroups, designated A, B, C_1, C_2, D, and E. Strains in these six serogroups cause ~99% of *Salmonella* infections in humans and other warm-blooded animals. Molecular typing methods, including pulsed-field gel electrophoresis and polymerase chain reaction (PCR) fingerprinting, are used in epidemiologic investigations to differentiate *Salmonella* strains of a common serotype.

PATHOGENESIS

All *Salmonella* infections begin with ingestion of organisms, most commonly in contaminated food or water. The infectious dose is 10^3–10^6 colony-forming units. Conditions that decrease either stomach acidity (an age

of <1 year, antacid ingestion, or achlorhydric disease) or intestinal integrity (inflammatory bowel disease, prior gastrointestinal surgery, or alteration of the intestinal flora by antibiotic administration) increase susceptibility to *Salmonella* infection.

Once *S. typhi* and *S. paratyphi* reach the small intestine, they penetrate the mucus layer of the gut and traverse the intestinal layer through phagocytic microfold (M) cells that reside within Peyer's patches. Salmonellae can trigger the formation of membrane ruffles in normally nonphagocytic epithelial cells. These ruffles reach out and enclose adherent bacteria within large vesicles by a process referred to as *bacteria-mediated endocytosis* (BME). BME is dependent on the direct delivery of *Salmonella* proteins into the cytoplasm of epithelial cells by a specialized bacterial secretion system (*type III secretion*). These bacterial proteins mediate alterations in the actin cytoskeleton that are required for *Salmonella* uptake.

After crossing the epithelial layer of the small intestine, *S. typhi* and *S. paratyphi*, which cause enteric (typhoid) fever, are phagocytosed by macrophages. These salmonellae survive the antimicrobial environment of the macrophage by sensing environmental signals that trigger alterations in regulatory systems of the phagocytosed bacteria. For example, PhoP/PhoQ (the best-characterized regulatory system) triggers the expression of outer-membrane proteins and mediates modifications in LPS so that the altered bacterial surface can resist microbicidal activities and potentially alter host cell signaling. In addition, salmonellae encode a second type III secretion system that directly delivers bacterial proteins across the phagosome membrane into the macrophage cytoplasm. This secretion system functions to remodel the *Salmonella*-containing vacuole, promoting bacterial survival and replication.

Once phagocytosed, typhoidal salmonellae disseminate throughout the body in macrophages via the lymphatics and colonize reticuloendothelial tissues (liver, spleen, lymph nodes, and bone marrow). Patients have relatively few or no signs and symptoms during this initial incubation stage. Signs and symptoms, including fever and abdominal pain, probably result from secretion of cytokines by macrophages and epithelial cells in response to bacterial products that are recognized by innate immune receptors when a critical number of organisms have replicated. Over time, the development of hepatosplenomegaly is likely to be related to the recruitment of mononuclear cells and the development of a specific acquired cell-mediated immune response to *S. typhi* colonization. The recruitment of additional mononuclear cells and lymphocytes to Peyer's patches during the several weeks after initial colonization/infection can result in marked enlargement and necrosis of the Peyer's patches, which may be mediated by bacterial products that promote cell death as well as the inflammatory response.

In contrast to enteric fever, which is characterized by an infiltration of mononuclear cells into the small-bowel mucosa, NTS gastroenteritis is characterized by massive polymorphonuclear leukocyte (PMN) infiltration into both the large- and small-bowel mucosa. This response appears to depend on the induction of interleukin (IL) 8, a strong neutrophil chemotactic factor, which is secreted by intestinal cells as a result of *Salmonella* colonization and translocation of bacterial proteins into host cell cytoplasm. The degranulation and release of toxic substances by neutrophils may result in damage to the intestinal mucosa, causing the inflammatory diarrhea observed with nontyphoidal gastroenteritis.

ENTERIC (TYPHOID) FEVER

Enteric (typhoid) fever is a systemic disease characterized by fever and abdominal pain and caused by dissemination of *S. typhi* or *S. paratyphi*. The disease was initially called *typhoid fever* because of its clinical similarity to typhus. However, in the early 1800s, typhoid fever was clearly defined pathologically as a unique illness on the basis of its association with enlarged Peyer's patches and mesenteric lymph nodes. In 1869, given the anatomic site of infection, the term *enteric fever* was proposed as an alternative designation to distinguish typhoid fever from typhus. However, to this day, the two designations are used interchangeably.

EPIDEMIOLOGY

In contrast to other *Salmonella* serotypes, the etiologic agents of enteric fever—*S. typhi* and *S. paratyphi* serotypes A, B, and C—have no known hosts other than humans. Most commonly, food-borne or waterborne transmission results from fecal contamination by ill or asymptomatic chronic carriers. Sexual transmission between male partners has been described. Health care workers occasionally acquire enteric fever after exposure to infected patients or during processing of clinical specimens and cultures.

With improvements in food handling and water/sewage treatment, enteric fever has become rare in developed nations. Worldwide, however, there are an estimated 22 million cases of enteric fever, with 200,000 deaths annually. The incidence is highest (>100 cases per 100,000 population per year) in south central and Southeast Asia; medium (10–100 cases per 100,000) in the rest of Asia, Africa, Latin America, and Oceania (excluding Australia and New Zealand); and low in other parts of the world **(Fig. 58-1)**. A high incidence of enteric fever correlates with poor sanitation and lack of access to clean drinking water. In endemic regions, enteric fever is more common in urban than rural areas and among young children and adolescents. Risk factors include contaminated water or ice, flooding, food and drinks purchased from street vendors, raw fruits and vegetables grown in fields fertilized with sewage, ill household contacts, lack of hand washing and toilet access, and evidence of prior *Helicobacter pylori* infection (an association probably related to chronically reduced

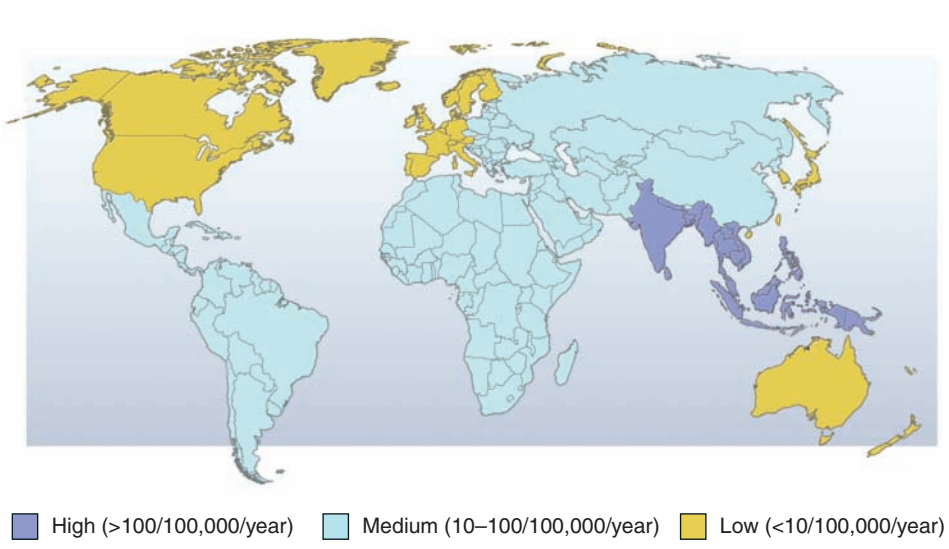


FIGURE 58-1
Annual incidence of typhoid fever per 100,000 population. (*Adapted from JA Crump et al: The global burden of typhoid fever. Bull World Health Organ 82:346, 2004.*)

gastric acidity). It is estimated that there is one case of paratyphoid fever for every four cases of typhoid fever, but the incidence of infection associated with *S. paratyphi* A appears to be increasing, especially in India; this increase may be a result of vaccination for *S. typhi*.

Multidrug-resistant (MDR) strains of *S. typhi* emerged in 1989 in China and Southeast Asia and have since disseminated widely. These strains contain plasmids encoding resistance to chloramphenicol, ampicillin, and trimethoprim—antibiotics long used to treat enteric fever. With the increased use of fluoroquinolones to treat MDR enteric fever in the 1990s, strains of *S. typhi* and *S. paratyphi* with reduced susceptibility to ciprofloxacin (minimal inhibitory concentration [MIC], 0.125–1 μg/mL) have emerged in the Indian subcontinent, southern Asia, and (most recently) sub-Saharan Africa and have been associated with clinical treatment failure. Testing of isolates for resistance to the first-generation quinolone nalidixic acid detects most but not all strains with reduced susceptibility to ciprofloxacin.

The incidence of enteric fever among U.S. travelers is estimated at 3–30 cases per 100,000. Of 1902 cases of *S. typhi*–associated enteric fever reported to the Centers for Disease Control and Prevention (CDC) in 1999–2006, 79% were associated with recent international travel, most commonly to India (47%), Pakistan (10%), Bangladesh (10%), Mexico (7%), and the Philippines (4%). Only 5% of travelers diagnosed with enteric fever had received *S. typhi* vaccine. Overall, 13% of *S. typhi* isolates in the United States were resistant to ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole (TMP-SMX), and the proportion of isolates resistant to nalidixic acid increased from 19% in 1999 to 58% in 2006. Infection with nalidixic acid-resistant (NAR) *S. typhi* was associated with travel to the Indian subcontinent. Of the 25–30% of reported cases of enteric fever in the United States that are domestically acquired, the majority are sporadic, but outbreaks linked to contaminated food products and previously unrecognized chronic carriers continue to occur.

CLINICAL COURSE

Enteric fever is a misnomer, in that the hallmark features of this disease—fever and abdominal pain—are variable. While fever is documented at presentation in >75% of cases, abdominal pain is reported in only 30–40%. Thus, a high index of suspicion for this potentially fatal systemic illness is necessary when a person presents with fever and a history of recent travel to a developing country.

The incubation period for *S. typhi* averages 10–14 days but ranges from 3–21 days, depending on the inoculum size and the host's health and immune status. The most prominent symptom is prolonged fever (38.8°–40.5°C; 101.8°–104.9°F), which can continue for up to 4 weeks if untreated. *S. paratyphi* A is thought to cause milder disease than *S typhi*, with predominantly gastrointestinal symptoms. However, a prospective study of 669 consecutive cases of enteric fever in Kathmandu, Nepal, found that the infections were clinically indistinguishable. In this series, symptoms reported on initial medical evaluation included headache (80%), chills (35–45%), cough (30%), sweating (20–25%), myalgias (20%), malaise (10%), and arthralgia (2–4%). Gastrointestinal symptoms included anorexia (55%), abdominal pain (30–40%), nausea (18–24%), vomiting (18%), and diarrhea (22–28%) more commonly than constipation (13–16%). Physical findings included coated tongue (51–56%), splenomegaly (5–6%), and abdominal tenderness (4–5%).

Early physical findings of enteric fever include rash ("rose spots"; 30%), hepatosplenomegaly (3–6%), epistaxis, and relative bradycardia at the peak of high fever (<50%). Rose spots (**Fig. 58-2**; see also Fig. 11-9) make up a faint, salmon-colored, blanching, maculopapular rash located primarily on the trunk and chest. The rash is evident in ~30% of patients at the end of

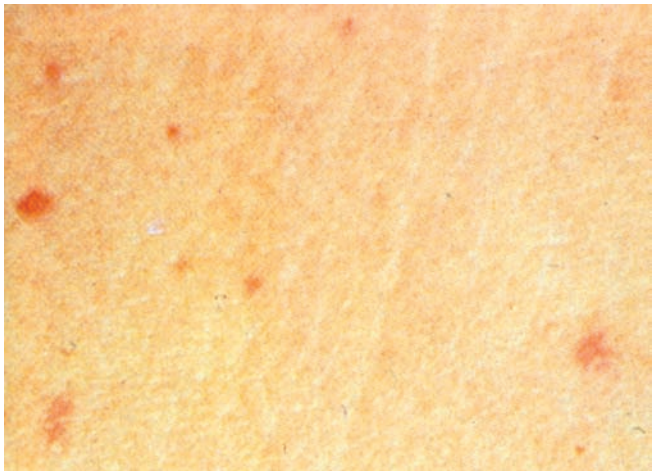


FIGURE 58-2
"Rose spots," the rash of enteric fever due to *S. typhi* or *S. paratyphi*.

the first week and resolves without a trace after 2–5 days. Patients can have two or three crops of lesions, and *Salmonella* can be cultured from punch biopsies of these lesions. The faintness of the rash makes it difficult to detect in highly pigmented patients.

The development of severe disease (which occurs in ~10–15% of patients) depends on host factors (immunosuppression, antacid therapy, previous exposure, and vaccination), strain virulence and inoculum, and choice of antibiotic therapy. Gastrointestinal bleeding (10–20%) and intestinal perforation (1–3%) most commonly occur in the third and fourth weeks of illness and result from hyperplasia, ulceration, and necrosis of the ileocecal Peyer's patches at the initial site of *Salmonella* infiltration. Both complications are life-threatening and require immediate fluid resuscitation and surgical intervention, with broadened antibiotic coverage for polymicrobial peritonitis (Chap. 25) and treatment of gastrointestinal hemorrhages, including bowel resection. Neurologic manifestations occur in 2–40% of patients and include meningitis, Guillain-Barré syndrome, neuritis, and neuropsychiatric symptoms (described as "muttering delirium" or "coma vigil"), with picking at bedclothes or imaginary objects.

Rare complications whose incidences are reduced by prompt antibiotic treatment include disseminated intravascular coagulation, hematophagocytic syndrome, pancreatitis, hepatic and splenic abscesses and granulomas, endocarditis, pericarditis, myocarditis, orchitis, hepatitis, glomerulonephritis, pyelonephritis and hemolytic-uremic syndrome, severe pneumonia, arthritis, osteomyelitis, and parotitis. Up to 10% of patients develop mild relapse, usually within 2–3 weeks of fever resolution and in association with the same strain type and susceptibility profile.

Up to 10% of untreated patients with typhoid fever excrete *S. typhi* in the feces for up to 3 months, and 1–4% develop chronic asymptomatic carriage, shedding *S. typhi* in either urine or stool for >1 year. Chronic carriage is more common among women, infants, and persons who have biliary abnormalities or concurrent bladder infection with *Schistosoma haematobium*. The anatomic abnormalities associated with the latter conditions presumably allow prolonged colonization.

DIAGNOSIS

Since the clinical presentation of enteric fever is relatively nonspecific, the diagnosis needs to be considered in any febrile traveler returning from a developing region, especially the Indian subcontinent, the Philippines, or Latin America. Other diagnoses that should be considered in these travelers include malaria, hepatitis, bacterial enteritis, dengue fever, rickettsial infections, leptospirosis, amebic liver abscesses, and acute HIV infection (Chap. 5). Other than a positive culture, no specific laboratory test is diagnostic for enteric fever. In 15–25% of cases, leukopenia and neutropenia are detectable. Leukocytosis is more common among children, during the first 10 days of illness, and in cases complicated by intestinal perforation or secondary infection. Other nonspecific laboratory findings include moderately elevated liver function tests and muscle enzyme levels.

The definitive diagnosis of enteric fever requires the isolation of *S. typhi* or *S. paratyphi* from blood, bone marrow, other sterile sites, rose spots, stool, or intestinal secretions. The sensitivity of blood culture is only 40–80%, probably because of high rates of antibiotic use in endemic areas and the small quantities of *S. typhi* (i.e., <15 organisms/mL) typically present in the blood. Since almost all *S. typhi* organisms in blood are associated with the mononuclear-cell/platelet fraction, centrifugation of blood and culture of the buffy coat can substantially reduce the time to isolation of the organism but do not increase sensitivity.

Bone marrow culture is 55–90% sensitive, and, unlike that of blood culture, its yield is not reduced by up to 5 days of prior antibiotic therapy. Culture of intestinal secretions (best obtained by a noninvasive duodenal string test) can be positive despite a negative bone marrow culture. If blood, bone marrow, and intestinal secretions are all cultured, the yield is >90%. Stool cultures, while negative in 60–70% of cases during the first week, can become positive during the third week of infection in untreated patients.

Several serologic tests, including the classic Widal test for "febrile agglutinins," are available. None of these tests is sufficiently sensitive or specific to replace culture-based methods for the diagnosis of enteric fever in developed countries. PCR and DNA probe assays to detect *S. typhi* in blood have been identified but have not yet been developed for clinical use.

TREATMENT Enteric (Typhoid) Fever

Prompt administration of appropriate antibiotic therapy prevents severe complications of enteric fever and results in a case-fatality rate of <1%. The initial choice of antibiotics depends on the susceptibility of the *S. typhi* and *S. paratyphi* strains in the area of residence or travel (Table 58-1). For treatment of drug-susceptible

TABLE 58-1

ANTIBIOTIC THERAPY FOR ENTERIC (TYPHOID) FEVER IN ADULTS

INDICATION	AGENT	DOSAGE (ROUTE)	DURATION, DAYS
Empirical Treatment			
	Ceftriaxone[a]	1–2 g/d (IV)	7–14
	Azithromycin	1 g/d (PO)	5
Fully Susceptible			
	Ciprofloxacin[b] (first line)	500 mg bid (PO) or 400 mg q12h (IV)	5–7
	Amoxicillin (second line)	1 g tid (PO) or 2 g q6h (IV)	14
	Chloramphenicol	25 mg/kg tid (PO or IV)	14–21
	Trimethoprim-sulfamethoxazole	160/800 mg bid (PO)	7–14
Multidrug-Resistant			
	Ciprofloxacin	500 mg bid (PO) or 400 mg q12h (IV)	5–7
	Ceftriaxone	2–3 g/d (IV)	7–14
	Azithromycin	1 g/d (PO)[c]	5
Nalidixic Acid–Resistant			
	Ceftriaxone	2–3 g/d (IV)	7–14
	Azithromycin	1 g/d (PO)	5
	High-dose ciprofloxacin	750 mg bid (PO) or 400 mg q8h (IV)	10–14

[a]Or another third-generation cephalosporin (e.g., cefotaxime, 2 g q8h (IV); or cefixime, 400 mg bid [PO]).
[b]Or ofloxacin, 400 mg bid (PO) for 2–5 days.
[c]Or 1 g on day 1 followed by 500 mg/d PO for 6 days.

typhoid fever, fluoroquinolones are the most effective class of agents, with cure rates of ~98% and relapse and fecal carriage rates of <2%. Experience is most extensive with ciprofloxacin. Short-course ofloxacin therapy is similarly successful against infection caused by nalidixic acid–susceptible strains. However, the increased incidence of NAR *S. typhi* in Asia, which is probably related to the widespread availability of fluoroquinolones over the counter, is now limiting the use of this drug class for empirical therapy. Patients infected with NAR *S. typhi* strains should be treated with ceftriaxone, azithromycin, or high-dose ciprofloxacin. High-dose fluoroquinolone therapy for 7 days for NAR enteric fever has been associated with delayed resolution of fever and high rates of fecal carriage during convalescence. For NAR strains, 10–14 days of high-dose ciprofloxacin is preferred.

Ceftriaxone, cefotaxime, and (oral) cefixime are effective for treatment of MDR enteric fever, including NAR and fluoroquinolone-resistant strains. These agents clear fever in ~1 week, with failure rates of ~5–10%, fecal carriage rates of <3%, and relapse rates of 3–6%. Oral azithromycin results in defervescence in 4–6 days, with rates of relapse and convalescent stool carriage of <3%. Against NAR strains, azithromycin is associated with lower rates of treatment failure and shorter durations of hospitalization than are fluoroquinolones. Despite efficient in vitro killing of *Salmonella*, first- and second-generation cephalosporins as well as aminoglycosides are ineffective in the treatment of clinical infections.

Most patients with uncomplicated enteric fever can be managed at home with oral antibiotics and antipyretics. Patients with persistent vomiting, diarrhea, and/or abdominal distension should be hospitalized and given supportive therapy as well as a parenteral third-generation cephalosporin or fluoroquinolone, depending on the susceptibility profile. Therapy should be administered for at least 10 days or for 5 days after fever resolution.

In a randomized, prospective, double-blind study of critically ill patients with enteric fever (i.e., those with shock and obtundation) in Indonesia in the early 1980s, the administration of dexamethasone (an initial dose of 3 mg/kg followed by eight doses of 1 mg/kg every 6 h) with chloramphenicol was associated with a substantially lower mortality rate than was treatment with chloramphenicol alone (10% vs 55%). Although this study has not been repeated in the "post-chloramphenicol era," severe enteric fever remains one of the few indications for glucocorticoid treatment of an acute bacterial infection.

The 1–5% of patients who develop chronic carriage of *Salmonella* can be treated for 4–6 weeks with an appropriate oral antibiotic. Treatment with oral amoxicillin, TMP-SMX, ciprofloxacin, or norfloxacin is ~80% effective in eradicating chronic carriage of susceptible organisms. However, in cases of anatomic abnormality (e.g., biliary or kidney stones), eradication often requires both antibiotic therapy and surgical correction.

PREVENTION AND CONTROL

Theoretically, it is possible to eliminate the salmonellae that cause enteric fever since they survive only in human hosts and are spread by contaminated food and water. However, given the high prevalence of the disease in developing countries that lack adequate sewage disposal and water treatment, this goal is currently unrealistic. Thus, travelers to developing countries should be advised to monitor their food and water intake carefully and to consider vaccination.

Two typhoid vaccines are commercially available: (1) Ty21a, an oral live attenuated *S. typhi* vaccine (given on days 1, 3, 5, and 7, with a booster every 5 years); and (2) Vi CPS, a parenteral vaccine consisting of purified Vi polysaccharide from the bacterial capsule (given in 1 dose, with a booster every 2 years). The old parenteral whole-cell typhoid/paratyphoid A and B vaccine is no longer licensed, largely because of significant side effects (see next). An acetone-killed whole-cell vaccine is available only for use by the U.S. military. The minimal age for vaccination is 6 years for Ty21a and 2 years for Vi CPS. Currently, there is no licensed vaccine for paratyphoid fever.

A large-scale meta-analysis of vaccine trials comparing whole-cell vaccine, Ty21a, and Vi CPS in populations in endemic areas indicates that, while all three vaccines are similarly effective for the first year, the 3-year cumulative efficacy of the whole-cell vaccine (73%) exceeds that of both Ty21a (51%) and Vi CPS (55%). In addition, the heat-killed whole-cell vaccine maintains its efficacy for 5 years, whereas Ty21a and Vi CPS maintain their efficacy for 4 and 2 years, respectively. However, the whole-cell vaccine is associated with a much higher incidence of side effects (especially fever: 16% vs 1–2%) than the other two vaccines.

Vi CPS typhoid vaccine is poorly immunogenic in children <5 years of age because of T cell–independent properties. In the recently developed Vi-rEPA vaccine, Vi is bound to a nontoxic recombinant protein that is identical to *Pseudomonas aeruginosa* exotoxin A. In 2- to 4-year-olds, two injections of Vi-rEPA induced higher T cell responses and higher levels of serum IgG antibody to Vi than did Vi CPS in 5- to 14-year-olds. In a two-dose trial in 2- to 5-year-old children in Vietnam, Vi-rEPA provided 91% efficacy at 27 months and 88% efficacy at 43 months and was very well tolerated. This vaccine is not yet commercially available in the United States. At least three new live vaccines are in clinical development and may prove more efficacious and longer-lasting than previous live vaccines.

Typhoid vaccine is not required for international travel, but it is recommended for travelers to areas where there is a moderate to high risk of exposure to *S. typhi*, especially those who are traveling to southern Asia and other developing regions of Asia, Africa, the Caribbean, and Central and South America and who will be exposed to potentially contaminated food and drink. Typhoid vaccine should be considered even for persons planning <2 weeks of travel to high-risk areas. In addition, laboratory workers who deal with *S. typhi* and household contacts of known *S. typhi* carriers should be vaccinated. Because the protective efficacy of vaccine can be overcome by the high inocula that are commonly encountered in food-borne exposures, immunization is an adjunct and not a substitute for avoiding high-risk foods and beverages. Immunization is not recommended for adults residing in typhoid-endemic areas or for the management of persons who may have been exposed in a common-source outbreak.

Enteric fever is a notifiable disease in the United States. Individual health departments have their own guidelines for allowing ill or colonized food handlers or health care workers to return to their jobs. The reporting system enables public health departments to identify potential source patients and to treat chronic carriers in order to prevent further outbreaks. In addition, since 1–4% of patients with *S. typhi* infection become chronic carriers, it is important to monitor patients (especially child-care providers and food handlers) for chronic carriage and to treat this condition if indicated.

NONTYPHOIDAL SALMONELLOSIS

EPIDEMIOLOGY

In the United States, the incidence of NTS infection has doubled in the past 2 decades; the 2009 figure is ~14 million cases annually. In 2007, the incidence of NTS infection in this country was 14.9 per 100,000 persons—the highest rate among the 11 food-borne enteric pathogens under active surveillance. Five serotypes accounted for one-half of U.S. infections in 2007: *typhimurium* (19%), *enteritidis* (14%), Newport (9%), Javiana (5%), and Heidelberg (4%).

The incidence of nontyphoidal salmonellosis is highest during the rainy season in tropical climates and during the warmer months in temperate climates, coinciding with the peak in food-borne outbreaks. Rates of morbidity and mortality associated with NTS are highest among the elderly, infants, and immunocompromised individuals, including those with hemoglobinopathies, HIV infection, or infections that cause blockade of the reticuloendothelial system (e.g., bartonellosis, malaria, schistosomiasis, and histoplasmosis).

Unlike *S. typhi* and *S. paratyphi*, whose only reservoir is humans, NTS can be acquired from multiple animal reservoirs. Transmission is most commonly associated with animal food products, especially eggs, poultry, undercooked ground meat, dairy products, and fresh produce contaminated with animal waste.

S. enteritidis infection associated with chicken eggs emerged as a major cause of food-borne disease during the 1980s and 1990s. *S. enteritidis* infection of the ovaries and upper oviduct tissue of hens results in contamination of egg contents before shell deposition. Infection is spread to egg-laying hens from breeding flocks and through contact with rodents and manure. Of the 997 outbreaks of *S. enteritidis* with a confirmed source that

were reported to the CDC in 1985–2003, 75% were associated with raw or undercooked eggs. After peaking at 3.9 cases per 100,000 U.S. population in 1995, the incidence of *S. enteritidis* infection declined substantially to 1.7 per 100,000 in 2003; this decrease probably reflected improved on-farm control measures, refrigeration, and education of consumers and food-service workers. Transmission via contaminated eggs can be prevented by cooking eggs until the yolk is solidified and through pasteurization of egg products.

Centralization of food processing and widespread food distribution have contributed to the increased incidence of NTS in developed countries. Manufactured foods to which recent *Salmonella* outbreaks have been traced include peanut butter; milk products, including infant formula; and various processed foods, including packaged breakfast cereal, salsa, frozen prepared meals, and snack foods. Large outbreaks have also been linked to fresh produce, including alfalfa sprouts, cantaloupe, fresh-squeezed orange juice, and tomatoes; these items become contaminated by manure or water at a single site and then are widely distributed.

An estimated 6% of sporadic *Salmonella* infections in the United States are attributed to contact with reptiles and amphibians, especially iguanas, snakes, turtles, and lizards. Reptile-associated *Salmonella* infection more commonly leads to hospitalization and more frequently involves infants than do other *Salmonella* infections. Other pets, including African hedgehogs, snakes, birds, rodents, baby chicks, ducklings, dogs, and cats, are also potential sources of NTS.

Increasing antibiotic resistance in NTS species is a global problem and has been linked to the widespread use of antimicrobial agents in food animals and especially in animal feed. In the early 1990s, *S. typhimurium* definitive phage type 104 (DT104), characterized by resistance to ≥5 antibiotics (ampicillin, chloramphenicol, streptomycin, sulfonamides, and tetracyclines; R-type ACSSuT), emerged worldwide. In 2005, resistance to at least ACSSuT was the most common MDR phenotype among NTS isolates in the United States. Acquisition is associated with exposure to ill farm animals and to various meat products, including uncooked or undercooked ground beef. Although probably no more virulent than susceptible *S. typhimurium* strains, DT104 strains are associated with an increased risk of bloodstream infection and hospitalization. NAR and trimethoprim-resistant DT104 strains are emerging, especially in the United Kingdom.

Because of increased resistance to conventional antibiotics such as ampicillin and TMP-SMX, extended-spectrum cephalosporins and fluoroquinolones have emerged as the agents of choice for the treatment of MDR NTS infections. In 2005, 2% of all NTS strains and 12.6% of *S.* Newport strains were resistant to ceftriaxone. Most ceftriaxone-resistant isolates were from children <18 years of age, in whom ceftriaxone is the antibiotic of choice for treatment of invasive NTS infection. These strains contained plasmid-encoded AmpC β-lactamases that were probably acquired by horizontal genetic transfer from *Escherichia coli* strains in food-producing animals—an event linked to the widespread use of the veterinary cephalosporin ceftiofur.

Resistance to nalidixic acid and fluoroquinolones also has begun to emerge and is most commonly associated with point mutations in the DNA gyrase genes *gyr*A and *gyr*B. Nalidixic acid resistance is a good predictor of reduced susceptibility to clinically useful fluoroquinolones. From 1996–2005, the rate of NAR NTS isolates in the United States increased fivefold (from 0.5–2.4%). In Denmark, infection with NAR *S. typhimurium* DT104 has been linked to swine and associated with a threefold higher risk of invasive disease or death within 90 days. In Taiwan in 2000, a strain of ciprofloxacin-resistant (MIC, ≥4 μg/mL) *S. choleraesuis* caused a large outbreak of invasive infections that was linked to the use of enrofloxacin in swine feed.

CLINICAL MANIFESTATIONS

Gastroenteritis

Infection with NTS most often results in gastroenteritis indistinguishable from that caused by other enteric pathogens. Nausea, vomiting, and diarrhea occur 6–48 h after the ingestion of contaminated food or water. Patients often experience abdominal cramping and fever (38–39°C; 100.5–102.2°F). Diarrheal stools are usually loose, nonbloody, and of moderate volume. However, large-volume watery stools, bloody stools, or symptoms of dysentery may occur. Rarely, NTS causes pseudoappendicitis or an illness that mimics inflammatory bowel disease.

Gastroenteritis caused by NTS is usually self-limited. Diarrhea resolves within 3–7 days and fever within 72 h. Stool cultures remain positive for 4–5 weeks after infection and—in rare cases of chronic carriage (<1%)—for >1 year. Antibiotic treatment usually is not recommended and may prolong fecal carriage. Neonates, the elderly, and immunosuppressed patients (e.g., transplant recipients, HIV-infected persons) with NTS gastroenteritis are especially susceptible to dehydration and dissemination and may require hospitalization and antibiotic therapy. Acute NTS gastroenteritis was associated with a threefold increased risk of dyspepsia and irritable bowel syndrome at 1 year in a recent study from Spain.

Bacteremia and endovascular infections

Up to 8% of patients with NTS gastroenteritis develop bacteremia; of these, 5–10% develop localized infections. Bacteremia and metastatic infection are most common with *S. choleraesuis* and *S.* Dublin and among infants, the elderly, and immunocompromised patients. NTS endovascular infection should be suspected in high-grade or persistent bacteremia, especially with preexisting valvular heart disease, atherosclerotic vascular disease, prosthetic vascular graft, or aortic aneurysm. Arteritis should be suspected in elderly patients with prolonged fever and back, chest, or abdominal pain

developing after an episode of gastroenteritis. Endocarditis and arteritis are rare (<1% of cases) but are associated with potentially fatal complications, including valve perforation, endomyocardial abscess, infected mural thrombus, pericarditis, mycotic aneurysms, aneurysm rupture, aortoenteric fistula, and vertebral osteomyelitis. In some areas of sub-Saharan Africa, NTS may be among the most common causes—or even the most common cause—of bacteremia in children. NTS bacteremia among these children is not associated with diarrhea and has been associated with nutritional status and HIV infection.

Localized infections

Intraabdominal infections

Intraabdominal infections due to NTS are rare and usually manifest as hepatic or splenic abscesses or as cholecystitis. Risk factors include hepatobiliary anatomic abnormalities (e.g., gallstones), abdominal malignancy, and sickle cell disease (especially with splenic abscesses). Eradication of the infection often requires surgical correction of abnormalities and percutaneous drainage of abscesses.

Central nervous system infections

NTS meningitis most commonly develops in infants 1–4 months of age. It often results in severe sequelae (including seizures, hydrocephalus, brain infarction, and mental retardation) with death in up to 60% of cases. Other rare central nervous system infections include ventriculitis, subdural empyema, and brain abscesses.

Pulmonary infections

NTS pulmonary infections usually present as lobar pneumonia, and complications include lung abscess, empyema, and bronchopleural fistula formation. The majority of cases occur in patients with lung cancer, structural lung disease, sickle cell disease, or glucocorticoid use.

Urinary and genital tract infections

Urinary tract infections caused by NTS present as either cystitis or pyelonephritis. Risk factors include malignancy, urolithiasis, structural abnormalities, HIV infection, and renal transplantation. NTS genital infections are rare and include ovarian and testicular abscesses, prostatitis, and epididymitis. Like other focal infections, both genital and urinary tract infections can be complicated by abscess formation.

Bone, joint, and soft tissue infections

Salmonella osteomyelitis most commonly affects the femur, tibia, humerus, or lumbar vertebrae and is most often seen in association with sickle cell disease, hemoglobinopathies, or preexisting bone disease (e.g., fractures). Prolonged antibiotic treatment is recommended to decrease the risk of relapse and chronic osteomyelitis. Septic arthritis occurs in the same patient population as osteomyelitis and usually involves the knee, hip, or shoulder joints. Reactive arthritis can follow NTS gastroenteritis and is seen most frequently in persons with the HLA-B27 histocompatibility antigen. NTS rarely can cause soft tissue infections, usually at sites of local trauma in immunosuppressed patients.

DIAGNOSIS

The diagnosis of NTS infection is based on isolation of the organism from freshly passed stool or from blood or another ordinarily sterile body fluid. All salmonellae isolated in clinical laboratories should be sent to local public health departments for serotyping. Blood cultures should be done whenever a patient has prolonged or recurrent fever. Endovascular infection should be suspected if there is high-grade bacteremia (>50% of three or more positive blood cultures). Echocardiography, CT, and indium-labeled white cell scanning are used to identify localized infection. When another localized infection is suspected, joint fluid, abscess drainage, or cerebrospinal fluid should be cultured, as clinically indicated.

TREATMENT Nontyphoidal Salmonellosis

Antibiotics should not be used routinely to treat uncomplicated NTS gastroenteritis. The symptoms are usually self-limited, and the duration of fever and diarrhea is not significantly decreased by antibiotic therapy. In addition, antibiotic treatment has been associated with increased rates of relapse, prolonged gastrointestinal carriage, and adverse drug reactions. Dehydration secondary to diarrhea should be treated with fluid and electrolyte replacement.

Preemptive antibiotic treatment (Table 58-2) should be considered for patients at increased risk for invasive NTS infection, including neonates (probably up to 3 months of age); persons >50 years of age with suspected atherosclerosis; and patients with immunosuppression, cardiac valvular or endovascular abnormalities, or significant joint disease. Treatment should consist of an oral or IV antibiotic administered for 48–72 h or until the patient becomes afebrile. Immunocompromised persons may require up to 7–14 days of therapy. The <1% of persons who develop chronic carriage of NTS should receive a prolonged antibiotic course, as described earlier for chronic carriage of S. *typhi*.

Because of the increasing prevalence of antibiotic resistance, empirical therapy for life-threatening NTS bacteremia or focal NTS infection should include a third-generation cephalosporin or a fluoroquinolone (Table 58-2). If the bacteremia is low-grade (<50% of positive blood cultures), the patient should be treated for 7–14 days. Patients with HIV/AIDS and NTS bacteremia should receive 1–2 weeks of IV antibiotic therapy followed by 4 weeks of oral therapy with a fluoroquinolone. Patients whose infections relapse after this regimen should receive long-term suppressive therapy with

TABLE 58-2

ANTIBIOTIC THERAPY FOR NONTYPHOIDAL *SALMONELLA* INFECTION IN ADULTS

INDICATION	AGENT	DOSAGE (ROUTE)	DURATION, DAYS
Preemptive Treatment[a]			
	Ciprofloxacin[b]	500 mg bid (PO)	2–3
Severe Gastroenteritis[c]			
	Ciprofloxacin	500 mg bid (PO) or 400 mg q12h (IV)	3–7
	Trimethoprim-sulfamethoxazole	160/800 mg bid (PO)	
	Amoxicillin	1 g tid (PO)	
	Ceftriaxone	1–2 g/d (IV)	
Bacteremia			
	Ceftriaxone[d]	2 g/d (IV)	7–14
	Ciprofloxacin	400 mg q12h (IV), then 500 mg bid (PO)	
Endocarditis or Arteritis			
	Ceftriaxone	2 g/d (IV)	42
	Ciprofloxacin	400 mg q8h (IV), then 750 mg bid (PO)	
	Ampicillin	2 g q4h (IV)	
Meningitis			
	Ceftriaxone	2 g q12 h (IV)	14–21
	Ampicillin	2 g q4h (IV)	
Other Localized Infection			
	Ceftriaxone	2 g/d (IV)	14–28
	Ciprofloxacin	500 mg bid (PO) or 400 mg q12h (IV)	
	Ampicillin	2 g q6h (IV)	

[a]Consider for neonates; persons >50 years of age with possible atherosclerotic vascular disease; and patients with immunosuppression, endovascular graft, or joint prosthesis.
[b]Or ofloxacin, 400 mg bid (PO).
[c]Consider on an individualized basis for patients with severe diarrhea and high fever who require hospitalization.
[d]Or cefotaxime, 2 g q8h (IV).

a fluoroquinolone or TMP-SMX, as indicated by bacterial sensitivities.

If the patient has endocarditis or arteritis, treatment for 6 weeks with an IV β-lactam antibiotic (such as ceftriaxone or ampicillin) is indicated. IV ciprofloxacin followed by prolonged oral therapy is an option, but published experience is limited. Early surgical resection of infected aneurysms or other infected endovascular sites is recommended. Patients with infected prosthetic vascular grafts that cannot be resected have been maintained successfully on chronic suppressive oral therapy. For extraintestinal nonvascular infections, a 2- to 4-week course of antibiotic therapy (depending on the infection site) is usually recommended. In chronic osteomyelitis, abscess, or urinary or hepatobiliary infection associated with anatomic abnormalities, surgical resection or drainage may be required in addition to prolonged antibiotic therapy for eradication of infection.

PREVENTION AND CONTROL

Despite widespread efforts to prevent or reduce bacterial contamination of animal-derived food products and to improve food-safety education and training, recent declines in the incidence of NTS in the United States have been modest compared with those of other foodborne pathogens. This observation probably reflects the complex epidemiology of NTS. Identifying effective risk-reduction strategies requires monitoring of every step of food production, from handling of raw animal or plant products to preparation of finished foods. Contaminated food can be made safe for consumption by pasteurization, irradiation, or proper cooking. All cases of NTS infection should be reported to local public health departments, since tracking and monitoring of these cases can identify the source(s) of infection and help authorities anticipate large outbreaks. Lastly, the prudent use of antimicrobial agents in both humans and animals is needed to limit the emergence of MDR *Salmonella*.

CHAPTER 59

SHIGELLOSIS

Philippe Sansonetti ■ Jean Bergounioux

The discovery of *Shigella* as the etiologic agent of dysentery—a clinical syndrome of fever, intestinal cramps, and frequent passage of small, bloody, mucopurulent stools—is attributed to the Japanese microbiologist Kiyoshi Shiga, who isolated the Shiga bacillus (now known as *Shigella dysenteriae* type 1) from patients' stools in 1897 during a large and devastating dysentery epidemic. *Shigella* cannot be distinguished from *Escherichia coli* by DNA hybridization and remains a separate species only on historical and clinical grounds.

DEFINITION

Shigella is a non-spore-forming, gram-negative bacterium that, unlike *E. coli*, is nonmotile and does not produce gas from sugars, decarboxylate lysine, or hydrolyze arginine. Some serovars produce indole, and occasional strains utilize sodium acetate. *S. dysenteriae*, *S. flexneri*, *S. boydii*, and *S. sonnei* (serogroups A, B, C, and D, respectively) can be differentiated on the basis of biochemical and serologic characteristics. Genome sequencing of *E. coli* K12, *S. flexneri* 2a, *S. sonnei*, *S. dysenteriae* type 1, and *S. boydii* has revealed that these species have ~93% of genes in common. The three major genomic "signatures" of *Shigella* are (1) a 215-kb virulence plasmid that carries most of the genes required for pathogenicity (particularly invasive capacity); (2) the lack or alteration of genetic sequences encoding products (e.g., lysine decarboxylase) that, if expressed, would attenuate pathogenicity; and (3) in *S. dysenteriae* type 1, the presence of genes encoding Shiga toxin, a potent cytotoxin.

EPIDEMIOLOGY

The human intestinal tract represents the major reservoir of *Shigella*, which is also found (albeit rarely) in the higher primates. Because excretion of shigellae is greatest in the acute phase of disease, the bacteria are transmitted most efficiently by the fecal-oral route via hand carriage; however, some outbreaks reflect food-borne or waterborne transmission. In impoverished areas, *Shigella* can be transmitted by flies. The high-level infectivity of *Shigella* is reflected by the very small inoculum required for experimental infection of volunteers (100 colony-forming units [CFU]), by the very high attack rates during outbreaks in day-care centers (33–73%), and by the high rates of secondary cases among family members of sick children (26–33%). Shigellosis can also be transmitted sexually.

Throughout history, *Shigella* epidemics have often occurred in settings of human crowding under conditions of poor hygiene—e.g., among soldiers in campaigning armies, inhabitants of besieged cities, groups on pilgrimages, and refugees in camps. Epidemics follow a cyclical pattern in areas such as the Indian subcontinent and sub-Saharan Africa. These devastating epidemics, which are most often caused by *S. dysenteriae* type 1, are characterized by high attack and mortality rates. In Bangladesh, for instance, an epidemic caused by *S. dysenteriae* type 1 was associated with a 42% increase in mortality rate among children 1–4 years of age. Apart from these epidemics, shigellosis is mostly an endemic disease, with 99% of cases occurring in the developing world and the highest prevalences in the most impoverished areas, where personal and general hygiene is below standard. *S. flexneri* isolates predominate in the least developed areas, whereas *S. sonnei* is more prevalent in economically emerging countries and in the industrialized world.

Prevalence in the developing world

In a review published under the auspices of the World Health Organization (WHO), the total annual number of cases in 1966–1997 was estimated at 165 million, and 69% of these cases occurred in children <5 years of age. In this review, the annual number of deaths was calculated to range between 500,000 and 1.1 million. More recent data (2000–2004) from six Asian countries indicate that even though the incidence of shigellosis remains stable, mortality rates associated with this disease may have decreased significantly, possibly as a result of improved nutritional status.

However, extensive and essentially uncontrolled use of antibiotics, which may also account for declining mortality rates, has increased the rate of emergence of multidrug-resistant *Shigella* strains. An often-overlooked complication of shigellosis is the short- and long-term impairment of the nutritional status of infected children in endemic areas. Combined with anorexia, the exudative enteropathy resulting from mucosal abrasions contributes to rapid deterioration of the patient's nutritional status. Shigellosis is thus a major contributor to stunted growth among children in developing countries.

Peaking in incidence in the pediatric population, endemic shigellosis is rare in young and middle-aged adults, probably because of naturally acquired immunity. Incidence then increases again in the elderly population.

Prevalence in the industrialized world

In pediatric populations, local outbreaks occur when proper and adapted hygiene policies are not implemented in group facilities like day-care centers and institutions for the mentally retarded. In adults, as in children, sporadic cases occur among travelers returning from endemic areas, and rare outbreaks of varying size can follow waterborne or food-borne infections.

PATHOGENESIS AND PATHOLOGY

Shigella infection occurs essentially through oral contamination via direct fecal-oral transmission, the organism being poorly adapted to survive in the environment. Resistance to low-pH conditions allows shigellae to survive passage through the gastric barrier, an ability that may explain in part why a small inoculum (as few as 100 CFU) is sufficient to cause infection.

The watery diarrhea that usually precedes the dysenteric syndrome is attributable to active secretion and abnormal water reabsorption—a secretory effect at the jejunal level described in experimentally infected rhesus monkeys. This initial purge is probably due to the combined action of an enterotoxin (ShET-1) and mucosal inflammation. The dysenteric syndrome, manifested by bloody and mucopurulent stools, reflects invasion of the mucosa.

The pathogenesis of *Shigella* is essentially determined by a large virulence plasmid of 214 kb comprising ~100 genes, of which 25 encode a type III secretion system that inserts into the membrane of the host cell to allow effectors to transit from the bacterial cytoplasm to the host cell cytoplasm **(Fig. 59-1)**. Bacteria are thereby able to invade intestinal epithelial cells by inducing their own uptake after the initial crossing of the epithelial barrier through M cells (the specialized translocating epithelial cells in the follicle-associated epithelium that covers mucosal lymphoid nodules). The organisms induce apoptosis of subepithelial resident macrophages. Once inside the cytoplasm of intestinal epithelial cells, *Shigella* effectors trigger the cytoskeletal rearrangements necessary to direct uptake of the organism into the epithelial cell. The *Shigella*-containing vacuole is then quickly lysed, releasing bacteria into the cytosol.

Intracellular shigellae next use cytoskeletal components to propel themselves inside the infected cell; when the moving organism and the host cell membrane come into contact, cellular protrusions form and are engulfed by neighboring cells. This series of events permits bacterial cell-to-cell spread.

Cytokines released by a growing number of infected intestinal epithelial cells attract increased numbers of immune cells (particularly polymorphonuclear leukocytes [PMNs]) to the infected site, thus further destabilizing the epithelial barrier, exacerbating inflammation, and leading to the acute colitis that characterizes shigellosis. Evidence indicates that some type III secretion

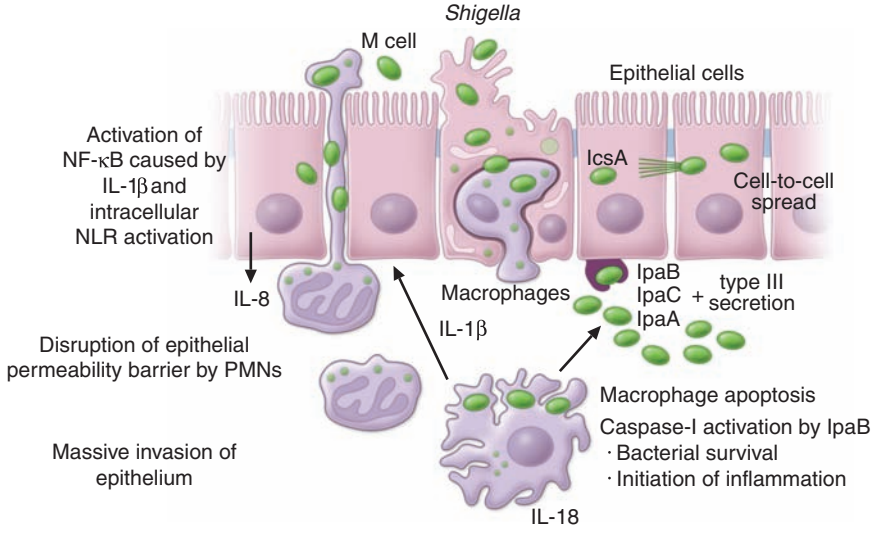


FIGURE 59-1
Invasive strategy of *Shigella flexneri.* IL, interleukin; NF-κB, nuclear factor κB; NLR, NOD-like receptor; PMN, polymorphonuclear leukocyte.

system–injected effectors can control the extent of inflammation, thus facilitating bacterial survival.

Shiga toxin produced by *S. dysenteriae* type 1 increases disease severity. This toxin belongs to a group of A1-B5 protein toxins whose B subunit binds to the receptor globotriaosylceramide on the target cell surface and whose catalytic A subunit is internalized by receptor-mediated endocytosis and interacts with the subcellular machinery to inhibit protein synthesis by expressing RNA N-glycosidase activity on 28S ribosomal RNA. This process leads to inhibition of binding of the amino-acyl-tRNA to the 60S ribosomal subunit and thus to a general shutoff of cell protein biosynthesis. Shiga toxins are translocated from the bowel into the circulation. After binding of the toxins to target cells in the kidney, pathophysiologic alterations may result in hemolytic-uremic syndrome (HUS; see next section).

CLINICAL MANIFESTATIONS

The presentation and severity of shigellosis depend to some extent on the infecting serotype but even more on the age and the immunologic and nutritional status of the host. Poverty and poor standards of hygiene are strongly related to the number and severity of diarrheal episodes, especially in children <5 years old who have been weaned.

Shigellosis typically evolves through four phases: incubation, watery diarrhea, dysentery, and the postinfectious phase. The incubation period usually lasts 1–4 days but may be as long as 8 days. Typical initial manifestations are transient fever, limited watery diarrhea, malaise, and anorexia. Signs and symptoms may range from mild abdominal discomfort to severe cramps, diarrhea, fever, vomiting, and tenesmus. The manifestations are usually exacerbated in children, with temperatures up to 40°–41°C (104.0°–105.8°F) and more severe anorexia and watery diarrhea. This initial phase may represent the only clinical manifestation of shigellosis, especially in developed countries. Otherwise, dysentery follows within hours or days and is characterized by uninterrupted excretion of small volumes of bloody mucopurulent stools with increased tenesmus and abdominal cramps. At this stage, *Shigella* produces acute colitis involving mainly the distal colon and the rectum. Unlike most diarrheal syndromes, dysenteric syndromes rarely present with dehydration as a major feature. Endoscopy shows an edematous and hemorrhagic mucosa, with ulcerations and possibly overlying exudates resembling pseudomembranes. The extent of the lesions correlates with the number and frequency of stools and with the degree of protein loss by exudative mechanisms. Most episodes are self-limited and resolve without treatment in 1 week. With appropriate treatment, recovery takes place within a few days to a week, with no sequelae.

Acute life-threatening complications are seen most often in children <5 years of age (particularly those who are malnourished) and in elderly patients. Risk factors for death in a clinically severe case include nonbloody diarrhea, moderate to severe dehydration, bacteremia, absence of fever, abdominal tenderness, and rectal prolapse. Major complications are predominantly intestinal (e.g., toxic megacolon, intestinal perforations, rectal prolapse) or metabolic (e.g., hypoglycemia, hyponatremia, dehydration). Bacteremia is rare and is reported most frequently in severely malnourished and HIV-infected patients. Alterations of consciousness, including seizures, delirium, and coma, may occur, especially in children <5 years old, and are associated with a poor prognosis; fever and severe metabolic alterations are more often the major causes of altered consciousness than is meningitis or the Ekiri syndrome (toxic encephalopathy associated with bizarre posturing, cerebral edema, and fatty degeneration of viscera), which has been reported mostly in Japanese children. Pneumonia, vaginitis, and keratoconjunctivitis due to *Shigella* are rarely reported. In the absence of serious malnutrition, severe and very unusual clinical manifestations, such as meningitis, may be linked to genetic defects in innate immune functions (i.e., deficiency in interleukin 1 receptor–associated kinase 4 [IRAK-4]) and may require genetic investigation.

Two complications of particular importance are toxic megacolon and HUS. Toxic megacolon is a consequence of severe inflammation extending to the colonic smooth-muscle layer and causing paralysis and dilatation. The patient presents with abdominal distention and tenderness, with or without signs of localized or generalized peritonitis. The abdominal x-ray characteristically shows marked dilatation of the transverse colon (with the greatest distention in the ascending and descending segments); thumbprinting caused by mucosal inflammatory edema; and loss of the normal haustral pattern associated with pseudopolyps, often extending into the lumen. Pneumatosis coli is an occasional finding. If perforation occurs, radiographic signs of pneumoperitoneum may be apparent. Predisposing factors (e.g., hypokalemia and use of opioids, anticholinergics, loperamide, psyllium seeds, and antidepressants) should be investigated.

Shiga toxin produced by *S. dysenteriae* type 1 has been linked to HUS in developing countries but rarely in industrialized countries, where enterohemorrhagic *E. coli* (EHEC) predominates as the etiologic agent of this syndrome. HUS is an early complication that most often develops after several days of diarrhea. Clinical examination shows pallor, asthenia, and irritability and, in some cases, bleeding of the nose and gums, oliguria, and increasing edema. HUS is a nonimmune (Coombs test–negative) hemolytic anemia defined by a diagnostic triad: microangiopathic hemolytic anemia (hemoglobin level typically <80 g/L [<8 g/dL]), thrombocytopenia (mild to moderate in severity; typically <60,000 platelets/μL), and acute renal failure due to thrombosis of the glomerular capillaries (with markedly elevated creatinine levels). Anemia is severe, with fragmented red blood cells (schizocytes) in the peripheral smear, high serum concentrations of lactate dehydrogenase and free circulating hemoglobin, and elevated reticulocyte counts. Acute renal failure occurs in 55–70% of cases; however, renal function recovers in most of these cases (up to 70% in various series). Leukemoid reactions, with leukocyte counts of 50,000/μL, are sometimes noted in association with HUS.

The postinfectious immunologic complication known as reactive arthritis can develop weeks or months after

shigellosis, especially in patients expressing the histocompatibility antigen HLA-B27. About 3% of patients infected with *S. flexneri* later develop this syndrome, with arthritis, ocular inflammation, and urethritis—a condition that can last for months or years and can progress to difficult-to-treat chronic arthritis. Postinfectious arthropathy occurs only after infection with *S. flexneri* and not after infection with the other *Shigella* serotypes.

LABORATORY DIAGNOSIS

The differential diagnosis in patients with a dysenteric syndrome depends on the clinical and environmental context. In developing areas, infectious diarrhea caused by other invasive pathogenic bacteria (*Salmonella*, *Campylobacter jejuni*, *Clostridium difficile*, *Yersinia enterocolitica*) or parasites (*Entamoeba histolytica*) should be considered. Only bacteriologic and parasitologic examinations of stool can truly differentiate among these pathogens. A first flare of inflammatory bowel disease, such as Crohn's disease or ulcerative colitis, should be considered in patients in industrialized countries. Despite similar symptoms, anamnesis discriminates between shigellosis, which usually follows recent travel in an endemic zone, and these other conditions.

Microscopic examination of stool smears shows the presence of erythrophagocytic trophozoites with very few PMNs in *E. histolytica* infection, whereas bacterial enteroinvasive infections (particularly shigellosis) are characterized by high PMN counts in each microscopic field. However, because shigellosis often manifests only as watery diarrhea, systematic attempts to isolate *Shigella* are necessary.

The "gold standard" for the diagnosis of *Shigella* infection remains the isolation and identification of the pathogen from fecal material. One major difficulty, particularly in endemic areas where laboratory facilities are not immediately available, is the fragility of *Shigella* and its common disappearance during transport, especially with rapid changes in temperature and pH. In the absence of a reliable enrichment medium, buffered glycerol saline or Cary-Blair medium can be used as a holding medium, but prompt inoculation onto isolation medium is essential. The probability of isolation is higher if the portion of stools that contains bloody and/or mucopurulent material is directly sampled. Rectal swabs can be used, as they offer the highest rate of successful isolation during the acute phase of disease. Blood cultures are positive in <5% of cases, but should be done when a patient presents with a clinical picture of severe sepsis.

In addition to quick processing, the use of several media increases the likelihood of successful isolation: a nonselective medium such as bromocresol-purple agar lactose; a low-selectivity medium such as MacConkey or eosin-methylene blue; and a high-selectivity medium such as Hektoen, *Salmonella-Shigella*, or xylose-lysine-deoxycholate agar. After incubation on these media for 12–18 h at 37°C (98.6°F), shigellae appear as nonlactose-fermenting colonies that measure 0.5–1 mm in diameter and have a convex, translucent, smooth surface. Suspected colonies on nonselective or low-selectivity medium can be subcultured on a high-selectivity medium before being specifically identified or can be identified directly by standard commercial systems on the basis of four major characteristics: glucose positivity (usually without production of gas), lactose negativity, H_2S negativity, and lack of motility. The four *Shigella* serogroups (A–D) can then be differentiated by additional characteristics. This approach adds time and difficulty to the identification process; however, after presumptive diagnosis, the use of serologic methods (e.g., slide agglutination, with group- and then type-specific antisera) should be considered. Group-specific antisera are widely available; in contrast, because of the large number of serotypes and sub-serotypes, type-specific antisera are rare and more expensive and thus are often restricted to reference laboratories.

TREATMENT Shigellosis

ANTIBIOTIC SUSCEPTIBILITY OF *SHIGELLA*

As an enteroinvasive disease, shigellosis requires antibiotic treatment. Since the mid-1960s, however, increasing resistance to multiple drugs has been a dominant factor in treatment decisions. Resistance rates are highly dependent on the geographic area. Clonal spread of particular strains and horizontal transfer of resistance determinants, particularly via plasmids and transposons, contribute to multidrug resistance. The current global status—i.e., high rates of resistance to classic first-line antibiotics such as amoxicillin—has led to a rapid switch to quinolones such as nalidixic acid. However, resistance to such early-generation quinolones has also emerged and spread quickly as a result of chromosomal mutations affecting DNA gyrase and topoisomerase IV; this resistance has necessitated the use of later-generation quinolones as first-line antibiotics in many areas. For instance, a review of the antibiotic resistance history of *Shigella* in India found that, after their introduction in the late 1980s, the second-generation quinolones norfloxacin, ciprofloxacin, and ofloxacin were highly effective in the treatment of shigellosis, including cases caused by multidrug-resistant strains of *S. dysenteriae* type 1. However, investigations of subsequent outbreaks in India and Bangladesh detected resistance to norfloxacin, ciprofloxacin, and ofloxacin in 5% of isolates. The incidence of multidrug resistance parallels the widespread, uncontrolled use of antibiotics and calls for the rational use of effective drugs.

ANTIBIOTIC TREATMENT OF SHIGELLOSIS

(Table 59-1) Because of the ready transmissibility of *Shigella*, current public health recommendations in the United States are that every case be treated with antibiotics. Ciprofloxacin is recommended as first-line treatment. A number of other drugs have been tested and shown to be effective, including ceftriaxone, azithromycin, pivmecillinam, and some fifth-generation quinolones. While infections caused by non-*dysenteriae Shigella* in immunocompetent individuals are routinely treated with a 3-day course of antibiotics, it is recommended

TABLE 59-1

RECOMMENDED ANTIMICROBIAL THERAPY FOR SHIGELLOSIS

ANTIMICROBIAL AGENT	TREATMENT SCHEDULE: CHILDREN	TREATMENT SCHEDULE: ADULTS	LIMITATIONS
First Line			
Ciprofloxacin	15 mg/kg 2 times per day for 3 days, PO	500 mg	
Second Line			
Pivmecillinam	20 mg/kg 4 times per day for 5 days, PO	100 mg	Cost No pediatric formulation Frequent administration Resistance emerging
Ceftriaxone	50–100 mg/kg Once a day IM for 2–5 days	—	Efficacy not validated Must be injected
Azithromycin	6–20 mg/kg Once a day for 1–5 days, PO	1–1.5 g	Cost Efficacy not validated MIC near serum concentration Rapid emergence of resistance and spread to other bacteria

Source: WHO Library Cataloguing-in-Publication Data: Guidelines for the control of shigellosis, including epidemics due to *Shigella dysenteriae* type 1 (*www.searo.who.int/LinkFiles/CAH_Publications_shigella.pdf*).

that *S. dysenteriae* type 1 infections be treated for 5 days and that *Shigella* infections in immunocompromised patients be treated for 7–10 days.

Treatment for shigellosis must be adapted to the clinical context, with the recognition that the most fragile patients are children <5 years old, who represent two-thirds of all cases worldwide. There are few data on the use of quinolones in children, but *Shigella*-induced dysentery is a well-recognized indication for their use. The half-life of ciprofloxacin is longer in infants than in older individuals. The ciprofloxacin dose generally recommended for children is 30 mg/kg per d in two divided doses. Adults living in areas with high standards of hygiene are likely to develop milder, shorter-duration disease, whereas infants in endemic areas can develop severe, sometimes fatal dysentery. In the former setting, treatment will remain minimal and bacteriologic proof of infection will often come after symptoms have resolved; in the latter setting, antibiotic treatment and more aggressive measures, possibly including resuscitation, are often required.

REHYDRATION AND NUTRITION *Shigella* infection rarely causes significant dehydration. Cases requiring aggressive rehydration (particularly in industrialized countries) are uncommon. In developing countries, malnutrition remains the primary indicator for diarrhea-related death, highlighting the importance of nutrition in early management. Rehydration should be oral unless the patient is comatose or presents in shock. Because of the improved effectiveness of reduced-osmolarity oral rehydration solution (especially for children with acute noncholera diarrhea), the WHO and UNICEF now recommend a standard solution of 245 mOsm/L (sodium, 75 mmol/L; chloride, 65 mmol/L; glucose [anhydrous], 75 mmol/L; potassium, 20 mmol/L; citrate, 10 mmol/L). In shigellosis, the coupled transport of sodium to glucose may be variably affected, but oral rehydration therapy remains the easiest and most efficient form of rehydration, especially in severe cases.

Nutrition should be started as soon as possible after completion of initial rehydration. Early refeeding is safe, well tolerated, and clinically beneficial. Because breastfeeding reduces diarrheal losses and the need for oral rehydration in infants, it should be maintained in the absence of contraindications (e.g., maternal HIV infection).

NONSPECIFIC, SYMPTOM-BASED THERAPY Antimotility agents have been implicated in prolonged fever in volunteers with shigellosis. These agents are suspected of increasing the risk of toxic megacolon and are thought to have been responsible for HUS in children infected by EHEC strains. For safety reasons, it is better to avoid antimotility agents in bloody diarrhea.

TREATMENT OF COMPLICATIONS There is no consensus regarding the best treatment for toxic megacolon. The patient should be assessed frequently by both medical and surgical teams. Anemia, dehydration, and electrolyte deficits (particularly hypokalemia) may aggravate colonic atony and should be actively treated. Nasogastric aspiration helps to deflate the colon. Parenteral nutrition has not been proven to be beneficial. Fever persisting beyond 48–72 h raises the possibility of local perforation or abscess. Most studies recommend colectomy if, after 48–72 h, colonic distention persists. However, some physicians recommend continuation of medical therapy for up to 7 days if the patient seems to be improving clinically despite persistent megacolon without free perforation. Intestinal perforation, either isolated or complicating toxic megacolon, requires surgical treatment and intensive medical support.

Rectal prolapse must be treated as soon as possible. With the health care provider using surgical gloves or a soft warm wet cloth and the patient in the knee-chest position, the prolapsed rectum is gently pushed back into place. If edema of the rectal mucosa is evident (rendering reintegration difficult), it can be osmotically reduced by applying gauze impregnated with a warm solution of saturated magnesium sulfate. Rectal prolapse often relapses but usually resolves along with the resolution of dysentery.

HUS must be treated by water restriction, including discontinuation of oral rehydration solution and potassium-rich alimentation. Hemofiltration is usually required.

PREVENTION

Hand washing after defecation or handling of children's feces and before handling of food is recommended. Stool decontamination (e.g., with sodium hypochlorite), together with a cleaning protocol for medical staff as well as for patients, has proven useful in limiting the spread of infection during *Shigella* outbreaks. Ideally, patients should have a negative stool culture before their infection is considered cured. Recurrences are rare if therapeutic and preventive measures are correctly implemented.

Although several live attenuated oral and subunit parenteral vaccine candidates have been produced and are undergoing clinical trials, no vaccine against shigellosis is currently available. Especially given the rapid progression of antibiotic resistance in *Shigella*, a vaccine is urgently needed.

CHAPTER 60

INFECTIONS DUE TO *CAMPYLOBACTER* AND RELATED ORGANISMS

Martin J. Blaser

DEFINITION

Bacteria of the genus *Campylobacter* and of the related genera *Arcobacter* and *Helicobacter* (Chap. 56) cause a variety of inflammatory conditions. Although acute diarrheal illnesses are most common, these organisms may cause infections in virtually all parts of the body, especially in compromised hosts, and these infections may have late nonsuppurative sequelae. The designation *Campylobacter* comes from the Greek for "curved rod" and refers to the organism's vibrio-like morphology.

ETIOLOGY

Campylobacters are motile, non-spore-forming, curved, gram-negative rods. Originally known as *Vibrio fetus*, these bacilli were reclassified as a new genus in 1973, after their dissimilarity to other vibrios was recognized. More than 15 species have since been identified. These species are currently divided into three genera: *Campylobacter*, *Arcobacter*, and *Helicobacter*. Not all of the species are pathogens of humans. The human pathogens fall into two major groups: those that primarily cause diarrheal disease and those that cause extraintestinal infection. The principal diarrheal pathogen is *C. jejuni*, which accounts for 80–90% of all cases of recognized illness due to campylobacters and related genera. Other organisms that cause diarrheal disease include *C. coli*, *C. upsaliensis*, *C. lari*, *C. hyointestinalis*, *C. fetus*, *A. butzleri*, *A. cryaerophilus*, *H. cinaedi*, and *H. fennelliae*. The two *Helicobacter* species causing diarrheal disease, *H. cinaedi* and *H. fennelliae*, are intestinal rather than gastric organisms; in terms of the clinical features of the illnesses they cause, these species most closely resemble *Campylobacter* rather than *H. pylori* (Chap. 56) and thus are considered in this chapter.

The major species causing extraintestinal illnesses is *C. fetus*. However, any of the diarrheal agents listed earlier may cause systemic or localized infection as well, especially in compromised hosts. Neither aerobes nor strict anaerobes, these microaerophilic organisms are adapted for survival in the gastrointestinal mucous layer. This chapter focuses on *C. jejuni* and *C. fetus* as the major pathogens in and prototypes for their groups. The key features of infection are listed by species (excluding *C. jejuni*, described in detail in the following text) in **Table 60-1**.

EPIDEMIOLOGY

Campylobacters are found in the gastrointestinal tract of many animals used for food (including poultry, cattle, sheep, and swine) and many household pets (including

TABLE 60-1

CLINICAL FEATURES ASSOCIATED WITH INFECTION DUE TO "ATYPICAL" *CAMPYLOBACTER* AND RELATED SPECIES IMPLICATED AS CAUSES OF HUMAN ILLNESS

SPECIES	COMMON CLINICAL FEATURES	LESS COMMON CLINICAL FEATURES	ADDITIONAL INFORMATION
Campylobacter coli	Fever, diarrhea, abdominal pain	Bacteremia[a]	Clinically indistinguishable from *C. jejuni*
Campylobacter fetus	Bacteremia,[a] sepsis, meningitis, vascular infections	Diarrhea, relapsing fevers	Not usually isolated from media containing cephalothin or incubated at 42°C
Campylobacter upsaliensis	Watery diarrhea, low-grade fever, abdominal pain	Bacteremia, abscesses	Difficult to isolate because of cephalothin susceptibility
Campylobacter lari	Abdominal pain, diarrhea	Colitis, appendicitis	Seagulls frequently colonized; organism often transmitted to humans via contaminated water
Campylobacter hyointestinalis	Watery or bloody diarrhea, vomiting, abdominal pain	Bacteremia	Causes proliferative enteritis in swine
Helicobacter fennelliae	Chronic mild diarrhea, abdominal cramps, proctitis	Bacteremia[a]	Best treated with fluoroquinolones
Helicobacter cinaedi	Chronic mild diarrhea, abdominal cramps, proctitis	Bacteremia[a]	Best treated with fluoroquinolones; identified in healthy hamsters
Campylobacter jejuni subspecies *doylei*	Diarrhea	Chronic gastritis, bacteremia[b]	Uncertain role as human pathogen
Arcobacter cryaerophilus	Diarrhea	Bacteremia	Cultured under aerobic conditions
Arcobacter butzleri	Fever, diarrhea, abdominal pain, nausea	Bacteremia, appendicitis	Cultured under aerobic conditions; enzootic in nonhuman primates
Campylobacter sputorum	Pulmonary, perianal, groin, and axillary abscesses; diarrhea	Bacteremia	Three clinically relevant biovars: *sputorum, faecalis,* and *paraureolyticus*

[a]In immunocompromised hosts, especially HIV-infected persons.
[b]In children.
Source: Adapted from BM Allos, MJ Blaser: Clin Infect Dis 20:1092, 1995.

birds, dogs, and cats). These microorganisms usually do not cause illness in their animal hosts. In most cases, campylobacters are transmitted to humans in raw or undercooked food products or through direct contact with infected animals. In the United States and other developed countries, ingestion of contaminated poultry that has not been sufficiently cooked is the most common mode of acquisition (30–70% of cases). Other modes include ingestion of raw (unpasteurized) milk or untreated water, contact with infected household pets, travel to developing countries (campylobacters being among the leading causes of traveler's diarrhea; Chaps. 5 and 26), oral-anal sexual contact, and (occasionally) contact with an index case who is incontinent of stool (e.g., a baby).

Campylobacter infections are common. Several studies indicate that, in the United States, diarrheal disease due to campylobacters is more common than that due to *Salmonella* and *Shigella* combined. Infections occur throughout the year, but their incidence peaks during summer and early autumn. Persons of all ages are affected; however, attack rates for *C. jejuni* are highest among young children and young adults, while those for *C. fetus* are highest at the extremes of age. Systemic infections due to *C. fetus* (and to other *Campylobacter* and related species) are most common among compromised hosts. Persons at increased risk include those with AIDS, hypogammaglobulinemia, neoplasia, liver disease, diabetes mellitus, and generalized atherosclerosis as well as neonates and pregnant women. However, apparently healthy nonpregnant persons occasionally develop transient *Campylobacter* bacteremia as part of a gastrointestinal illness.

In contrast, in many developing countries, *C. jejuni* infections are hyperendemic, with the highest rates among children <2 years old. Infection rates fall with age, as does the illness-to-infection ratio. These observations suggest that frequent exposure to *C. jejuni* leads to the acquisition of immunity.

PATHOLOGY AND PATHOGENESIS

C. jejuni infections may be subclinical, especially in hosts in developing countries who have had multiple prior infections and thus are partially immune.

Symptomatic infections mostly occur within 2–4 days (range, 1–7 days) of exposure to the organism in food or water. The sites of tissue injury include the jejunum, ileum, and colon. Biopsies show an acute nonspecific inflammatory reaction, with neutrophils, monocytes, and eosinophils in the lamina propria, as well as damage to the epithelium, including loss of mucus, glandular degeneration, and crypt abscesses. Biopsy findings may be consistent with Crohn's disease or ulcerative colitis, but these "idiopathic" chronic inflammatory diseases should not be diagnosed unless infectious colitis, *specifically including* that due to infection with *Campylobacter* species and related organisms, has been ruled out.

The high frequency of *C. jejuni* infections and their severity and recurrence among hypogammaglobulinemic patients suggest that antibodies are important in protective immunity. The pathogenesis of infection is uncertain. Both the motility of the strain and its capacity to adhere to host tissues appear to favor disease, but classic enterotoxins and cytotoxins (although described and including cytolethal distending toxin, or CDT) appear not to play substantial roles in tissue injury or disease production. The organisms have been visualized within the epithelium, albeit in low numbers. The documentation of a significant tissue response and occasionally of *C. jejuni* bacteremia further suggests that tissue invasion is clinically significant, and in vitro studies are consistent with this pathogenetic feature.

The pathogenesis of *C. fetus* infections is better defined. Virtually all clinical isolates of *C. fetus* possess a proteinaceous capsule-like structure (an S-layer) that renders the organisms resistant to complement-mediated killing and opsonization. As a result, *C. fetus* can cause bacteremia and can seed sites beyond the intestinal tract. The ability of the organism to switch the S-layer proteins expressed—a phenomenon that results in antigenic variability—may contribute to the chronicity and high rate of recurrence of *C. fetus* infections in compromised hosts.

CLINICAL MANIFESTATIONS

The clinical features of infections due to *Campylobacter* and the related *Arcobacter* and intestinal *Helicobacter* species causing enteric disease appear to be highly similar. *C. jejuni* can be considered the prototype, in part because it is by far the most common enteric pathogen in the group. A prodrome of fever, headache, myalgia, and/or malaise often occurs 12–48 h before the onset of diarrheal symptoms. The most common signs and symptoms of the intestinal phase are diarrhea, abdominal pain, and fever. The degree of diarrhea varies from several loose stools to grossly bloody stools; most patients presenting for medical attention have ≥10 bowel movements on the worst day of illness. Abdominal pain usually consists of cramping and may be the most prominent symptom. Pain is usually generalized but may become localized; *C. jejuni* infection may cause pseudoappendicitis. Fever may be the only initial manifestation of *C. jejuni* infection, a situation mimicking the early stages of typhoid fever. Febrile young children may develop convulsions. *Campylobacter* enteritis is generally self-limited; however, symptoms persist for >1 week in 10–20% of patients seeking medical attention, and clinical relapses occur in 5–10% of such untreated patients. Studies of common-source epidemics indicate that milder illnesses or asymptomatic infections may commonly occur.

C. fetus may cause a diarrheal illness similar to that due to *C. jejuni*, especially in normal hosts. This organism also may cause either intermittent diarrhea or nonspecific abdominal pain without localizing signs. Sequelae are uncommon, and the outcome is benign. *C. fetus* may also cause a prolonged relapsing systemic illness (with fever, chills, and myalgias) that has no obvious primary source; this manifestation is especially common among compromised hosts. Secondary seeding of an organ (e.g., meninges, brain, bone, urinary tract, or soft tissue) complicates the course, which may be fulminant. *C. fetus* infections have a tropism for vascular sites: endocarditis, mycotic aneurysm, and septic thrombophlebitis may all occur. Infection during pregnancy often leads to fetal death. A variety of *Campylobacter* species and *H. cinaedi* can cause recurrent cellulitis with fever and bacteremia in immunocompromised hosts.

COMPLICATIONS

Except in infection with *C. fetus*, bacteremia is uncommon, developing most often in immunocompromised hosts and at the extremes of age. Three patterns of extraintestinal infection have been noted: (1) transient bacteremia in a normal host with enteritis (benign course, no specific treatment needed); (2) sustained bacteremia or focal infection in a normal host (bacteremia originating from enteritis, with patients responding well to antimicrobial therapy); and (3) sustained bacteremia or focal infection in a compromised host. Enteritis may not be clinically apparent. Antimicrobial therapy, possibly prolonged, is necessary for suppression or cure of the infection.

Campylobacter, *Arcobacter*, and intestinal *Helicobacter* infections in patients with AIDS or hypogammaglobulinemia may be severe, persistent, and extraintestinal; relapse after cessation of therapy is common. Hypogammaglobulinemic patients also may develop osteomyelitis and an erysipelas-like rash or cellulitis.

Local suppurative complications of infection include cholecystitis, pancreatitis, and cystitis; distant complications include meningitis, endocarditis, arthritis, peritonitis, cellulitis, and septic abortion. All these complications are rare, except in immunocompromised hosts. Hepatitis, interstitial nephritis, and the hemolytic-uremic syndrome occasionally complicate acute infection. Reactive arthritis and other rheumatologic complaints may develop several weeks after infection, especially in persons with the HLA-B27 phenotype. Guillain-Barré syndrome or its Miller Fisher (cranial polyneuropathy) variant follows *Campylobacter* infections uncommonly—i.e., in 1 of every 1000–2000 cases or, for certain *C. jejuni* serotypes

(such as O19), in 1 of every 100–200 cases. Despite the low frequency of this complication, it is now estimated that *Campylobacter* infections, because of their high incidence, may trigger 20–40% of all cases of Guillain-Barré syndrome. Asymptomatic *Campylobacter* infection also may trigger this syndrome. Immunoproliferative small-intestinal disease (*alpha chain disease*), a form of lymphoma that originates in small-intestinal mucosa-associated lymphoid tissue, has been associated with *C. jejuni*; antimicrobial therapy has led to marked clinical improvement.

DIAGNOSIS

In patients with *Campylobacter* enteritis, peripheral leukocyte counts reflect the severity of the inflammatory process. However, stools from nearly all *Campylobacter*-infected patients presenting for medical attention in the United States contain leukocytes or erythrocytes. Gram- or Wright-stained fecal smears should be examined in all suspected cases. When the diagnosis of *Campylobacter* enteritis is suspected on the basis of findings indicating inflammatory diarrhea (fever, fecal leukocytes), clinicians can ask the microbiology laboratory to attempt the visualization of organisms with characteristic vibrioid morphology by direct microscopic examination of stools with Gram's staining or to use phase-contrast or dark-field microscopy to identify the organisms' characteristic "darting" motility. Confirmation of the diagnosis of *Campylobacter* infection is based on identification of an isolate from cultures of stool, blood, or another site. *Campylobacter*-specific media should be used to culture stools from all patients with inflammatory or bloody diarrhea. Since all *Campylobacter* species are fastidious, they will not be isolated unless selective media or other selective techniques are used. Not all media are equally useful for isolation of the broad array of campylobacters; therefore, failure to isolate campylobacters from stool does not entirely rule out their presence. The detection of the organisms in stool almost always implies infection; there is a brief period of postconvalescent fecal carriage and no obvious commensalism in humans. In contrast, *C. sputorum* and related organisms found in the oral cavity are commensals that only rarely have pathogenic significance. Because of the low levels of metabolic activity of *Campylobacter* species in standard blood culture media, *Campylobacter* bacteremia may be difficult to detect unless laboratorians check for low-positive results in quantitative assays.

DIFFERENTIAL DIAGNOSIS

The symptoms of *Campylobacter* enteritis are not sufficiently unusual to distinguish this illness from that due to *Salmonella*, *Shigella*, *Yersinia*, and other pathogens. The combination of fever and fecal leukocytes or erythrocytes is indicative of inflammatory diarrhea, and definitive diagnosis is based on culture or demonstration of the characteristic organisms on stained fecal smears. Similarly, extraintestinal *Campylobacter* illness is diagnosed by culture. Infection due to *Campylobacter* should be suspected in the setting of septic abortion, and that due to *C. fetus* should be suspected specifically in the setting of septic thrombophlebitis. It is important to reiterate that (1) the presentation of *Campylobacter* enteritis may mimic that of ulcerative colitis or Crohn's disease, (2) *Campylobacter* enteritis is much more common than either of the latter (especially among young adults), and (3) biopsy may not distinguish among these entities. Thus a diagnosis of inflammatory bowel disease should not be made until *Campylobacter* infection has been ruled out, especially in persons with a history of foreign travel, significant animal contact, immunodeficiency, or exposure incurring a high risk of transmission.

TREATMENT *Campylobacter* Infection

Fluid and electrolyte replacement is central to the treatment of diarrheal illnesses (Chap. 26). Even among patients presenting for medical attention with *Campylobacter* enteritis, not all clearly benefit from specific antimicrobial therapy. Indications for therapy include high fever, bloody diarrhea, severe diarrhea, persistence for >1 week, and worsening of symptoms. A 5- to 7-day course of erythromycin (250 mg orally four times daily or—for children—30–50 mg/kg per day, in divided doses) is the regimen of choice. Both clinical trials and in vitro susceptibility testing indicate that other macrolides, including azithromycin (a 1- or 3-day regimen), also are useful therapeutic agents. An alternative regimen for adults is ciprofloxacin (500 mg orally twice daily) or another fluoroquinolone for 5–7 days, but resistance to this class of agents as well as to tetracyclines has been increasing. Patients infected with antibiotic-resistant strains are at increased risk of adverse outcomes. Use of antimotility agents, which may prolong the duration of symptoms and have been associated with toxic megacolon and with death, is not recommended.

For systemic infections, treatment with gentamicin (1.7 mg/kg IV every 8 h after a loading dose of 2 mg/kg), imipenem (500 mg IV every 6 h), or chloramphenicol (50 mg/kg IV each day in three or four divided doses) should be started empirically, but susceptibility testing should then be performed. Ciprofloxacin and amoxicillin/clavulanate are alternative agents for susceptible strains. In the absence of immunocompromise or endovascular infections, therapy should be administered for 14 days. For immunocompromised patients with systemic infections due to *C. fetus* and for patients with endovascular infections, prolonged therapy (for up to 4 weeks) is usually necessary. For recurrent infections in immunocompromised hosts, lifelong therapy/prophylaxis is sometimes necessary.

PROGNOSIS

Nearly all patients recover fully from *Campylobacter* enteritis, either spontaneously or after antimicrobial therapy.

Volume depletion probably contributes to the few deaths that are reported. As stated earlier, occasional patients develop reactive arthritis or Guillain-Barré syndrome or its variants. Systemic infection with *C. fetus* is much more often fatal than that due to related species; this higher mortality rate reflects in part the population affected. Prognosis depends on the rapidity with which appropriate therapy is begun. Otherwise-healthy hosts usually survive *C. fetus* infections without sequelae. Compromised hosts often have recurrent and/or life-threatening infections due to a variety of *Campylobacter* species.

CHAPTER 61

CHOLERA AND OTHER VIBRIOSES

Matthew K. Waldor ■ Edward T. Ryan

Members of the genus *Vibrio* cause a number of important infectious syndromes. Classic among them is cholera, a devastating diarrheal disease caused by *V. cholerae* that has been responsible for seven global pandemics and much suffering over the past two centuries. Epidemic cholera remains a significant public health concern in the developing world today. Other vibrioses caused by other *Vibrio* species include syndromes of diarrhea, soft tissue infection, or primary sepsis. All *Vibrio* species are highly motile, facultatively anaerobic, curved gram-negative rods with one or more flagella. In nature, vibrios most commonly reside in tidal rivers and bays under conditions of moderate salinity. They proliferate in the summer months when water temperatures exceed 20°C. As might be expected, the illnesses they cause also increase in frequency during the warm months.

CHOLERA

DEFINITION

Cholera is an acute diarrheal disease that can, in a matter of hours, result in profound, rapidly progressive dehydration and death. Accordingly, cholera gravis (the severe form of cholera) is a much-feared disease, particularly in its epidemic presentation. Fortunately, prompt aggressive fluid repletion and supportive care can obviate the high mortality that cholera has historically wrought. While the term *cholera* has occasionally been applied to any severely dehydrating secretory diarrheal illness, whether infectious in etiology or not, it now refers to disease caused by *V. cholerae* serogroup O1 or O139—i.e., the serogroups with epidemic potential.

MICROBIOLOGY AND EPIDEMIOLOGY

The species *V. cholerae* is classified into more than 200 serogroups based on the carbohydrate determinants of their lipopolysaccharide (LPS) O antigens. Although some non-O1 *V. cholerae* serogroups (strains that do not agglutinate in antisera to the O1 group antigen) have occasionally caused sporadic outbreaks of diarrhea, serogroup O1 was, until the emergence of serogroup O139 in 1992, the exclusive cause of epidemic cholera. Two biotypes of *V. cholerae* O1, classical and El Tor, are distinguished. Each biotype is further subdivided into two serotypes, termed *Inaba* and *Ogawa*.

The natural habitat of *V. cholerae* is coastal salt water and brackish estuaries, where the organism lives in close relation to plankton. Humans become infected incidentally but, once infected, can act as vehicles for spread. Ingestion of water contaminated by human feces is the most common means of acquisition of *V. cholerae*. Consumption of contaminated food also can contribute to spread. There is no known animal reservoir. While the infectious dose is relatively high, it is markedly reduced in hypochlorhydric persons, in those using antacids, and when gastric acidity is buffered by a meal. Cholera is predominantly a pediatric disease in endemic areas, but it affects adults and children equally when newly introduced into a population. In endemic areas, the burden of disease is often greatest during "cholera seasons" associated with high temperatures, heavy rainfall, and flooding, but cholera can occur year-round. For unexplained reasons, susceptibility to cholera is significantly influenced by ABO blood group status; persons with type O blood are at greatest risk of severe disease if infected, while those with type AB are at least risk.

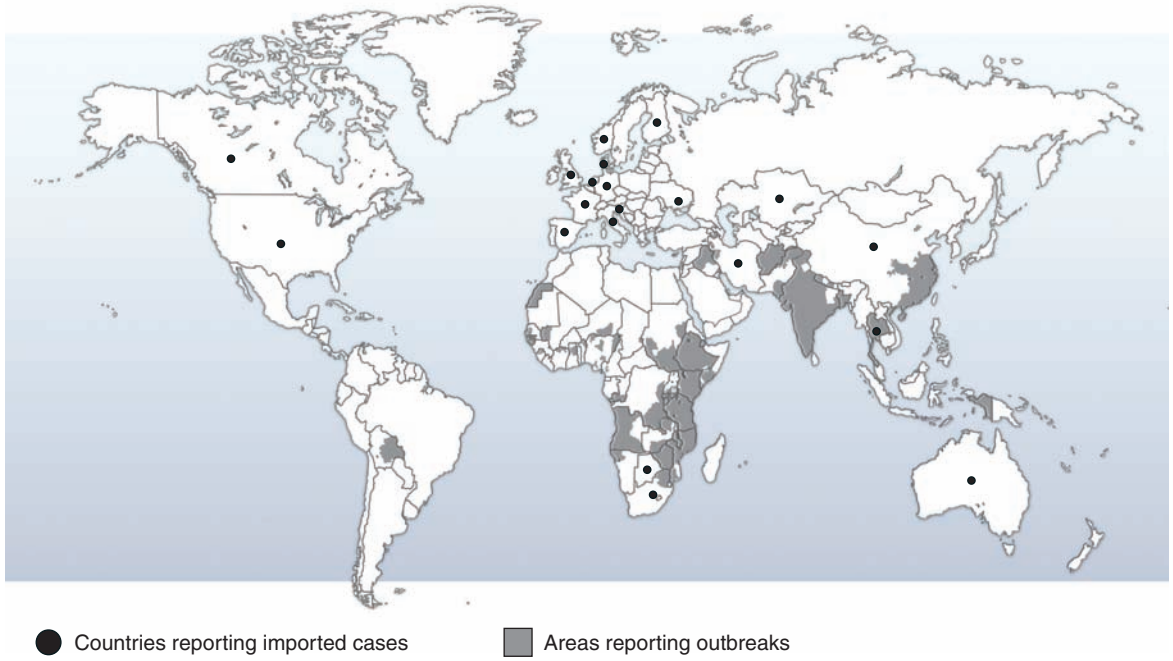


FIGURE 61-1
World distribution of cholera in 2009. (*Adapted from WHO: Wkly Epidemiol Rec 84:309, 2009.*)

Cholera is native to the Ganges delta in the Indian subcontinent. Since 1817, seven global pandemics have occurred. The current (seventh) pandemic—the first due to the El Tor biotype—began in Indonesia in 1961 and spread throughout Asia as *V. cholerae* El Tor displaced the endemic classical biotype. In the early 1970s, El Tor cholera erupted in Africa, causing major epidemics before becoming a persistent endemic problem. Currently, >90% of cholera cases reported annually to the World Health Organization (WHO) are from Africa (Fig. 61-1), but the true burden in Africa as well as in Asia is unknown since diagnosis is often syndromic and since many countries with endemic cholera do not report cholera to the WHO. It is possible that >3 million cases of cholera occur yearly (of which only ~200,000 are reported to the WHO), resulting in >100,000 deaths annually (of which <5000 are reported to the WHO).

The recent history of cholera has been punctuated by severe outbreaks, especially among impoverished or displaced persons. Such outbreaks are often precipitated by war or other circumstances that lead to the breakdown of public health measures. Such was the case in the camps for Rwandan refugees set up in 1994 around Goma, Zaire (now the Democratic Republic of the Congo); in 2008–2009 in Zimbabwe; and in 2010 in Haiti. Since 1973, sporadic endemic infections due to *V. cholerae* O1 strains related to the seventh-pandemic strain have been recognized along the U.S. Gulf Coast of Louisiana and Texas. These infections are typically associated with the consumption of contaminated, locally harvested shellfish. Occasionally, cases in U.S. locations remote from the Gulf Coast have been linked to shipped-in Gulf Coast seafood.

After a century without cholera in Latin America, the current cholera pandemic reached Central and South America in 1991. Following an initial explosive spread that affected millions (Fig. 61-2), the burden of disease has markedly decreased in Latin America, although, as it did in Africa two decades earlier, the epidemic El Tor strain proved capable of establishing itself

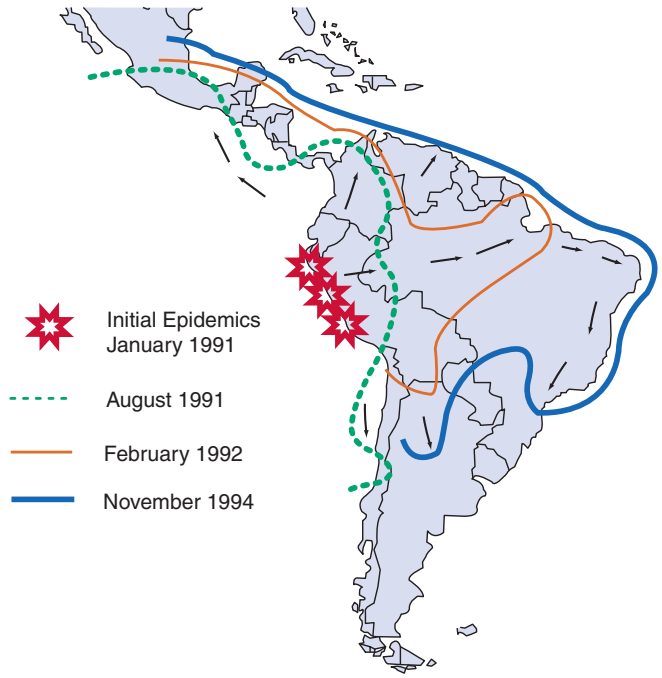


FIGURE 61-2
Spread of *Vibrio cholerae* O1 in the Americas, 1991–1994. (*Courtesy of Dr. Robert V. Tauxe, Centers for Disease Control and Prevention, Atlanta; with permission.*)

in inland fresh waters rather than in its classic niche of coastal salt waters. In 2010, cholera reappeared in Haiti after a century-long absence.

In October 1992, a large-scale outbreak of clinical cholera caused by a new serogroup, O139, occurred in southeastern India. The organism appears to be a derivative of El Tor O1, but has a distinct LPS and an immunologically related O-antigen polysaccharide capsule. (O1 organisms are not encapsulated.) After an initial spread across 11 Asian countries **(Fig. 61-3)**, *V. cholerae* O139 has once again been largely replaced by O1, although O139 still causes a minority of cases in some Asian countries. The clinical manifestations of disease caused by *V. cholerae* O139 are indistinguishable from those of O1 cholera. Immunity to one, however, is not protective against the other.

PATHOGENESIS

In the final analysis, cholera is a toxin-mediated disease. The watery diarrhea characteristic of cholera is due to the action of cholera toxin, a potent protein enterotoxin elaborated by the organism in the small intestine. The toxin-coregulated pilus (TCP), so named because its synthesis is regulated in parallel with that of cholera toxin, is essential for *V. cholerae* to survive and multiply in (colonize) the small intestine. Cholera toxin, TCP, and several other virulence factors are coordinately regulated by ToxR. This protein modulates the expression of genes coding for virulence factors in response to environmental signals via a cascade of regulatory proteins. Additional regulatory processes, including bacterial responses to the density of the bacterial population (in a phenomenon known as *quorum sensing*), control the virulence of *V. cholerae*.

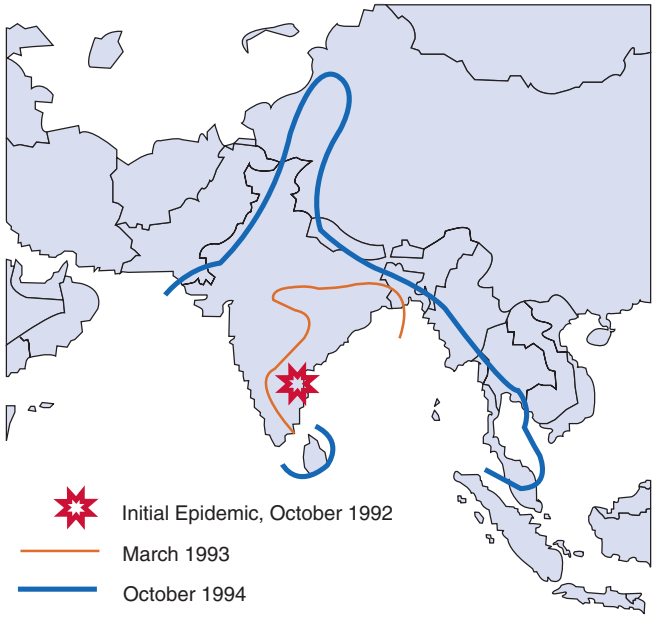


FIGURE 61-3
Spread of *Vibrio cholerae* O139 in the Indian subcontinent and elsewhere in Asia, 1992–1994. (*Courtesy of Dr. Robert V. Tauxe, CDC, Atlanta; with permission.*)

Once established in the human small bowel, the organism produces cholera toxin, which consists of a monomeric enzymatic moiety (the A subunit) and a pentameric binding moiety (the B subunit). The B pentamer binds to GM_1 ganglioside, a glycolipid on the surface of epithelial cells that serves as the toxin receptor and makes possible the delivery of the A subunit to its cytosolic target. The activated A subunit (A_1) irreversibly transfers ADP-ribose from nicotinamide adenine dinucleotide to its specific target protein, the GTP-binding regulatory component of adenylate cyclase. The ADP-ribosylated G protein upregulates the activity of adenylate cyclase; the result is the intracellular accumulation of high levels of cyclic AMP. In intestinal epithelial cells, cyclic AMP inhibits the absorptive sodium transport system in villus cells and activates the secretory chloride transport system in crypt cells, and these events lead to the accumulation of sodium chloride in the intestinal lumen. Since water moves passively to maintain osmolality, isotonic fluid accumulates in the lumen. When the volume of that fluid exceeds the capacity of the rest of the gut to resorb it, watery diarrhea results. Unless the wasted fluid and electrolytes are adequately replaced, shock (due to profound dehydration) and acidosis (due to loss of bicarbonate) follow. Although perturbation of the adenylate cyclase pathway is the primary mechanism by which cholera toxin causes excess fluid secretion, cholera toxin also enhances intestinal secretion via prostaglandins and/or neural histamine receptors.

The *V. cholerae* genome comprises two circular chromosomes. Lateral gene transfer has played a key role in the evolution of epidemic *V. cholerae*. The genes encoding cholera toxin (*ctxAB*) are part of the genome of a bacteriophage, CTXΦ. The receptor for this phage on the *V. cholerae* surface is the intestinal colonization factor TCP. Since *ctxAB* is part of a mobile genetic element (CTXΦ), horizontal transfer of this bacteriophage may account for the emergence of new toxigenic *V. cholerae* serogroups. Many of the other genes important for *V. cholerae* pathogenicity, including the genes encoding the biosynthesis of TCP, those encoding accessory colonization factors, and those regulating virulence gene expression, are clustered together in the *V. cholerae* pathogenicity island. Similar clustering of virulence genes is found in other bacterial pathogens. It is believed that pathogenicity islands are acquired by horizontal gene transfer. *V. cholerae* O139 is probably derived from an El Tor O1 strain that acquired the genes for O139 O-antigen synthesis by horizontal gene transfer.

CLINICAL MANIFESTATIONS

Individuals infected with *V. cholerae* O1 or O139 exhibit a range of clinical manifestations. Some individuals are asymptomatic or have only mild diarrhea; others present with the sudden onset of explosive and life-threatening diarrhea (*cholera gravis*). The reasons for the range in signs and symptoms of disease are incompletely understood but include the level of preexisting immunity, blood type, and nutritional status. In a nonimmune individual,

after a 24- to 48-h incubation period, cholera characteristically begins with the sudden onset of painless watery diarrhea that may quickly become voluminous. Patients often vomit. In severe cases, volume loss can exceed 250 mL/kg in the first 24 h. If fluids and electrolytes are not replaced, hypovolemic shock and death may ensue. Fever is usually absent. Muscle cramps due to electrolyte disturbances are common. The stool has a characteristic appearance: a nonbilious, gray, slightly cloudy fluid with flecks of mucus, no blood, and a somewhat fishy, inoffensive odor. It has been called "rice-water" stool because of its resemblance to the water in which rice has been washed **(Fig. 61-4)**. Clinical symptoms parallel volume contraction: At losses of <5% of normal body weight, thirst develops; at 5–10%, postural hypotension, weakness, tachycardia, and decreased skin turgor are documented; and at >10%, oliguria, weak or absent pulses, sunken eyes (and, in infants, sunken fontanelles), wrinkled ("washerwoman") skin, somnolence, and coma are characteristic. Complications derive exclusively from the effects of volume and electrolyte depletion and include renal failure due to acute tubular necrosis. Thus, if the patient is adequately treated with fluid and electrolytes, complications are averted and the process is self-limited, resolving in a few days.

Laboratory data usually reveal an elevated hematocrit (due to hemoconcentration) in nonanemic patients; mild neutrophilic leukocytosis; elevated levels of blood urea nitrogen and creatinine consistent with prerenal azotemia; normal sodium, potassium, and chloride levels; a markedly reduced bicarbonate level (<15 mmol/L); and an elevated anion gap (due to increases in serum lactate, protein, and phosphate). Arterial pH is usually low (~7.2).

FIGURE 61-4
Rice water cholera stool. Note floating mucus and gray watery appearance. (*Courtesy of Dr. ASG Faruque, International Centre for Diarrhoeal Disease Research, Dhaka; with permission.*)

DIAGNOSIS

The clinical suspicion of cholera can be confirmed by the identification of *V. cholerae* in stool; however, the organism must be specifically sought. With experience, it can be detected directly by dark-field microscopy on a wet mount of fresh stool, and its serotype can be discerned by immobilization with specific antiserum. Laboratory isolation of the organism requires the use of a selective medium such as taurocholate-tellurite-gelatin (TTG) agar or thiosulfate–citrate–bile salts–sucrose (TCBS) agar. If a delay in sample processing is expected, Carey-Blair transport medium and/or alkaline-peptone water-enrichment medium may be used as well. In endemic areas, there is little need for biochemical confirmation and characterization, although these tasks may be worthwhile in places where *V. cholerae* is an uncommon isolate. Standard microbiologic biochemical testing for Enterobacteriaceae will suffice for identification of *V. cholerae*. All vibrios are oxidase-positive. A point-of-care antigen-detection cholera dipstick assay is now commercially available for use in the field or where laboratory facilities are lacking.

TREATMENT Cholera

Death from cholera is due to hypovolemic shock; thus treatment of individuals with cholera first and foremost requires fluid resuscitation and management. In light of the level of dehydration **(Table 61-1)** and the patient's age and weight, euvolemia should first be rapidly restored, and adequate hydration should then be

TABLE 61-1
ASSESSING THE DEGREE OF DEHYDRATION IN PATIENTS WITH CHOLERA

DEGREE OF DEHYDRATION	CLINICAL FINDINGS
None or mild, but diarrhea	Thirst in some cases; <5% loss of total body weight
Moderate	Thirst, postural hypotension, weakness, tachycardia, decreased skin turgor, dry mouth/tongue, no tears; 5–10% loss of total body weight
Severe	Unconsciousness, lethargy, or "floppiness"; weak or absent pulse; inability to drink; sunken eyes (and, in infants, sunken fontanelles); >10% loss of total body weight

maintained to replace ongoing fluid losses (Table 61-2). Administration of oral rehydration solution (ORS) takes advantage of the hexose-Na^+ co-transport mechanism to move Na^+ across the gut mucosa together with an actively transported molecule such as glucose (or galactose). Cl^- and water follow. This transport mechanism remains intact even when cholera toxin is active. ORS may be made by adding safe water to prepackaged sachets containing salts and sugar or by adding 0.5 teaspoon of table salt (NaCl; 3.5 g) and 4 tablespoons of table sugar (glucose; 40 g) to 1 L of safe water. Potassium intake in bananas or green coconut water should be encouraged. A number of ORS formulations are available, and the WHO now recommends "low-osmolarity" ORS for treatment of individuals with dehydrating diarrhea of any cause (Table 61-3). If available, rice-based ORS is considered superior to standard ORS in the treatment of cholera. ORS can be administered via a nasogastric tube to individuals who cannot ingest fluid; however, optimal management of individuals with severe dehydration includes the administration of IV fluid and electrolytes. Because profound acidosis (pH < 7.2) is common in this group, Ringer's lactate is the best choice among commercial products (Table 61-4). It must be used with additional potassium supplements, preferably given by mouth. The total fluid deficit in severely dehydrated patients (>10% of body weight) can be replaced safely within the first 3–6 h of therapy, half within the first hour. Transient muscle cramps and tetany are common. Thereafter, oral therapy can usually be initiated, with the goal of maintaining fluid intake equal to fluid output. However, patients with continued large-volume diarrhea may require prolonged IV treatment to match gastrointestinal fluid losses. Severe hypokalemia can develop but will respond to potassium given either IV or orally. In the absence of adequate staff to monitor the patient's progress, the oral route of rehydration and potassium replacement is safer than the IV route.

TABLE 61-2

TREATMENT OF CHOLERA, BASED ON DEGREE OF DEHYDRATION[a]

DEGREE OF DEHYDRATION, PATIENT'S AGE (WEIGHT)	TREATMENT
None or Mild, but Diarrhea[b]	
<2 years	1/4–1/2 cup (50–100 mL) of ORS, to a maximum of 0.5 L/d
2–9 years	1/2–1 cup (100–200 mL) of ORS, to a maximum of 1 L/d
≥10 years	As much ORS as desired, to a maximum of 2 L/d
Moderate[b,c]	
<4 months (<5 kg)	200–400 mL of ORS
4–11 months (5–<8 kg)	400–600 mL of ORS
12–23 months (8–<11 kg)	600–800 mL of ORS
2–4 years (11–<16 kg)	800–1200 mL of ORS
5–14 years (16–<30 kg)	1200–2200 mL of ORS
≥15 years (≥30 kg)	2200–4000 mL of ORS
Severe[b]	
All ages and weights	IV fluid replacement with Ringer's lactate (or, if not available, normal saline): 100 mL/kg in first 3-h period (or first 6-h period for children <12 months old); start rapidly, then slow down; total of 200 mL/kg in first 24 h; continue until patient is awake, can ingest ORS, and no longer has a weak pulse

Note: Continue normal feeding during treatment.
[a]Adapted from World Health Organization: First steps for managing an outbreak of acute diarrhoea. Global Task Force on Cholera Control, 2009 (www.who.int/topics/cholera). ORS, oral rehydration solution.
[b]Reassess regularly; monitor stool and vomit output.
[c]Amounts of ORS listed should be given within the first 4 h.

TABLE 61-3

COMPOSITION OF WORLD HEALTH ORGANIZATION REDUCED-OSMOLARITY ORAL REHYDRATION SOLUTION (ORS)[a,b]

CONSTITUENT	CONCENTRATION, mmol/L
Na^+	75
K^+	20
Cl^-	65
Citrate[c]	10
Glucose	75
Total osmolarity	245

[a]Contains (per package, to be added to 1 L of drinking water): NaCl, 2.6 g; $Na_3C_6H_5O_7 \cdot 2H_2O$, 2.9 g; KCl, 1.5 g; and glucose (anhydrous), 13.5 g.
[b]If prepackaged ORS is unavailable, a simple homemade alternative can be prepared by combining 3.5 g (~1/2 teaspoon) of NaCl with either 50 g of precooked rice cereal or 40 g (4 tablespoons) of table sugar (sucrose) in 1 L of drinking water. In that case, potassium must be supplied separately (e.g., in orange juice or coconut water).
[c]10 mmol citrate per liter, which supplies 30 mmol HCO_3/L.

TABLE 61-4

ELECTROLYTE COMPOSITION OF CHOLERA STOOL AND OF INTRAVENOUS REHYDRATION SOLUTION

	CONCENTRATION, mmol/L			
SUBSTANCE	Na^+	K^+	Cl^-	BASE
Stool				
Adult	135	15	100	45
Child	100	25	90	30
Ringer's lactate	130	4[a]	109	28

[a]Potassium supplements, preferably administered by mouth, are required to replace the usual potassium losses from stool.

Although not necessary for cure, the use of an antibiotic to which the organism is susceptible diminishes the duration and volume of fluid loss and hastens clearance of the organism from the stool. The WHO recommends administration of antibiotics to cholera patients only if they are severely dehydrated, although wider use is often justifiable. Doxycycline (a single dose of 300 mg) or tetracycline (12.5 mg/kg four times a day for 3 days) may be effective in adults but is not recommended for children <8 years of age because of possible deposition in bone and developing teeth. Emerging drug resistance is an ever-present concern. For nonpregnant adults with cholera in areas where tetracycline resistance is prevalent, ciprofloxacin (either in a single dose [30 mg/kg, not to exceed a total dose of 1 g] or in a short course [15 mg/kg bid for 3 days, not to exceed a total daily dose of 1 g]), erythromycin (40–50 mg/kg daily in three divided doses for 3 days), or azithromycin (a single 1-g dose) may be a clinically effective substitute. Pregnant women and children are usually treated with erythromycin or azithromycin (10 mg/kg in children).

PREVENTION

Provision of safe water and facilities for sanitary disposal of feces, improved nutrition, and attention to food preparation and storage in the household can significantly reduce the incidence of cholera.

Much effort has been devoted to the development of an effective cholera vaccine over the past few decades, with a particular focus on oral vaccine strains. Traditional killed cholera vaccine given intramuscularly provides little protection to nonimmune subjects and predictably causes adverse effects, including pain at the injection site, malaise, and fever. The vaccine's limited efficacy is due, at least in part, to its failure to induce a local immune response at the intestinal mucosal surface.

Two types of oral cholera vaccines have been developed. The first is a killed whole-cell (WC) vaccine. Two formulations of the killed WC vaccine have been prepared: one that also contains the nontoxic B subunit of cholera toxin (WC/BS) and one composed solely of killed bacteria. In placebo-controlled field trials in Bangladesh, both of the killed vaccines offered significant protection from cholera for the first 6 months after vaccination, with protection rates of ~58% for WC vaccine and 85% for WC/BS vaccine. Protective efficacy rates for both vaccines declined to ~50% by 3 years after vaccine administration. Immunity was relatively sustained in persons vaccinated at an age of >5 years but was not well sustained in younger vaccinees. The WC/BS vaccine proved effective in a trial conducted in a sub-Saharan African population with a high prevalence of HIV infection. Trials of locally produced killed WC vaccines have yielded promising results in Vietnam and in Kolkata (Calcutta), India. Killed oral vaccines also confer herd protection to unvaccinated individuals living in proximity to vaccinated individuals. The WHO now recommends that vaccination against cholera be part of a larger response plan for populations at risk for epidemic cholera. The oral killed vaccines are available in Europe and Asia but (like other cholera vaccines) are not available in the United States.

The second type of cholera vaccine under development involves the use of oral live attenuated vaccine strains developed, for example, by the isolation or creation of mutants lacking the genes encoding cholera toxin. One such vaccine, CVD 103-HgR, was safe and immunogenic in phase 1 and 2 studies but afforded minimal protection in a large field trial in Indonesia. Other live attenuated vaccine candidate strains have been prepared from El Tor and O139 *V. cholerae* and are now undergoing clinical trials. The development of effective and safe cholera vaccines and strategies that provide long-lasting protective mucosal immunity, especially among malnourished, impoverished, and potentially HIV-infected adults and children (the individuals most at risk for cholera), is a priority. As mentioned earlier, no cholera vaccine is commercially available in the United States.

OTHER *VIBRIO* SPECIES

The genus *Vibrio* includes several human pathogens that do not cause cholera. Abundant in coastal waters throughout the world, noncholera vibrios can reach high concentrations in the tissues of filter-feeding mollusks. As a result, human infection commonly follows the ingestion of seawater or of raw or undercooked shellfish **(Table 61-5)**. Most noncholera vibrios can be cultured on blood or MacConkey agar, which contains enough salt to support the growth of these halophilic species. In the microbiology laboratory, the species of noncholera vibrios are distinguished by standard biochemical tests. The most important of these organisms are *V. parahaemolyticus* and *V. vulnificus*.

The two major types of syndromes for which these species are responsible are gastrointestinal illness (due to *V. parahaemolyticus*, non-O1/O139 *V. cholerae*, *V. mimicus*, *V. fluvialis*, *V. hollisae*, and *V. furnissii*) and soft tissue infections (due to *V. vulnificus*, *V. alginolyticus*, and *V. damselae*). *V. vulnificus* is also a cause of primary sepsis in some compromised individuals.

SPECIES ASSOCIATED PRIMARILY WITH GASTROINTESTINAL ILLNESS

V. parahaemolyticus

Widespread in marine environments, the halophilic *V. parahaemolyticus* causes food-borne enteritis worldwide. This species was originally implicated in enteritis in Japan in 1953, accounting for 24% of reported cases in one study—a rate that presumably was due to the common practice of eating raw seafood in that country. In the United States, common-source outbreaks of diarrhea caused by this organism have been linked to the consumption of undercooked or improperly handled seafood or of other foods contaminated by seawater. Since the mid-1990s, the incidence of

TABLE 61-5

FEATURES OF SELECTED NONCHOLERA VIBRIOSES

ORGANISM	VEHICLE OR ACTIVITY	HOST AT RISK	SYNDROME
V. parahaemolyticus	Shellfish, seawater Seawater	Normal Normal	Gastroenteritis Wound infection
Non-O1/O139 *V. cholerae*	Shellfish, travel Seawater	Normal Normal	Gastroenteritis Wound infection, otitis media
V. vulnificus	Shellfish Seawater	Immunosuppressed[a] Normal, immunosuppressed[a]	Sepsis, secondary cellulitis Wound infection, cellulitis
V. alginolyticus	Seawater Seawater	Normal Burned, other immunosuppressed	Wound infection, cellulitis, otitis Sepsis

[a]Especially with liver disease or hemochromatosis.

Source: Table 161-3 in *Harrison's Principles of Internal Medicine,* 14th edition.

V. parahaemolyticus infections has increased in several countries, including the United States. Serotypes O3:K6, O4:K68, and O1:K-untypable, which are genetically related to one another, account for this increase. The enteropathogenicity of *V. parahaemolyticus* is linked to its ability to cause hemolysis on Wagatsuma agar (i.e., the *Kanagawa phenomenon*). Although the mechanism by which the organism causes diarrhea remains unclear, the genome sequence of *V. parahaemolyticus* contains two type III secretion systems, which directly inject toxic bacterial proteins into host cells. *V. parahaemolyticus* should be considered a possible etiologic agent in all cases of diarrhea that can be linked epidemiologically to seafood consumption or to the sea itself.

Infections with *V. parahaemolyticus* can result in two distinct gastrointestinal presentations. The more common of the two presentations (including nearly all cases in North America) is characterized by watery diarrhea, usually occurring in conjunction with abdominal cramps, nausea, and vomiting and accompanied in ~25% of cases by fever and chills. After an incubation period of 4 h to 4 days, symptoms develop and persist for a median of 3 days. Dysentery, the less common presentation, is characterized by severe abdominal cramps, nausea, vomiting, and bloody or mucoid stools. *V. parahaemolyticus* also causes rare cases of wound infection and otitis and very rare cases of sepsis.

Most cases of *V. parahaemolyticus*–associated gastrointestinal illness, regardless of the presentation, are self-limited and require neither antimicrobial treatment nor hospitalization. Deaths are extremely rare among immunocompetent individuals. Severe infections are associated with underlying diseases, including diabetes, preexisting liver disease, iron-overload states, or immunosuppression. The occasional severe case should be treated with fluid replacement and antibiotics, as described earlier for cholera.

Non-O1/O139 (noncholera) V. cholerae

The heterogeneous non-O1/O139 *V. cholerae* organisms cannot be distinguished from *V. cholerae* O1 or O139 by routine biochemical tests but do not agglutinate in O1 or O139 antiserum. Non-O1/O139 strains have caused several well-studied food-borne outbreaks of gastroenteritis and have also been responsible for sporadic cases of otitis media, wound infection, and bacteremia; although gastroenteritis outbreaks can occur, non-O1/O139 *V. cholerae* strains do not cause epidemics of cholera. Like other vibrios, non-O1/O139 *V. cholerae* organisms are widely distributed in marine environments. In most instances, recognized cases in the United States have been associated with the consumption of raw oysters or with recent travel, typically to Mexico. The broad clinical spectrum of diarrheal illness caused by these organisms is probably due to the group's heterogeneous virulence attributes.

In the United States, about half of all non-O1/O139 *V. cholerae* isolates are from stool samples. The typical incubation period for gastroenteritis due to these organisms is <2 days, and the illness lasts for ~2–7 days. Patients' stools may be copious and watery or may be partly formed, less voluminous, and bloody or mucoid. Diarrhea can result in severe dehydration. Many cases include abdominal cramps, nausea, vomiting, and fever. Like those with cholera, patients who are seriously dehydrated should receive oral or IV fluids; the value of antibiotics is not clear.

Extraintestinal infections due to non-O1/O139 *V. cholerae* commonly follow occupational or recreational exposure to seawater. Around 10% of non-O1/O139 *V. cholerae* isolates come from cases of wound infection, 10% from cases of otitis media, and 20% from cases of bacteremia (which is particularly likely to develop in patients with liver disease). Extraintestinal infections should be treated with antibiotics. Information to guide antibiotic selection and dosing is limited, but most strains are sensitive in vitro to tetracycline, ciprofloxacin, and third-generation cephalosporins.

SPECIES ASSOCIATED PRIMARILY WITH SOFT TISSUE INFECTION OR BACTEREMIA

(See also Chap. 22)

V. vulnificus

Infection with *V. vulnificus* is rare, but this organism is the most common cause of severe *Vibrio* infections in the United States. Like most vibrios, *V. vulnificus* proliferates in the warm summer months and requires a saline environment for growth. In this country, infections in humans typically occur in coastal states between May and October and most commonly affect men >40 years of age. *V. vulnificus* has been linked to two distinct syndromes: primary sepsis, which usually occurs in patients with underlying liver disease, and primary wound infection, which generally affects people without underlying disease. (*Vulnificus* is Latin for "wound maker.") Some authors have suggested that *V. vulnificus* also causes gastroenteritis independent of other clinical manifestations. *V. vulnificus* is endowed with a number of virulence attributes, including a capsule that confers resistance to phagocytosis and to the bactericidal activity of human serum as well as a cytolysin. Measured as the 50% lethal dose in mice, the organism's virulence is considerably increased under conditions of iron overload; this observation is consistent with the propensity of *V. vulnificus* to infect patients who have hemochromatosis.

Primary sepsis most often develops in patients who have cirrhosis or hemochromatosis. However, *V. vulnificus* bacteremia can also affect individuals who have hematopoietic disorders or chronic renal insufficiency, those who are using immunosuppressive medications or alcohol, or (in rare instances) those who have no known underlying disease. After a median incubation period of 16 h, the patient develops malaise, chills, fever, and prostration. One-third of patients develop hypotension, which is often apparent at admission. Cutaneous manifestations develop in most cases (usually within 36 h of onset) and characteristically involve the extremities (the lower more often than the upper). In a common sequence, erythematous patches are followed by ecchymoses, vesicles, and bullae. In fact, sepsis and hemorrhagic bullous skin lesions suggest the diagnosis in appropriate settings. Necrosis and sloughing may also be evident. Laboratory studies reveal leukopenia more often than leukocytosis, thrombocytopenia, or elevated levels of fibrin split products. *V. vulnificus* can be cultured from blood or cutaneous lesions. The mortality rate approaches 50%, with most deaths due to uncontrolled sepsis. Accordingly, prompt treatment is critical and should include empirical antibiotic administration, aggressive debridement, and general supportive care. *V. vulnificus* is sensitive in vitro to a number of antibiotics, including tetracycline, fluoroquinolones, and third-generation cephalosporins. Data from animal models suggest that either a fluoroquinolone or the combination of minocycline and cefotaxime should be used in the treatment of *V. vulnificus* septicemia.

V. vulnificus can infect either a fresh or an old wound that comes into contact with seawater; the patient may or may not have underlying disease. After a short incubation period (4 h to 4 days; mean, 12 h), the disease begins with swelling, erythema, and (in many cases) intense pain around the wound. These signs and symptoms are followed by cellulitis, which spreads rapidly and is sometimes accompanied by vesicular, bullous, or necrotic lesions. Metastatic events are uncommon. Most patients have a fever and leukocytosis. *V. vulnificus* can be cultured from skin lesions and occasionally from the blood. Prompt antibiotic therapy and debridement are usually curative.

V. alginolyticus

First identified as a pathogen of humans in 1973, *V. alginolyticus* occasionally causes eye, ear, and wound infections. This species is the most salt-tolerant of the vibrios and can grow in salt concentrations of >10%. Most clinical isolates come from superinfected wounds that presumably become contaminated at the beach. Although its severity varies, *V. alginolyticus* infection tends not to be serious and generally responds well to antibiotic therapy and drainage. A few cases of otitis externa, otitis media, and conjunctivitis due to this pathogen have been described. Tetracycline treatment usually results in cure. *V. alginolyticus* is a rare cause of bacteremia in immunocompromised hosts.

Acknowledgments

The authors gratefully acknowledge the valuable contributions of Drs. Robert Deresiewicz and Gerald T. Keusch, coauthors of this chapter for previous editions of Harrison's Principles of Internal Medicine.

CHAPTER 62

BRUCELLOSIS

Michael J. Corbel ■ Nicholas J. Beeching

DEFINITION

Brucellosis is a bacterial zoonosis transmitted directly or indirectly to humans from infected animals, predominantly domesticated ruminants and swine. The disease is known colloquially as *undulant fever* because of its remittent character. Its distribution is worldwide apart from the few countries where it has been eradicated from the animal reservoir. Although brucellosis commonly presents as an acute febrile illness, its clinical manifestations vary widely, and definitive signs indicative of the diagnosis may be lacking. Thus the clinical diagnosis usually must be supported by the results of bacteriologic and/or serologic tests.

ETIOLOGIC AGENTS

Human brucellosis is caused by strains of *Brucella*, a bacterial genus that was previously suggested, on genetic grounds, to comprise a single species, *B. melitensis,* with a number of biologic variants exhibiting particular host preferences. This view was challenged on the basis of detailed differences in chromosomal structure and host preference. The traditional classification into nomen species is now favored both because of these differences and because this classification scheme closely reflects the epidemiologic patterns of the infection. The nomen system recognizes *B. melitensis*, which is the most common cause of symptomatic disease in humans and for which the main sources are sheep, goats, and camels; *B. abortus,* which is usually acquired from cattle or buffalo: *B. suis,* which generally is acquired from swine but has one variant enzootic in reindeer and caribou and another in rodents; and *B. canis*, which is acquired most often from dogs. *B. ovis,* which causes reproductive disease in sheep, and *B. neotomae,* which is specific for desert rodents, have not been clearly implicated in human disease. Other brucellae have been isolated from marine mammals, and two new nomen species, *B. ceti* sp. nov. and *B. pinnipedialis* sp. nov., have been proposed for these isolates; at least one case of laboratory-acquired human disease due to one of these proposed species has been described, and apparent cases of natural human infection have been reported. As infections in marine mammals seem widespread, more cases of zoonotic infection may be identified. Other newly proposed species include *B. microti* sp. nov. isolated from field voles and *B. inopinata* sp. nov. isolated from a patient with a breast implant. Moreover, it has become apparent that *Brucella* is closely related to the genus *Ochrobactrum*, which includes environmental bacteria sometimes associated with opportunistic infections.

All brucellae are small, gram-negative, unencapsulated, nonsporulating, nonmotile rods or coccobacilli. They grow aerobically on peptone-based medium incubated at 37°C; the growth of some types is improved by supplementary CO_2. In vivo, brucellae behave as facultative intracellular parasites. The organisms are sensitive to sunlight, ionizing radiation, and moderate heat; they are killed by boiling and pasteurization but are resistant to freezing and drying. Their resistance to drying renders brucellae stable in aerosol form, facilitating airborne transmission. The organisms can survive for up to 2 months in soft cheeses made from goat's or sheep's milk; for at least 6 weeks in dry soil contaminated with infected urine, vaginal discharge, or placental or fetal tissues; and for at least 6 months in damp soil or liquid manure kept under cool dark conditions. Brucellae are easily killed by a wide range of common disinfectants used under optimal conditions but are likely to be much more resistant at low temperatures or in the presence of heavy organic contamination.

EPIDEMIOLOGY

Brucellosis is a zoonosis whose occurrence is closely related to its prevalence in domesticated animals. The true global prevalence of human brucellosis is unknown because of the imprecision of diagnosis and the inadequacy of reporting and surveillance systems in many countries. Even in developed countries, the true incidence may be 10–20 times higher than the reported figures. Bovine brucellosis has been the target of control programs in many parts of the world and has been

eradicated from the cattle populations of Australia, New Zealand, Bulgaria, Canada, Cyprus, Great Britain (including the Channel Islands), Japan, Luxembourg, Romania, the Scandinavian countries, Switzerland, and the Czech and Slovak Republics, among other nations. Its incidence has been reduced to a low level in the United States and most Western European countries, with a varied picture in other parts of the world. There is evidence of a resurgence in Eastern Europe following economic changes in recent years, and outbreaks have also occurred in Ireland. Efforts to eradicate *B. melitensis* infection from sheep and goat populations have been much less successful. These efforts have relied heavily on vaccination programs, which have tended to fluctuate with changing economic and political conditions. In some countries (e.g., Israel), *B. melitensis* has caused serious outbreaks in cattle. Infections with *B. melitensis* still pose a major public health problem in Mediterranean countries; in western, central, and southern Asia; and in parts of Africa and South and Central America.

Human brucellosis is usually associated with occupational or domestic exposure to infected animals or their products. Farmers, shepherds, goatherds, veterinarians, and employees in slaughterhouses and meat-processing plants in endemic areas are occupationally exposed to infection. Family members of individuals involved in animal husbandry may be at risk, although it is often difficult to differentiate food-borne infection from environmental contamination under these circumstances. Laboratory workers who handle cultures or infected samples are also at risk. Travelers and urban residents usually acquire the infection through consumption of contaminated foods. In countries that have eradicated the disease, new cases are most commonly acquired abroad. Dairy products, especially soft cheeses, unpasteurized milk, and ice cream, are the most frequently implicated sources of infection; raw meat and bone marrow may be sources under exceptional circumstances. Infections acquired through cosmetic treatments using materials of fetal origin have been reported. Person-to-person transmission is extremely rare, as is transfer of infection by blood or tissue donation. Although brucellosis is a chronic intracellular infection, there is no evidence for increased prevalence or severity among individuals with HIV infection or with immunodeficiency or immunosuppression of other etiologies.

Brucellosis may be acquired by ingestion, inhalation, or mucosal or percutaneous exposure. Accidental injection of the live vaccine strains of *B. abortus* (19 and RB51) and *B. melitensis* (Rev 1) can cause disease. *B. melitensis* and *B. suis* have been developed as biological weapons by several countries and could be exploited for bioterrorism (Chap. 7). This possibility should be borne in mind in the event of sudden unexplained outbreaks.

IMMUNITY AND PATHOGENESIS

Exposure to brucellosis elicits both humoral and cell-mediated immune responses. The mechanisms of protective immunity against human brucellosis are presumed to be similar to those documented in laboratory animals. The response to infection and its outcome are influenced by the virulence, phase, and species of the infecting strain. Differences have been reported between *B. abortus* and *B. suis* in modes of cellular entry and subsequent compartmentalization and processing. Antibodies promote clearance of extracellular brucellae by bactericidal action and by facilitation of phagocytosis by polymorphonuclear and mononuclear phagocytes; however, antibodies alone cannot eradicate infection. Organisms taken up by macrophages and other cells can establish persistent intracellular infections. The key target cell is the macrophage, and bacterial mechanisms for suppressing intracellular killing and apoptosis result in very large intracellular populations. Opsonized bacteria are actively phagocytosed by neutrophilic granulocytes and by monocytes. In these and other cells, initial attachment takes place via specific receptors, including Fc, C3, fibronectin, and mannose-binding proteins. Opsonized—but not unopsonized—bacteria trigger an oxidative burst inside phagocytes. Unopsonized bacteria are internalized via similar receptors but at much lower efficiency. Smooth strains enter host cells via lipid rafts. Smooth lipopolysaccharide (LPS), β-cyclic glucan, and possibly an invasion-attachment protein (IalB) are involved in this process. Tumor necrosis factor α (TNF-α) produced early in the course of infection stimulates cytotoxic lymphocytes and activates macrophages, which can kill intracellular brucellae (probably mainly through production of reactive oxygen and nitrogen intermediates) and may clear infection. However, virulent *Brucella* cells can suppress the TNF-α response, and control of infection in this situation depends on macrophage activation and interferon γ (IFN-γ) responses. Cytokines such as interleukin (IL) 12 promote production of IFN-γ, which drives T_H1-type responses and stimulates macrophage activation. Inflammatory cytokines, including IL-4, IL-6, and IL-10, downregulate the protective response. As in other types of intracellular infection, it is assumed that initial replication of brucellae takes place within cells of the lymph nodes draining the point of entry. Subsequent hematogenous spread may result in chronic localizing infection at almost any site, although the reticuloendothelial system, musculoskeletal tissues, and genitourinary system are most frequently targeted. Both acute and chronic inflammatory responses develop in brucellosis, and the local tissue response may include granuloma formation with or without necrosis and caseation. Abscesses may also develop, especially in chronic localized infection.

The determinants of pathogenicity of *Brucella* have not been fully characterized, and the mechanisms underlying the manifestations of brucellosis are incompletely understood. The organism is a "stealth" pathogen whose survival strategy is centered on processes that avoid triggering innate immune responses and that permit survival within monocytic cells. The smooth *Brucella* LPS, which has an unusual O-chain and core-lipid composition, has relatively low endotoxin activity and plays a key role in pyrogenicity and in resistance to phagocytosis and serum killing in the nonimmune host.

In addition, LPS is believed to play a key role in suppressing phagosome-lysosome fusion and diverting the internalized bacteria into vacuoles located in endoplasmic reticulum, where intracellular replication takes place. Specific exotoxins have not been isolated, but a type IV secretion system (VirB) that regulates intracellular survival and trafficking has been identified. In *B. abortus* this system can be activated extracellularly, but in *B. suis* it is activated (by low pH) only during intracellular growth. Brucellae then produce acid-stable proteins that facilitate the organisms' survival in phagosomes and may enhance their resistance to reactive oxygen intermediates. A type III secretion system based on modified flagellar structures has also been identified. Virulent brucellae are resistant to defensins and produce a Cu-Zn superoxide dismutase that increases their resistance to reactive oxygen intermediates. A hemolysin-like protein may trigger the release of brucellae from infected cells.

CLINICAL FEATURES

Brucellosis almost invariably causes fever, which may be associated with profuse sweats, especially at night. In endemic areas, brucellosis may be difficult to distinguish from the many other causes of fever. However, two features recognized in the nineteenth century distinguish brucellosis from other tropical fevers, such as typhoid and malaria: (1) Left untreated, the fever of brucellosis shows an undulating pattern that persists for weeks before the commencement of an afebrile period that may be followed by relapse. (2) The fever of brucellosis is associated with musculoskeletal symptoms and signs in about one-half of all patients.

The clinical syndromes caused by the different nomen species are similar, although *B. melitensis* tends to be associated with a more acute and aggressive presentation and *B. suis* with focal abscess induction. *B. abortus* infections may be more insidious in onset and more likely to become chronic. *B. canis* infections are reported to present frequently with acute gastrointestinal symptoms.

The incubation period varies from 1 week to several months, and the onset of fever and other symptoms may be abrupt or insidious. In addition to experiencing fever and sweats, patients become increasingly apathetic and fatigued; lose appetite and weight; and have nonspecific myalgia, headache, and chills. Overall, the presentation of brucellosis often fits one of three patterns: febrile illness that resembles typhoid but is less severe; fever and acute monoarthritis, typically of the hip or knee, in a young child; and long-lasting fever, misery, and low-back or hip pain in an older man. In an endemic area (e.g., much of the Middle East), a patient with fever and difficulty walking into the clinic would be regarded as having brucellosis until it was proved otherwise.

Diagnostic clues in the patient's history include travel to an endemic area, employment in a diagnostic microbiology laboratory, consumption of unpasteurized milk products (including soft cheeses), contact with animals, accidental inoculation with veterinary *Brucella* vaccines, and—in an endemic setting—a history of similar illness in the family (documented in almost 50% of cases). Focal features are present in the majority of patients. The most common are musculoskeletal pain and physical findings in the peripheral and axial skeleton (~40% of cases). Osteomyelitis more commonly involves the lumbar and low thoracic vertebrae than the cervical and high thoracic spine. Individual joints that are most commonly affected by septic arthritis are the knee, hip, sacroiliac, shoulder, and sternoclavicular joints; the pattern may be one of monoarthritis or polyarthritis. Osteomyelitis may also accompany septic arthritis.

In addition to the usual causes of vertebral osteomyelitis or septic arthritis, the most important differential diagnosis is tuberculosis. This point influences the therapeutic approach as well as the prognosis, given that several antimicrobial agents used to treat brucellosis are also used to treat tuberculosis. Septic arthritis in brucellosis progresses slowly, starting with small pericapsular erosions. In the vertebrae, anterior erosions of the superior end plate are typically the first features to become evident, with eventual involvement and sclerosis of the whole vertebra. Anterior osteophytes eventually develop, but vertebral destruction or impingement on the spinal cord is rare and usually suggests tuberculosis **(Table 62-1)**.

TABLE 62-1

RADIOLOGY OF THE SPINE: DIFFERENTIATION OF BRUCELLOSIS FROM TUBERCULOSIS

	BRUCELLOSIS	TUBERCULOSIS
Site	Lumbar and others	Dorsolumbar
Vertebrae	Multiple or contiguous	Contiguous
Diskitis	Late	Early
Body	Intact until late	Morphology lost early
Canal compression	Rare	Common
Epiphysitis	Anterosuperior (Pom's sign)	General: upper and lower disk regions, central, subperiosteal
Osteophyte	Anterolateral (parrot beak)	Unusual
Deformity	Wedging uncommon	Anterior wedge, gibbus
Recovery	Sclerosis, whole body	Variable
Paravertebral abscess	Small, well-localized	Common and discrete loss, transverse process
Psoas abscess	Rare	More likely

Other systems may be involved in a manner that resembles typhoid. About one-quarter of patients have a dry cough, usually with few changes visible on the chest x-ray, although pneumonia, empyema, intrathoracic adenopathy, or lung abscess can occur. One-quarter of patients have hepatosplenomegaly, and 10–20% have significant lymphadenopathy; the differential diagnosis includes glandular fever–like illness such as that caused by Epstein-Barr virus, *Toxoplasma*, cytomegalovirus, HIV, or *Mycobacterium tuberculosis*. Up to 10% of men have acute epididymoorchitis, which must be distinguished from mumps and from surgical problems such as torsion. Prostatitis, inflammation of the seminal vesicles, salpingitis, and pyelonephritis all occur. There is an increased incidence of fetal loss among infected pregnant women, although teratogenicity has not been described and the tendency toward abortions is much less pronounced in humans than in farm animals.

Neurologic involvement is common, with depression and lethargy whose severity may not be fully appreciated by either the patient or the physician until after treatment. A small proportion of patients develop lymphocytic meningoencephalitis that mimics neurotuberculosis, atypical leptospirosis, or noninfectious conditions and that may be complicated by intracerebral abscess, a variety of cranial nerve deficits, or ruptured mycotic aneurysms.

Endocarditis occurs in ~1% of cases, most often affecting the aortic valve (natural or prosthetic). Any site in the body may be involved in metastatic abscess formation or inflammation; the female breast and the thyroid gland are affected particularly often. Nonspecific maculopapular rashes and other skin manifestations are uncommon and are rarely noticed by the patient even if they develop.

DIAGNOSIS

Because the clinical picture of brucellosis is not distinctive, the diagnosis must be based on a history of potential exposure, a presentation consistent with the disease, and supporting laboratory findings. Results of routine biochemical assays are usually within normal limits, although serum levels of hepatic enzymes and bilirubin may be elevated. Peripheral leukocyte counts are usually normal or low, with relative lymphocytosis. Mild anemia may be documented. Thrombocytopenia and disseminated intravascular coagulation with raised levels of fibrinogen degradation products can develop. The erythrocyte sedimentation rate and C-reactive protein levels are often normal but may be raised.

In body fluids such as cerebrospinal fluid (CSF) or joint fluid, lymphocytosis and low glucose levels are the norm. Elevated CSF levels of adenosine deaminase cannot be used to distinguish tubercular meningitis, as they may also be found in brucellosis. Biopsied samples of tissues such as lymph node or liver may show noncaseating granulomas **(Fig. 62-1)** without acid/alcohol-fast bacilli. The radiologic features of bony disease develop late and are much more subtle than those of tuberculosis or septic arthritis of other etiologies, with less bone and joint destruction. Isotope scanning is more sensitive than plain x-ray and continues to give positive results long after successful treatment.

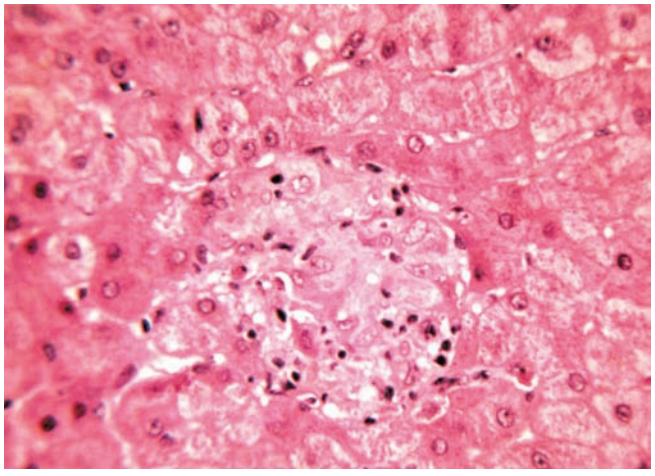


FIGURE 62-1
Liver biopsy specimen from a patient with brucellosis shows a noncaseating granuloma. (*From Mandell's Atlas of Infectious Diseases, Vol II, in DL Stevens [ed]: Skin, Soft Tissue, Bone and Joint Infections, Fig. 5-9; with permission.*)

Isolation of brucellae from blood, CSF, bone marrow, or joint fluid or from a tissue aspirate or biopsy sample is definitive, and attempts at isolation are usually successful in 50–70% of cases. Duplicate cultures should be incubated for up to 6 weeks (in air and 10% CO_2, respectively). Concentration and lysis of buffy coat cells before culture may increase the isolation rate. Cultures in modern nonradiometric or similar signaling systems (e.g., Bactec) usually become positive within 7–10 days but should be maintained for at least 3 weeks before the results are declared negative. All cultures should be handled under containment conditions appropriate for dangerous pathogens. *Brucella* species may be misidentified as *Agrobacterium, Ochrobactrum*, or *Psychrobacter (Moraxella) phenylpyruvicus* by the gallery identification strips commonly used in the diagnostic laboratory.

The peripheral blood–based polymerase chain reaction has enormous potential to detect bacteremia, to predict relapse, and to exclude "chronic brucellosis." This method is probably more sensitive and is certainly quicker than blood culture, and it does not carry the attendant biohazard risk posed by culture. Nucleic acid amplification techniques are now quite widely used, although no single standardized procedure has been adopted. Primers for the spacer region between the genes encoding the 16S and 23S ribosomal RNAs (*rrs-rrl*), the outer-membrane protein Omp2, the insertion sequence *IS711*, and the protein BCSP31 are sensitive and specific. Blood and other tissues are the most suitable samples for analysis.

Serologic examination often provides the only positive laboratory findings in brucellosis. In acute infection, IgM antibodies appear early and are followed by IgG and IgA. All these antibodies are active in agglutination tests, whether performed by tube, plate, or microagglutination

methods. The majority of patients have detectable agglutinins at this stage. As the disease progresses, IgM levels decline, and the avidity and subclass distribution of IgG and IgA change. The result is reduced or undetectable agglutinin titers. However, the antibodies are detectable by alternative tests, including the complement fixation test, Coomb's antiglobulin test, and enzyme-linked immunosorbent assay. There is no clear cutoff value for a diagnostic titer. Rather, serology results must be interpreted in the context of exposure history and clinical presentation. In endemic areas or in settings of potential occupational exposure, agglutinin titers of 1:320–1:640 or higher are considered diagnostic; in nonendemic areas, a titer of ≥1:160 is considered significant. Repetition of tests after 2–4 weeks may demonstrate a rising titer.

In most centers, the standard agglutination test (SAT) is still the mainstay of serologic diagnosis, although some investigators rely on the rose bengal test, which has not been fully validated for human diagnostic use. Dipstick assays for anti-*Brucella* IgM are useful for the diagnosis of acute infection but are less sensitive for infection with symptoms of several months' duration. In an endemic setting, >90% of patients with acute bacteremia have SAT titers of at least 1:320. Other screening tests are used in some centers.

Antibody to the *Brucella* LPS O chain—the dominant antigen—is detected by all the conventional tests that employ smooth *B. abortus* cells as antigen. Since *B. abortus* cross-reacts with *B. melitensis* and *B. suis*, there is no advantage in replicating the tests with these antigens. Cross-reactions also occur with the O chains of some other gram-negative bacteria, including *Escherichia coli* O157, *Francisella tularensis*, *Salmonella enterica* group N, *Stenotrophomonas maltophilia*, and *Vibrio cholerae*. Cross-reactions do not occur with the cell-surface antigens of rough *Brucella* strains such as *B. canis* or *B. ovis*; serologic tests for these nomen species must employ an antigen prepared from either one. The live *B. abortus* vaccine strain RB51 does not elicit responses in standard serologic testing. Most protein antigens are shared by all *Brucella* strains, and some are also common to *Ochrobactrum* species. Immunoblotting against protein extracts has been advocated as a differential test, but no validated procedure is yet available.

TREATMENT Brucellosis

The broad aims of antimicrobial therapy are to treat and relieve the symptoms of current infection and to prevent relapse. Focal disease presentations may require specific intervention in addition to more prolonged and tailored antibiotic therapy. In addition, tuberculosis must always be excluded, or—to prevent the emergence of resistance—therapy must be tailored to specifically exclude drugs active against tuberculosis (e.g., rifampin used alone) or to include a full antituberculous regimen.

Early experience with streptomycin monotherapy showed that relapse was common; thus, dual therapy with tetracyclines became the norm. This is still the most effective combination, but alternatives may be used, with the options depending on local or national policy about the use of rifampin for the treatment of nonmycobacterial infection. For the several antimicrobial agents that are active in vivo, efficacy can usually be predicted by in vitro testing. However, numerous *Brucella* strains show in vitro sensitivity to a whole range of antimicrobials that are therapeutically ineffective, including assorted β-lactams. Moreover, the use of fluoroquinolones remains controversial despite the good in vitro activity and white-cell penetration of most agents of this class. Low intravacuolar pH is probably a factor in the poor performance of these drugs.

For adults with acute nonfocal brucellosis (duration, <1 month), a 6-week course of therapy incorporating at least two antimicrobial agents is required. Complex or focal disease necessitates ≥3 months of therapy. Adherence to the therapeutic regimen is very important, and poor adherence underlies almost all cases of apparent treatment failure; such failure is rarely due to the emergence of drug resistance, although increasing resistance to trimethoprim-sulfamethoxazole (TMP-SMX) has been reported at one center. There is good retrospective evidence that a 3-week course of two agents is as effective as a 6-week course for treatment and prevention of relapse in children, but this point has not yet been proven in prospective studies.

The gold standard for the treatment of brucellosis in adults is IM streptomycin (0.75–1 g daily for 14–21 days) together with doxycycline (100 mg twice daily for 6 weeks). In both clinical trials and observational studies, relapse follows such treatment in 5–10% of cases. The usual alternative regimen (and the current World Health Organization recommendation) is rifampin (600–900 mg/d) plus doxycycline (100 mg twice daily) for 6 weeks. The relapse/failure rate is ~10% in trial conditions but rises to >20% in many non-trial situations, possibly because doxycycline levels are reduced and clearance rates increased by concomitant rifampin administration. Patients who cannot tolerate or receive tetracyclines (children, pregnant women) can be given high-dose TMP-SMX instead (two or three standard-strength tablets twice daily for adults, depending on weight).

Increasing evidence supports the use of an aminoglycoside such as gentamicin (5–6 mg/kg per day for at least 2 weeks) instead of streptomycin. Shorter courses have been associated with high failure rates in adults. A 5- to 7-day course of therapy with gentamicin and a 3-week course of TMP-SMX may be adequate for children with uncomplicated disease, but prospective trials are still needed to support this recommendation. Early experience with fluoroquinolone monotherapy was disappointing, although it was suggested that ofloxacin or ciprofloxacin, given together with rifampin for 6 weeks, might be an acceptable alternative to the other 6-week regimens for adults. However, a meta-analysis

did not support the use of fluoroquinolones in first-line treatment regimens, and these drugs are not recommended by an expert consensus group (the Ioannina Group) except in the context of well-designed clinical trials. A triple-drug regimen—doxycycline and rifampin combined with an initial course of an aminoglycoside—was superior to double-drug regimens in a meta-analysis. The triple-drug regimen should be considered for all patients with complicated disease and for those for whom treatment adherence is likely to be a problem.

Significant neurologic disease due to *Brucella* species requires prolonged treatment (i.e., for 3–6 months), usually with ceftriaxone supplementation of a standard regimen. *Brucella* endocarditis is treated with at least three drugs (an aminoglycoside, a tetracycline, and rifampin), and many experts add ceftriaxone and/or a fluoroquinolone to reduce the need for valve replacement. Treatment is usually given for at least 6 months, and clinical endpoints for its discontinuation are often difficult to define. Surgery is still required for the majority of cases of infection of prosthetic heart valves and prosthetic joints. There is no evidence base to guide prophylaxis after exposure to *Brucella* organisms (e.g., in the laboratory), inadvertent immunization with live vaccine intended for use in animals, or exposure to deliberately released brucellae. Most authorities have recommended the administration of rifampin plus doxycycline for 3 weeks after a low-risk exposure (e.g., a nonspecific laboratory accident) and for 6 weeks after a major exposure to aerosol or injected material. However, such regimens are poorly tolerated, and doxycycline monotherapy of the same duration may be substituted. Rifampin should be omitted after exposure to vaccine strain RB51, which is resistant to rifampin but sensitive to doxycycline. After significant brucellosis exposure, expert consultation is advised for women who are (or may be) pregnant.

PROGNOSIS AND FOLLOW-UP

Relapse occurs in up to 30% of poorly compliant patients. Thus, patients should ideally be followed clinically for up to 2 years to detect relapse, which responds to a prolonged course of the same therapy used originally. The general well-being and the body weight of the patient are more useful guides than serology to lack of relapse. IgG antibody levels detected by the SAT and its variants can remain in the diagnostic range for >2 years after successful treatment. Complement fixation titers usually fall to normal within 1 year of cure. Immunity is not solid; patients can be reinfected after repeated exposures. Fewer than 1% of patients die of brucellosis. When the outcome is fatal, death is usually a consequence of cardiac involvement; more rarely, it results from severe neurologic disease. Despite the low mortality rate, recovery from brucellosis is slow, and the illness can cause prolonged inactivity, with domestic and economic consequences.

The existence of a prolonged chronic brucellosis state after successful treatment remains controversial. Evaluation of patients in whom this state is considered (often those with work-related exposure to brucellae) includes careful exclusion of malingering, nonspecific chronic fatigue syndromes, and other causes of excessive sweating, such as alcohol abuse and obesity. In the future, the availability of more sensitive assays to detect *Brucella* antigen or DNA may help to identify patients with ongoing infection.

PREVENTION

Vaccines based on live attenuated *Brucella* strains, such as *B. abortus* strain 19BA or 104M, have been used in some countries to protect high-risk populations but have displayed only short-term efficacy and high reactogenicity. Subunit vaccines have been developed but are of uncertain value and cannot be recommended at present. Research in this area has been stimulated by interest in biodefense (Chap. 7) and may eventually yield new products, some of which may be based on the live attenuated WR 201 variant of *B. melitensis* strain 16M. The mainstay of veterinary prevention is a national commitment to testing and slaughter of infected herds/flocks (with compensation for owners), control of animal movement, and active immunization of animals. These measures are usually sufficient to control human disease as well. In their absence, pasteurization of all milk products before consumption is sufficient to prevent nonoccupational animal-to-human transmission. All cases of brucellosis in animals and humans should be reported to the appropriate public health authorities.

CHAPTER 63

TULAREMIA

Richard F. Jacobs ■ Gordon E. Schutze

Tularemia is a zoonosis caused by *Francisella tularensis*. Humans of any age, sex, or race are universally susceptible to this systemic infection. Tularemia is primarily a disease of wild animals and persists in contaminated environments, ectoparasites, and animal carriers. Human infection is incidental and usually results from interaction with biting or blood-sucking insects, contact with wild or domestic animals, ingestion of contaminated water or food, or inhalation of infective aerosols. The illness is characterized by various clinical syndromes, the most common of which consists of an ulcerative lesion at the site of inoculation, with regional lymphadenopathy and lymphadenitis. Systemic manifestations, including pneumonia, typhoidal tularemia, meningitis, and fever without localizing findings, pose a greater diagnostic challenge.

ETIOLOGY AND EPIDEMIOLOGY

Tularemia is common in Arkansas, Oklahoma, Missouri, and South Dakota; these states account for more than half of all reported cases in the United States. Small outbreaks in higher-risk populations (e.g., professional landscapers cutting up brush, mowing, and using a leaf blower) have been reported from the island of Martha's Vineyard in Massachusetts. Although the irregular distribution of cases of tularemia makes worldwide estimates difficult, increasing numbers of cases have been reported from the Scandinavian countries, Eastern Europe, and Siberia.

With rare exceptions, tularemia is the only disease produced by *F. tularensis*—a small (0.2 μm by 0.2–0.7 μm), gram-negative, pleomorphic, nonmotile, non-spore-forming bacillus. Bipolar staining results in a coccoid appearance. The organism is a thinly encapsulated, nonpiliated strict aerobe that invades host cells. In nature, *F. tularensis* is a hardy organism that persists for weeks or months in mud, water, and decaying animal carcasses. Dozens of biting and blood-sucking insects, especially ticks and tabanid flies, serve as vectors. Ticks and wild rabbits are the source for most human cases in endemic areas of the southeastern and Rocky Mountain states. In Utah, Nevada, and California, tabanid flies are the most common vectors. Animal reservoirs include wild rabbits, squirrels, birds, sheep, beavers, muskrats, and domestic dogs and cats. Person-to-person transmission is rare or nonexistent. Tularemia is more common among men than among women.

The four subspecies of *F. tularensis* are *tularensis*, *holarctica*, *novicida*, and *mediasiatica*. The first three of these subspecies are found in North America; in fact, subspecies *tularensis* has been isolated only in North America, where it accounts for >70% of cases of tularemia and produces more serious human disease than other subspecies (although, with treatment, the associated fatality rate is <2%). The progression of illness depends on the infecting strain's virulence, the inoculum size, the portal of entry, and the host's immune status. *F. tularensis* is a class A bioterrorism agent (Chap. 7).

Ticks pass *F. tularensis* to their offspring transovarially. The organism is found in tick feces but not in large quantities in tick salivary glands. In the United States, the disease is carried by *Dermacentor andersoni* (Rocky Mountain wood tick), *D. variabilis* (American dog tick), *D. occidentalis* (Pacific Coast dog tick), and *Amblyomma americanum* (Lone Star tick). *F. tularensis* is transmitted frequently during blood meals taken by embedded ticks after hours of attachment. It is the taking of a blood meal through a fecally contaminated field that transmits the organism. Transmission by ticks and tabanid flies takes place mainly in the spring and summer. However, continued transmission in the winter by trapped or hunted animals has been documented.

PATHOGENESIS AND PATHOLOGY

The most common portal of entry for human infection is through skin or mucous membranes, either directly—through the bite of ticks, other arthropods, or other animals—or via inapparent abrasions. Inhalation or ingestion of *F. tularensis* also can result in infection. *F. tularensis* is extremely infectious: Although $>10^8$ organisms are usually required to produce infection via the oral route (oropharyngeal or gastrointestinal

tularemia), as few as 10 organisms can result in infection when injected into the skin (ulceroglandular/glandular tularemia) or inhaled (pulmonary tularemia). After inoculation into the skin, the organism multiplies locally; within 2–5 days (range, 1–10 days), it produces an erythematous, tender, or pruritic papule. The papule rapidly enlarges and forms an ulcer with a black base (chancriform lesion). The bacteria spread to regional lymph nodes, producing lymphadenopathy (buboes). All forms can lead to bacteremia with spread to distant organs, including the central nervous system.

Tularemia is characterized by mononuclear cell infiltration with pyogranulomatous pathology. The histopathologic findings can be quite similar to those in tuberculosis, although tularemia develops more rapidly. As a facultatively intracellular bacterium, *F. tularensis* can parasitize both phagocytic and nonphagocytic host cells and can survive intracellularly for prolonged periods. In the acute phase of infection, the primary organs affected (skin, lymph nodes, liver, and spleen) include areas of focal necrosis, which are initially surrounded by polymorphonuclear leukocytes (PMNs). Subsequently, granulomas form, with epithelioid cells, lymphocytes, and multinucleated giant cells surrounded by areas of necrosis. These areas may resemble caseation necrosis but later coalesce to form abscesses.

Conjunctival inoculation can result in infection of the eye, with regional lymph node enlargement (preauricular lymphadenopathy, Parinaud's complex). Aerosolization and inhalation or hematogenous spread of organisms can result in pneumonia. In the lung, an inflammatory reaction develops, including foci of alveolar necrosis and cell infiltration (initially polymorphonuclear and later mononuclear) with granulomas. Chest roentgenograms usually reveal bilateral patchy infiltrates rather than large areas of consolidation. Pleural effusions are common and may contain blood. Lymphadenopathy occurs in regions draining infected organs. Therefore, in pulmonary infection, mediastinal adenopathy may be evident, whereas patients with oropharyngeal tularemia develop cervical lymphadenopathy. In gastrointestinal or typhoidal tularemia, mesenteric lymphadenopathy may follow the ingestion of large numbers of organisms. (The term *typhoidal tularemia* may be used to describe severe bacteremic disease, irrespective of the mode of transmission or portal of entry.) Meningitis has been reported as a primary or secondary manifestation of bacteremia. Patients may also present with fever and no localizing signs.

IMMUNOLOGY

Although a complete and widely accepted understanding of the protective immune response to *F. tularensis* is lacking, significant advances in the study of natural and protective immunity have been made in recent years and may ultimately result in a vaccine candidate. The availability of attenuated *F. tularensis* strains developed through genetic manipulation is facilitating research that will expand our knowledge in this area.

A number of investigators have studied various models and proposed various hypotheses regarding the induction of protective immunity to *F. tularensis*. Although further research is needed, a synergy between humoral and cell-mediated immune (CMI) responses appears to be critical in inducing effective immune protection. Elucidation of the molecular mechanisms for the organism's evasion of the host response, pathogen-associated molecular patterns, and effective host immune protection has led to novel vaccination strategies tested in animal models. Antibodies to Fc receptors on antigen-presenting cells have been shown to be protective in animal models of pulmonary tularemia, resulting in both mucosal and CMI responses. This enhanced understanding of mucosal and serum antibodies in combination with a targeted CMI response holds great promise for future vaccine development.

CLINICAL MANIFESTATIONS

Tularemia often starts with a sudden onset of fever, chills, headache, and generalized myalgias and arthralgias **(Table 63-1)**. This onset takes place when the organism penetrates the skin, is ingested, or is inhaled. An incubation period of 2–10 days is followed by the formation of an ulcer at the site of penetration, with local inflammation. The ulcer may persist for several months as organisms are transported via the lymphatics to the regional lymph nodes. These nodes enlarge and may become necrotic and suppurative. If the organism enters the bloodstream, widespread dissemination can result.

In the United States, most patients with tularemia (75–85%) acquire the infection by inoculation of the skin. In adults, the most common localized form is inguinal/femoral lymphadenopathy; in children, it is cervical lymphadenopathy. About 20% of patients develop a generalized maculopapular rash, which occasionally becomes pustular. Erythema nodosum occurs infrequently. The clinical manifestations of tularemia have been divided into various syndromes, which are listed in **Table 63-2**.

TABLE 63-1

CLINICAL PRESENTATION OF TULAREMIA

	RATE OF OCCURRENCE, %	
SIGN OR SYMPTOM	CHILDREN	ADULTS
Lymphadenopathy	96	65
Fever (≥38.3°C or ≥101°F)	87	21
Ulcer/eschar/papule	45	51
Myalgias/arthralgias	39	2
Headache	9	5
Cough	9	5
Pharyngitis	43	—
Diarrhea	43	—

Source: Adapted from RF Jacobs, JP Narain: Pediatrics 76:818, 1985; with permission.

TABLE 63-2

CLINICAL SYNDROMES OF TULAREMIA

	RATE OF OCCURRENCE, %	
SYNDROME	**CHILDREN**	**ADULTS**
Ulceroglandular	45	51
Glandular	25	12
Pulmonary (pneumonia)	14	18
Oropharyngeal	4	—
Oculoglandular	2	—
Typhoidal	2	12
Unclassified	6	11

Source: Adapted from RF Jacobs, JP Narain: Pediatrics 76:818, 1985; with permission.

Ulceroglandular/glandular tularemia

These two forms of tularemia account for ~75–85% of cases. The predominant form in children involves cervical or posterior auricular lymphadenopathy and is usually related to tick bites on the head and neck. In adults, the most common form is inguinal/femoral lymphadenopathy resulting from insect and tick exposures on the lower limbs. In cases related to wild game, the usual portal of entry for *F. tularensis* is either an injury sustained while skinning or cleaning an animal carcass or a bite (usually on the hand). Epitrochlear lymphadenopathy/lymphadenitis is common in patients with bite-related injuries.

In ulceroglandular tularemia, the ulcer is erythematous, indurated, and nonhealing, with a punched-out appearance that lasts 1–3 weeks. The papule may begin as an erythematous lesion that is tender or pruritic; it evolves over several days into an ulcer with sharply demarcated edges and a yellow exudate. The ulcer gradually develops a black base, and simultaneously the regional lymph nodes become tender and severely enlarged **(Fig. 63-1)**. The affected lymph nodes may become fluctuant and drain spontaneously, but the condition usually resolves with effective treatment.

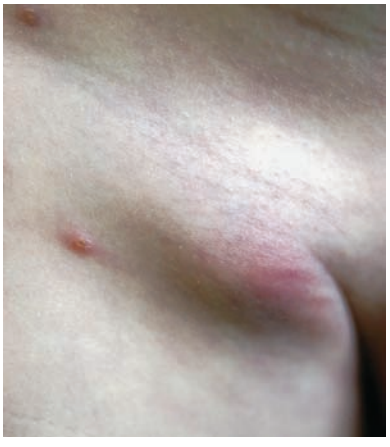


FIGURE 63-1

An 8-year-old boy with inguinal lymphadenitis and associated tick-bite site characteristic of ulceroglandular tularemia.

Late suppuration of lymph nodes has been described in up to 25% of patients with ulceroglandular/glandular tularemia. Examination of material taken from these late fluctuant nodes after successful antimicrobial treatment reveals sterile necrotic tissue. In 5–10% of patients, the skin lesion may be inapparent, with lymphadenopathy plus systemic signs and symptoms the only physical findings (*glandular tularemia*). Conversely, a tick or deerfly bite on the trunk may result in an ulcer without evident lymphadenopathy.

Oculoglandular tularemia

In ~1% of patients, the portal of entry for *F. tularensis* is the conjunctiva, which the organism usually reaches through contact with contaminated fingers. The inflamed conjunctiva is painful, with numerous yellowish nodules and pinpoint ulcers. Purulent conjunctivitis with regional lymphadenopathy (preauricular, submandibular, or cervical) is evident. Because of debilitating pain, the patient may seek medical attention before regional lymphadenopathy develops. Painful preauricular lymphadenopathy is unique to tularemia and distinguishes it from tuberculosis, sporotrichosis, and syphilis. Corneal perforation may occur.

Oropharyngeal and gastrointestinal tularemia

Rarely, tularemia follows ingestion of contaminated undercooked meat, oral inoculation of *F. tularensis* from the hands in association with the skinning and cleaning of animal carcasses, or consumption of contaminated food or water. Oral inoculation may result in acute, exudative, or membranous pharyngitis associated with cervical lymphadenopathy or in ulcerative intestinal lesions associated with mesenteric lymphadenopathy, diarrhea, abdominal pain, nausea, vomiting, and gastrointestinal bleeding. Infected tonsils become enlarged and develop a yellowish-white pseudomembrane, which can be confused with that of diphtheria. The clinical severity of gastrointestinal tularemia varies from mild, unexplained, persistent diarrhea with no other symptoms to a fulminant, fatal disease. In fatal cases, the extensive intestinal ulceration found at autopsy suggests an enormous inoculum.

Pulmonary tularemia

Pneumonia due to *F. tularensis* presents as variable parenchymal infiltrates that are unresponsive to treatment with β-lactam antibiotics. Tularemia must be considered in the differential diagnosis of atypical pneumonia in a patient with a history of travel to an endemic area. The disease can result from inhalation of an infectious aerosol or can spread to the lungs and pleura via bacteremia. Inhalation-related pneumonia has been described in laboratory workers after exposure to contaminated materials and, if untreated, can be associated with a relatively high mortality rate. Exposure to *F. tularensis* in aerosols from live domestic animals or dead wildlife (including birds) has been reported to cause pneumonia. Hematogenous dissemination to the lungs occurs in 10–15%

of cases of ulceroglandular tularemia and in about half of cases of typhoidal tularemia. Previously, tularemia pneumonia was thought to be a disease of older patients, but as many as 10–15% of children with clinical manifestations of tularemia have parenchymal infiltrates detected by chest roentgenography. Patients with pneumonia usually have a nonproductive cough and may have dyspnea or pleuritic chest pain. Roentgenograms of the chest usually reveal bilateral patchy infiltrates (described as ovoid or lobar densities), lobar parenchymal infiltrates, and cavitary lesions. Pleural effusions may have a predominance of mononuclear leukocytes or PMNs and sometimes red blood cells. Empyema may develop. Blood cultures may be positive for *F. tularensis*.

Typhoidal tularemia

The typhoidal presentation is now considered rare in the United States. The source of infection in typhoidal tularemia is usually associated with pharyngeal and/or gastrointestinal inoculation or bacteremic disease. Fever usually develops without apparent skin lesions or lymphadenopathy. Some patients have cervical and mesenteric lymphadenopathy. In the absence of a history of possible contact with a vector, diagnosis can be extremely difficult. Blood cultures may be positive and patients may present with classic sepsis or septic shock in this acute systemic form of the infection. Typhoidal tularemia is usually associated with a huge inoculum or with a preexisting compromising condition. High continuous fevers, signs of sepsis, and severe headache are common. The patient may be delirious and may develop prostration and shock. If presumptive antibiotic therapy in culture-negative cases does not include an aminoglycoside, the estimated mortality rate is relatively high.

Other manifestations

F. tularensis infection has been associated with meningitis, pericarditis, hepatitis, peritonitis, endocarditis, osteomyelitis, and sepsis and septic shock with rhabdomyolysis and acute renal failure. In cases of tularemia meningitis, a mean white blood cell count of 1788/μL, a predominantly mononuclear cell response (70–100%), a depressed glucose level, an elevated protein concentration, and a negative Gram's stain are typically found on examination of cerebrospinal fluid.

DIFFERENTIAL DIAGNOSIS

When patients in endemic areas present with fever, chronic ulcerative skin lesions, and large tender lymph nodes (Fig. 63-1), a diagnosis of tularemia should be made presumptively, and confirmatory diagnostic testing and appropriate therapy should be undertaken. When the possibility of tularemia is considered in a nonendemic area, an attempt should be made to identify contact with a potential animal vector. The level of suspicion should be especially high in hunters, trappers, game wardens, professional landscapers, veterinarians, laboratory workers, and individuals exposed to an insect or another animal vector. However, up to 40% of patients with tularemia have no known history of epidemiologic contact with an animal vector.

The characteristic presentation of ulceroglandular tularemia does not pose a diagnostic problem, but a less classic progression of regional lymphadenopathy or glandular tularemia must be differentiated from other diseases **(Table 63-3)**. The skin lesion of tularemia may resemble those seen in various other diseases but is generally accompanied by more impressive regional

TABLE 63-3

TULAREMIA: DIFFERENTIAL DIAGNOSIS, BY CLINICAL DISEASE CATEGORY

GLANDULAR	OROPHARYNGEAL	TYPHOIDAL	PULMONARY
Pyogenic bacterial infection[a]	Group A streptococcal pharyngitis	Typhoid fever	*Mycoplasma pneumoniae* pneumonia
Nontuberculous mycobacterial infection	*Arcanobacterium haemolyticum* pharyngitis	Other *Salmonella* bacteremias	*Chlamydia pneumoniae* pneumonia
Sporotrichosis	Diphtheria	Rocky Mountain spotted fever	Psittacosis
Tuberculosis	Infectious mononucleosis	Human monocytotropic ehrlichiosis	*Legionella pneumophila* pneumonia
Syphilis	Various viral infections[b]	Human granulocytotropic anaplasmosis	Q fever
Anthrax		Infectious mononucleosis	Histoplasmosis
Rat-bite fever		Brucellosis	Blastomycosis
Scrub typhus		Toxoplasmosis	Coccidioidomycosis
Plague		Tuberculosis	Various viral infections[d]
Lymphogranuloma venereum		Sarcoidosis	
Cat-scratch disease		Malignancy[c]	

[a] *Staphylococcus aureus, Streptococcus pyogenes*.
[b] Adenovirus, enteroviruses, parainfluenza virus, influenza viruses A and B, respiratory syncytial virus.
[c] Hematologic and reticuloendothelial malignancies.
[d] Influenza viruses A and B, parainfluenza virus, respiratory syncytial virus, adenovirus, enteroviruses, hantavirus.

lymphadenopathy. In children, the differentiation of tularemia from cat-scratch disease is made more difficult by the chronic papulovesicular lesion associated with *Bartonella henselae* infection (Chap. 65). Oropharyngeal tularemia can resemble and must be differentiated from pharyngitis due to other bacteria or viruses. Pulmonary tularemia may resemble any atypical pneumonia. Typhoidal tularemia and tularemia meningitis may resemble a variety of other infections.

LABORATORY DIAGNOSIS

The diagnosis of tularemia is most frequently confirmed by agglutination testing. Microagglutination and tube agglutination are the techniques most commonly used to detect antibody to *F. tularensis*. In the standard tube agglutination test, a single titer of ≥1:160 is interpreted as a presumptive positive result. A fourfold increase in titer between paired serum samples collected 2–3 weeks apart is considered diagnostic. False-negative serologic responses are obtained early in infection; up to 30% of patients infected for 3 weeks have sera that test negative. Late in infection, titers into the thousands are common, and titers of 1:20–1:80 may persist for years. Enzyme-linked immunosorbent assays have proved useful for the detection of both antibodies and antigens.

Culture and isolation of *F. tularensis* are difficult. In one study, the organism was isolated in only 10% of more than 1000 human cases, 84% of which were confirmed by serology. The medium of choice is cysteine-glucose-blood agar. *F. tularensis* can be isolated directly from infected ulcer scrapings, lymph-node biopsy specimens, gastric washings, sputum, and blood cultures. Colonies are blue-gray, round, smooth, and slightly mucoid. On media containing blood, a small zone of α hemolysis usually surrounds the colony. Slide agglutination tests or direct fluorescent antibody tests with commercially available antisera can be applied directly to culture suspensions for identification. Most clinical laboratories will not attempt to culture *F. tularensis* because of the infectivity of the organism from the culture media and the consequent risk of a laboratory-acquired infection. Although tularemia is not spread from person to person, the organism can be inhaled from culture plates and infect unsuspecting laboratory workers. In most clinical laboratories, biosafety level 2 practices are recommended to handle clinical specimens thought to contain *F. tularensis*; however, biosafety level 3 conditions are required for procedures that produce aerosols or droplets during manipulation of cultures containing or possibly containing this organism.

A variety of polymerase chain reaction (PCR) methods have been used to detect *F. tularensis* DNA in many clinical specimens but mostly in ulceroglandular disease. The majority of these methods target the genes encoding the outer-membrane proteins (e.g., *fopA* or *tul4*). A 16S rDNA sequence identification PCR may be helpful when the patient's clinical information does not lead the clinician to suspect a diagnosis of tularemia.

TREATMENT Tularemia

Only aminoglycosides, tetracyclines, chloramphenicol, and rifampin are currently approved by the U.S. Food and Drug Administration for the treatment of tularemia. Gentamicin is considered the drug of choice for both adults and children. The dosage for adults is 5 mg/kg daily in two divided doses. The dosage for children is 2.5 mg/kg three times daily or 5 mg/kg twice daily. Gentamicin therapy is typically continued for 7–10 days; however, in mild to moderate cases of tularemia in which the patient becomes afebrile within the first 48–72 h of gentamicin treatment, a 5- to 7-day course has been successful.

If available, streptomycin given intramuscularly is also effective. The dosage for adults is 2 g/d in two divided doses. For children, the dosage is 30 mg/kg daily in two divided doses (maximal daily dose, 2 g). After a clinical response is demonstrated at 3–5 days, the dosage for children can be reduced to 10–15 mg/kg daily in two divided doses. The total duration of streptomycin therapy in both adults and children is usually 10 days. Unlike streptomycin and gentamicin, tobramycin is ineffective in the treatment of tularemia and should not be used.

Since doxycycline is bacteriostatic against *F. tularensis*, there is a risk of relapse if the patient is not treated for a long enough period. Therefore, if doxycycline is used, it should be given for at least 14 days. The lack of availability of chloramphenicol limits the utility of this agent as a viable treatment option. Fluoroquinolones—specifically, ciprofloxacin and levofloxacin—have been used with good outcomes to treat infections caused by subspecies *holarctica*, which is most often found in Europe. The lack of data on the efficacy of these agents against subspecies *tularensis* limits their use in North America at this time.

F. tularensis cannot be subjected to standardized antimicrobial susceptibility testing because the organism will not grow on the media used. A wide variety of antibiotics, including all β-lactam antibiotics and the newer cephalosporins, are ineffective for the treatment of tularemia. Several studies indicated that third-generation cephalosporins were active against *F. tularensis* in vitro, but clinical case reports suggested a nearly universal failure rate of ceftriaxone in pediatric patients with tularemia. Although in vitro data indicate that imipenem may be active, therapy with imipenem, sulfanilamides, and macrolides is not presently recommended because of the lack of relevant clinical data.

Virtually all strains of *F. tularensis* are susceptible to streptomycin and gentamicin. In successfully treated patients, defervescence usually occurs within 2 days, but skin lesions and lymph nodes may take 1–2 weeks to heal. When therapy is not initiated within the first several days of illness, defervescence may be delayed. Relapses are uncommon with streptomycin or gentamicin therapy. Late lymph-node suppuration, however, occurs in ~40% of children, regardless of the treatment received.

These nodes have typically been found to contain sterile necrotic tissue without evidence of active infection. Patients with fluctuant nodes should receive several days of antibiotic therapy before drainage to minimize the risk to hospital personnel.

PROGNOSIS

If tularemia goes untreated, symptoms usually last 1–4 weeks but may continue for months. The mortality rate from severe untreated infection (including all cases of untreated pulmonary and typhoidal tularemia) can be as high as 30%. However, the overall mortality rate for untreated tularemia is <8%. With appropriate treatment, the mortality rate is <1%. Poor outcomes are often associated with long delays in diagnosis and treatment. Lifelong immunity usually follows tularemia.

PREVENTION

The prevention of tularemia is based on avoidance of exposure to biting and blood-sucking insects, especially ticks and deerflies. A wide range of approaches to vaccine development are being evaluated, but no vaccine against tularemia is yet licensed. Prophylaxis of tularemia has not proved effective in patients with embedded ticks or insect bites. However, in patients who are known to have been exposed to large quantities of organisms (e.g., in the laboratory) and who have incubating infection with *F. tularensis*, early treatment can prevent the development of significant clinical disease.

CHAPTER 64

PLAGUE AND OTHER *YERSINIA* INFECTIONS

Michael B. Prentice

PLAGUE

Plague is a systemic zoonosis caused by *Yersinia pestis*. It predominantly affects small rodents in rural areas of Africa, Asia, and the Americas and is usually transmitted to humans by an arthropod vector (the flea). Less often, infection follows contact with animal tissues or respiratory droplets. Plague is an acute febrile illness that is treatable with antimicrobial agents, but mortality rates among untreated patients are high. Patients can present with the bubonic, septicemic, or pneumonic form of the disease. Although there is concern among the general public about epidemic spread of plague by the respiratory route, this is not the usual route of plague transmission, and established infection-control measures for respiratory plague exist. However, the fatalities associated with plague and the capacity for infection via the respiratory tract mean that *Y. pestis* fits the profile of a potential agent of bioterrorism. Consequently, measures have been taken to restrict access to the organism, including legislation affecting diagnostic and research procedures in some countries (e.g., the United States).

ETIOLOGY

The genus *Yersinia* comprises gram-negative bacteria of the family Enterobacteriaceae (gamma proteobacteria). Overwhelming taxonomic evidence showing *Y. pestis* strains as a clonal group within *Y. pseudotuberculosis* suggests recent evolution from the latter organism—an enteric pathogen of mammals that is spread by the fecal-oral route and thus has a phenotype distinctly different from that of *Y. pestis*. When grown in vivo or at 37°C, *Y. pestis* forms an amorphous capsule made from a plasmid-specified fimbrial protein, Caf or fraction 1 (F1) antigen, which is an immunodiagnostic marker of infection.

EPIDEMIOLOGY

Human plague generally follows an outbreak in a host rodent population (epizootic). Mass deaths among the rodent primary hosts lead to a search by fleas for new hosts, with consequent incidental infection of other mammals. The precipitating cause for an epizootic may ultimately be related to climate or other

environmental factors. The reservoir for *Y. pestis* causing enzootic plague in natural endemic foci between epizootics (i.e., when the organism may be difficult to detect in rodents or fleas) is a topic of ongoing research and may not be the same in all regions. The enzootic/epizootic pattern may be the result of complex dynamic interactions of host rodents that have different plague susceptibilities and different flea vectors; alternatively, an environmental reservoir may be important.

In general, the enzootic areas for plague are lightly populated regions of Asia, Africa, and the Americas **(Fig. 64-1)**. Between 1989 and 2003, 38,359 cases of plague were reported to the World Health Organization (WHO) under the International Health Regulations then in force, which required national authorities to report all cases of plague in their jurisdiction and according to which plague was one of just three infectious diseases to be so reported. More than 80% of these cases were in Africa, and the percentage of all cases in Africa increased over this period; the majority of cases were reported from East Africa and the island of Madagascar. In 2007, the second edition of the International Health Regulations came into force, widening reporting to any disease event that could have a serious public health impact or could rapidly spread internationally. For plague, this requirement entails specific reporting of pneumonic plague or any suspected case of plague in an area not known to be endemic for plague. Recent outbreaks of pneumonic plague have been recorded in Uganda, the Democratic Republic of the Congo, and China.

Plague was introduced into North America via the port of San Francisco in 1900 as part of the Third Pandemic, which spread around the world from Hong Kong. The disease is presently enzootic on the western side of the continent from southwestern Canada to Mexico. Most human cases in the United States occur in two regions: "Four Corners" (the junction point of New Mexico, Arizona, Colorado, and Utah), especially northern New Mexico, northern Arizona, and southern Colorado; and further west in California, southern Oregon, and western Nevada *(http://www.cdc.gov/ncidod/dvbid/plague/epi.htm)*. From 1990 to 2005, 107 cases of plague were reported in the United States, with a median of seven cases per year. Most cases occurred from May to October—the time of year when people are outdoors and rodents and their fleas are most plentiful. Infection is most often acquired by fleabite in peridomestic environments. Infection can also occur through the handling of living or dead small mammals (e.g., rabbits, hares, and prairie dogs) or wild carnivores (e.g., wildcats, coyotes, or mountain lions). Dogs and cats may bring plague-infected fleas into the home, and infected cats may transmit plague directly to humans by the respiratory route. The last recorded case of person-to-person transmission in the United States occurred in 1925.

Plague most often develops in areas with poor sanitary conditions and infestations of rats—in particular, the widely distributed roof rat *Rattus rattus* and the brown rat *R. norvegicus* (which serves as a laboratory model of plague). Rat control in warehouses and shipping facilities has been recognized as important in preventing the spread of plague since the early twentieth century and features in the current WHO International Health Regulations. Urban rodents acquire infection from wild rodents, and the proximity of the former to humans increases the risk of transmission. The oriental rat flea *Xenopsylla cheopis* is the most efficient vector for transmission of plague among rats and onward to humans in Asia, Africa, and South America.

Worldwide, bubonic plague is the predominant form reported (80–95% of suspected cases), with mortality rates of 10–20%. The mortality rate is higher (22%) in the small proportion of patients (10–20%) with primary septicemic plague (i.e., systemic *Y. pestis* sepsis with no bubo;

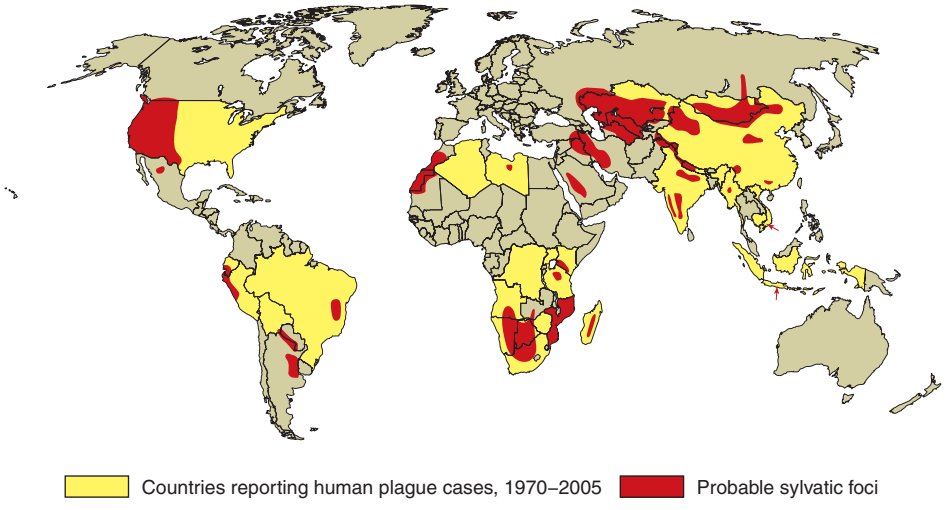


FIGURE 64-1
Approximate global distribution of *Yersinia pestis*. (*Compiled from WHO, CDC, and country sources. Reprinted with permission from DT Dennis, GL Campbell: Plague and other Yersinia infections, in Harrison's Principles of Internal Medicine, 17th ed, AS Fauci et al [eds]. New York, McGraw-Hill, Chap. 152, 2008.*)

see "Clinical Manifestations," below) and is highest with primary pulmonary plague; in this, the least common of the main plague presentations, mortality rate approaches 100% without antimicrobial treatment and is >50% even with such treatment. Rare outbreaks of pharyngeal plague following consumption of raw or undercooked camel or goat meat have been reported.

A total of 81 (76%) of the 107 plague cases reported in the United States from 1990 to 2005 were primary bubonic disease, 19 (18%) were primary septicemic disease, and 5 (5%) were primary pneumonic disease; 2 cases (2%) were not classified. Eleven cases (10%) were fatal.

PATHOGENESIS

As mentioned earlier, genetic evidence suggests that *Y. pestis* is a clone derived from the enteric pathogen *Y. pseudotuberculosis* in the recent evolutionary past (9000–40,000 years ago). The change from infection by the fecal-oral route to a two-stage life cycle, with alternate parasitization of arthropod and mammalian hosts, followed the acquisition of two plasmids—pFra and pPst—in conjunction with some adaptation of preexisting properties of the *Y. pseudotuberculosis* ancestor, including the presence of a third plasmid, pYV. In the arthropod-parasitizing portion of its life cycle, *Y. pestis* multiplies and forms biofilm-embedded aggregates in the flea midgut after ingestion of a blood meal containing bacteria. In some fleas, biofilm-embedded bacteria eventually fill the proventriculus (a valve connecting the esophagus to the midgut) and block normal blood feeding. "Blocked" fleas die within a few days but in the interim make persistent efforts to feed, regurgitating esophageal contents and inoculating *Y. pestis* into each bite site. The ability of *Y. pestis* to colonize and multiply in the flea requires phospholipase D encoded by the *ymt* gene on the pFra plasmid, and biofilm synthesis requires the chromosomal *hms* locus shared with *Y. pseudotuberculosis*. Blockage takes days or weeks to come about after initial infection of the flea and is followed by the flea's death. Historically, blockage was thought to be required for efficient transmission, but many flea vectors (including *X. cheopis*) are, in fact, able to transmit plague in an early unblocked state or without blockage.

Y. pestis disseminates from the site of inoculation in the mammalian host in a process initially dependent on plasminogen activator Pla, which is encoded by the small pPst plasmid. This surface protease activates mammalian plasminogen, degrades complement, and adheres to the extracellular matrix component laminin. Pla is essential for the high-level virulence of *Y. pestis* in mice given an inoculum by subcutaneous or intradermal injection (laboratory proxies for fleabites) and for the development of primary pneumonic plague. When actual fleabite inoculation is used in mouse models, the fimbrial capsule-forming protein (Ca1 or fraction 1; F1 antigen) encoded on pFra increases the efficiency of transmission, and plasminogen activator is required for the formation of buboes. Because the antiphagocytic systems in *Y. pestis* are not fully operational at the time of inoculation into the mammalian host, the organism is taken up by macrophages from the inoculation site and transported to regional lymph nodes. After intracellular replication, *Y. pestis* switches to extracellular replication with full expression of its antiphagocytic systems: the type III secretion machines and their effectors encoded by pYV as well as the F1 capsule. Overproduction of the type III secretion substrate and translocation protein LcrV exerts an anti-inflammatory effect, reducing host immune responses. Likewise, *Y. pestis* lipopolysaccharide is modified to minimize stimulation of host Toll-like receptor 4, thereby reducing protective host inflammatory responses during peripheral infection and prolonging host survival with high-grade bacteremia—an effect that probably enhances the pathogen's subsequent transmission by fleabite.

Replication of *Y. pestis* in a regional lymph node results in the local swelling of the lymph node and periglandular region known as a *bubo*. On histology, the node is found to be hemorrhagic or necrotic, with thrombosed blood vessels, and the lymphoid cells and normal architecture are replaced by large numbers of bacteria and fibrin. Periglandular tissues are inflamed and also contain large numbers of bacteria in a serosanguineous, gelatinous exudate.

Continued spread through the lymphatic vessels to contiguous lymph nodes produces second-order primary buboes. Infection is initially contained in the infected regional lymph nodes, although transient bacteremia can be detected. As the infection progresses, spread via efferent lymphatics to the thoracic duct produces high-grade bacteremia. Hematogenous spread to the spleen, liver, and secondary buboes follows, with subsequent uncontrolled septicemia, endotoxic shock, and disseminated intravascular coagulation leading to death. In some patients, this septicemic phase occurs without obvious prior bubo development or lung disease (septicemic plague). Hematogenous spread to the lungs results in secondary plague pneumonia, with bacteria initially more prominent in the interstitium than in the air spaces (the reverse being the case in primary plague pneumonia). Hematogenous spread to other organs, including the meninges, can occur.

CLINICAL MANIFESTATIONS

Bubonic plague

After an incubation period of 2–6 days, the onset of bubonic plague is sudden and is characterized by fever (>38°C), malaise, myalgia, dizziness, and increasing pain due to progressive lymphadenitis in the regional lymph nodes near the fleabite or other inoculation site. Lymphadenitis manifests as a tense, tender swelling (bubo) that, when palpated, has a boggy consistency with an underlying hard core. Generally, there is one painful and erythematous bubo with surrounding periganglionic edema. The bubo is most commonly inguinal but can also be crural, axillary **(Fig. 64-2)**, cervical, or submaxillary,

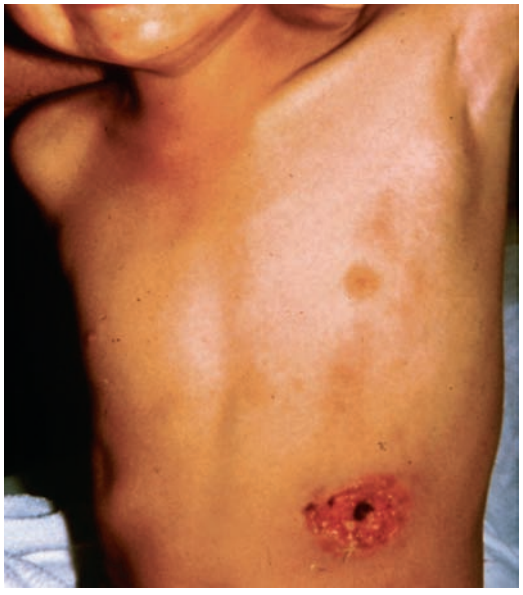


FIGURE 64-2
Plague patient in the southwestern United States with a left axillary bubo and an unusual plague ulcer and eschar at the site of the infective flea bite. (*Reprinted with permission from DT Dennis, GL Campbell: Plague and other Yersinia infections, in Harrison's Principles of Internal Medicine, 17th ed, AS Fauci et al [eds]. New York, McGraw-Hill, Chap. 152, 2008.*)

depending on the site of the bite. Abdominal pain from intraabdominal node involvement can occur without other visible signs. Children are most likely to present with cervical or axillary buboes.

The differential diagnosis includes acute focal lymphadenopathy of other etiologies, such as streptococcal or staphylococcal infection, tularemia, cat-scratch disease, tick typhus, infectious mononucleosis, or lymphatic filariasis. These infections do not progress as rapidly, are not as painful, and are associated with visible cellulitis or ascending lymphangitis—both of which are absent in plague.

Without treatment, *Y. pestis* dissemination occurs and causes serious illness, including pneumonia (secondary pneumonic plague) and meningitis. Secondary pneumonic plague can be the source of person-to-person transmission of respiratory infection by productive cough (droplet infection), with the consequent development of primary plague pneumonia. Appropriate treatment of bubonic plague results in fever resolution within 2–5 days, but buboes may remain enlarged for >1 week after initial treatment and can become fluctuant.

Primary septicemic plague

A minority (10–25%) of infections with *Y. pestis* present as gram-negative septicemia (hypotension, shock) without preceding lymphadenopathy. Septicemic plague occurs in all age groups, but persons older than age 40 years are at elevated risk. The term *septicemic plague* can be confusing since most patients with buboes have detectable bacteremia at some stage, with or without systemic signs of sepsis. In laboratory experiments, however, septicemic disease without histologic changes in lymph nodes is seen in a minority of mice infected via fleabites.

Pneumonic plague

Primary pneumonic plague results from inhalation of infectious bacteria in droplets expelled from another person or an animal with primary or secondary plague pneumonia. This syndrome has a short incubation period, averaging from a few hours to 2–3 days (range, 1–7 days), and is characterized by a sudden onset of fever, headache, myalgia, weakness, nausea, vomiting, and dizziness. Respiratory signs—cough, dyspnea, chest pain, and sputum production with hemoptysis—typically arise after 24 h. Progression of initial segmental pneumonitis to lobar pneumonia and then to bilateral lung involvement may occur **(Fig. 64-3)**. The possible release of aerosolized *Y. pestis* bacteria in a bioterrorist

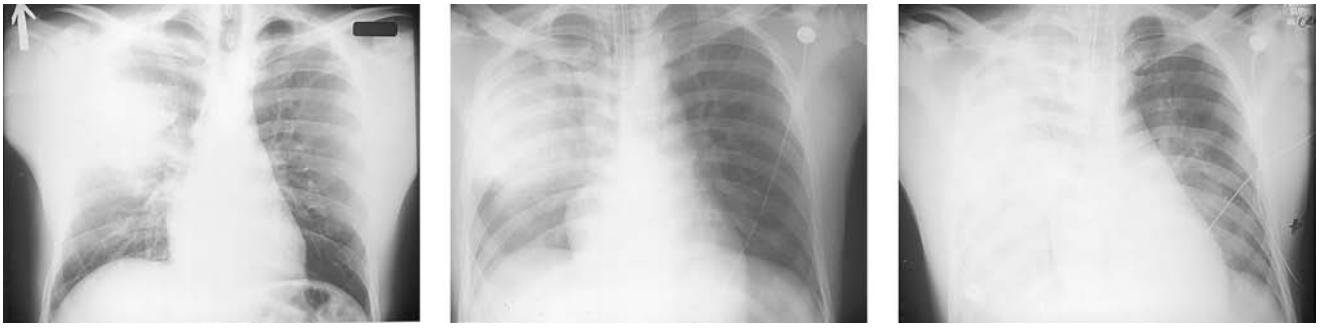


FIGURE 64-3
Sequential chest radiographs of a patient with fatal primary plague pneumonia. ***Left:*** Upright posteroanterior film taken at admission to hospital emergency department on third day of illness, showing segmental consolidation of right upper lobe. ***Center:*** Portable anteroposterior film taken 8 h after admission, showing extension of pneumonia to right middle and right lower lobes. ***Right:*** Portable anteroposterior film taken 13 h after admission (when patient had clinical adult respiratory distress syndrome), showing diffuse infiltration throughout right lung and patchy infiltration of left lower lung. A cavity later developed at the site of initial right-upper-lobe consolidation. (*Reprinted with permission from DT Dennis, GL Campbell: Plague and other Yersinia infections, in Harrison's Principles of Internal Medicine, 17th ed. AS Fauci et al [eds]. New York, McGraw-Hill, Chap. 152, 2008.*)

attack, manifesting as an outbreak of primary pneumonic plague in nonendemic regions or in an urban setting where plague is rarely seen, has been a source of public health concern. Secondary pneumonic plague is a consequence of bacteremia occurring in ~10–15% of patients with bubonic plague. Bilateral alveolar infiltrates are seen on chest x-ray, and diffuse interstitial pneumonitis with scanty sputum production is typical.

Meningitis

Meningeal plague is uncommon, occurring in ≥6% of plague cases reported in the United States. Presentation with headache and fever typically occurs >1 week after the onset of bubonic or septicemic plague and may be associated with suboptimal antimicrobial therapy (delayed therapy, penicillin administration, or low-dose tetracycline treatment) and cervical or axillary buboes.

Pharyngitis

Symptomatic plague pharyngitis can follow the consumption of contaminated meat from an animal dying of plague or contact with persons or animals with pneumonic plague. This condition can resemble tonsillitis, with peritonsillar abscess and cervical lymphadenopathy. Asymptomatic pharyngeal carriage of *Y. pestis* can also occur in close contacts of patients with pneumonic plague.

LABORATORY DIAGNOSIS

Because of the scarcity of laboratory facilities in regions where human *Y. pestis* infection is most common, and because of the potential significance of *Y. pestis* isolation in a nonendemic area or an area from which human plague has been absent for many years, the WHO recommends an initial presumptive diagnosis followed by reference laboratory confirmation **(Table 64-1)**. In the United States, comprehensive national diagnostic facilities for plague have been in place since a federal Laboratory Response Network (LRN; *www.bt.cdc.gov/lrn/*) was set up in 1999 to detect possible use of biological terrorism agents, including *Y. pestis*. Routine diagnostic clinical microbiology laboratories that are included in this network as sentinel-level laboratories use joint protocols from the Centers for Disease Control and Prevention (CDC) and the American Society for Microbiology to identify suspected *Y. pestis* isolates and to refer these specimens to LRN reference laboratories for confirmatory tests. *Y. pestis* is designated a "select agent" under the Public Health Security and Bioterrorism Preparedness and Response Act of 2002 (Chap. 7); the provisions of this act and of the Patriot Act of 2001 apply to all U.S. laboratories and individuals working with *Y. pestis*. Details of the applicable regulations are available from the CDC.

Yersinia species are gram-negative coccobacilli (short rods with rounded ends) 1–3 μm in length and

TABLE 64-1

WORLD HEALTH ORGANIZATION CASE DEFINITIONS OF PLAGUE

Suspected case	Compatible clinical presentation ***and*** Consistent epidemiologic features, such as exposure to infected animals or humans and/or evidence of fleabites and/or residence in or travel to a known endemic focus within the previous 10 days
Presumptive case	Meeting the definition of a suspected case ***plus***: **Putative new or reemerging focus**: ≥2 of the following tests positive • Microscopy: gram-negative coccobacilli in material from bubo, blood, or sputum; bipolar appearance on Wayson or Wright-Giemsa staining • F1 antigen detected in bubo aspirate, blood, or sputum • A single anti-F1 serology without evidence of previous *Y. pestis* infection or immunization • PCR detection of *Y. pestis* in bubo aspirate, blood, or sputum **Known endemic focus**: ≥1 of the following tests positive • Microscopic evidence of gram-negative or bipolar (Wayson, Wright-Giemsa) coccobacilli from bubo, blood, or sputum sample • A single anti-F1 serology without evidence of previous plague infection or immunization • F1 antigen detected in bubo aspirate, blood, or sputum • PCR detection of *Y. pestis* in bubo aspirate, blood, or sputum
Confirmed case	Meeting the definition of a suspected case ***plus***: • Identification of an isolate from a clinical sample as *Y. pestis* (colonial morphology and 2 of the 4 following tests positive: phage lysis of cultures at 20–25°C and 37°C; F1 antigen detection; PCR; *Y. pestis* biochemical profile) *or* • A fourfold rise in anti-F1 antibody titer in paired serum samples *or* • In endemic areas when no other confirmatory test can be performed, a positive rapid diagnostic test with immunochromatography to detect F1 antigen

Source: Interregional Meeting on Prevention and Control of Plague, Antananarivo, Madagascar, 7–11 April 2006 (*www.who.int/entity/csr/resources/publications/WHO_HSE_EPR_2008_3w.pdf*).

0.5–0.8 μm in diameter. *Y. pestis* in particular appears bipolar (with a "closed safety pin" appearance) and pleomorphic when stained with a polychromatic stain (Wayson or Wright-Giemsa; **Fig. 64-4**). Its lack of motility distinguishes *Y. pestis* from other *Yersinia* species, which are motile at 25°C and nonmotile at 37°C. Transport medium (e.g., Cary-Blair medium) preserves the viability of *Y. pestis* if transport is delayed.

The appropriate specimens for diagnosis of bubonic, pneumonic, and septicemic plague are bubo aspirate, bronchoalveolar lavage fluid or sputum, and blood, respectively. Culture of postmortem organ biopsy samples can also be diagnostic. A bubo aspirate is obtained by injection of 1 mL of sterile normal saline into a bubo under local anesthetic and aspiration of a small amount of (usually blood-stained) fluid. Gram's staining of these specimens may reveal gram-negative rods, which are shown by Wayson or Wright-Giemsa staining to be bipolar. These bacteria may even be visible in direct blood smears in septicemic plague (Fig. 64-4); this finding indicates very high numbers of circulating bacteria and a poor prognosis.

Y. pestis grows on nutrient agar and other standard laboratory media but forms smaller colonies than do other Enterobacteriaceae. Specimens should be inoculated onto nutrient-rich media such as sheep blood agar (SBA), into nutrient-rich broth such as brain-heart infusion broth, and onto selective agar such as MacConkey or eosin methylene blue (EMB) agar. *Yersinia*-specific CIN (cefsulodin, triclosan [Irgasan], novobiocin) agar can be useful for culture of contaminated specimens, such as sputum. Blood should be cultured in a standard blood culture system. The optimal growth temperature is <37°C (25–29°C), with pinpoint colonies only on SBA at 24 h. Slower growth occurs at 37°C. *Y. pestis* is oxidase-negative, catalase-positive, urea-negative, indole-negative, and lactose-negative. Automated biochemical identification systems can misidentify *Y. pestis* as *Y. pseudotuberculosis* or other bacterial species.

Reference laboratory tests for definitive identification of isolates include direct immunofluorescence for F1 antigen; specific polymerase chain reaction (PCR) for targets such as F1 antigen, the pesticin gene, and the plasminogen activator gene; and specific bacteriophage lysis. PCR can also be applied to diagnostic specimens, as can direct immunofluorescence for F1 antigen (produced in large amounts by *Y. pestis*) by slide microscopy. An immunochromatographic test strip for F1 antigen detection by monoclonal antibodies in clinical specimens has been devised in Madagascar. This method is effective for both laboratory and near-patient use but is not yet commercially available. Several other rapid diagnostic kits for possible bioterrorism pathogens, including *Y. pestis*, have been described in recent years, but none is widely used for primary or reference laboratory identification.

In the absence of other positive laboratory diagnostic tests, a retrospective serologic diagnosis may be made on the basis of rising titers of hemagglutinating antibody to F1 antigen. Enzyme-linked immunosorbent assays (ELISAs) for IgG and IgM antibodies to F1 antigen are also available.

The white blood cell (WBC) count is generally raised (to 10,000–20,000/μL) in plague, with neutrophilic leukocytosis and a left shift (numerous immature neutrophils); in some cases, however, the WBC count is normal or leukopenia develops. WBC counts are occasionally very high, especially in children (>100,000/μL). Levels of fibrinogen degradation products are elevated in a majority of patients, but platelet counts are usually normal or low-normal. However, disseminated intravascular coagulation, with low platelet counts, prolonged prothrombin times, reduced fibrinogen, and elevated fibrinogen degradation product levels, occurs in a significant minority of patients.

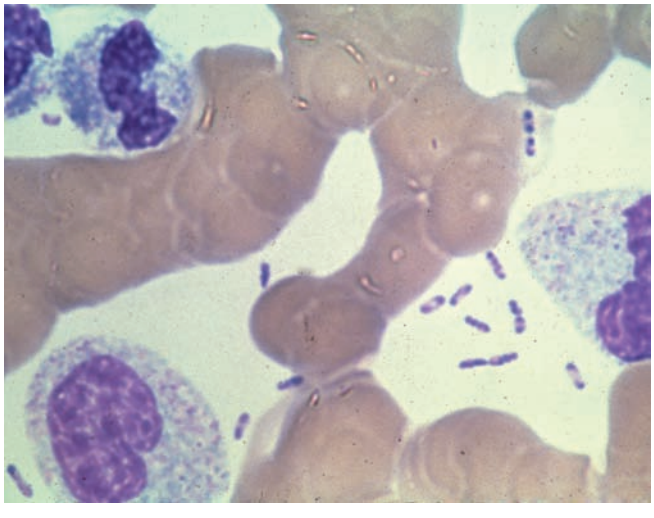


FIGURE 64-4
Peripheral blood smear from a patient with fatal plague septicemia and shock, showing characteristic bipolar-staining *Yersinia pestis* bacilli (Wright's stain, oil immersion). (*Reprinted with permission from DT Dennis, GL Campbell: Plague and other Yersinia infections, in Harrison's Principles of Internal Medicine, 17th ed, AS Fauci et al [eds]. New York, McGraw-Hill, Chap. 152, 2008.*)

TREATMENT **Plague**

Guidelines for the treatment of plague are given in Table 64-2. A 10-day course of antimicrobial therapy is recommended. Streptomycin has historically been the parenteral treatment of choice for plague and is approved for this indication by the U.S. Food and Drug Administration (FDA). Although not yet approved by the FDA for plague, gentamicin has proven safe and effective in clinical trials in Tanzania and Madagascar and in retrospective reviewed cases in the United States. In view of streptomycin's adverse-reaction profile and limited availability, some experts now recommend gentamicin over streptomycin. Likewise, while systemic chloramphenicol therapy is available in the resource-poor countries primarily affected by plague, it is less likely to be available or used in high-income countries because of its adverse-effect profile. Tetracyclines are

TABLE 64-2

GUIDELINES FOR THE TREATMENT OF PLAGUE

DRUG	DAILY DOSE	INTERVAL, h	ROUTE
Gentamicin			
Adult	5 mg/kg[a]	24	IM/IV
	3–5 mg/kg	8 (2-mg/kg loading dose followed by 1.7 mg/kg tid, then by 1 mg/kg tid as soon as clinically indicated)	IM/IV
Child	5 mg/kg[a]	24	IM/IV
	7.5 mg/kg	8 (2.5 mg/kg tid)	IM/IV
Streptomycin			
Adult	2 g	12	IM
Child	30 mg/kg	12	IM
Doxycycline			
Adult	200 mg	12 or 24	PO/IV
Child ≥8 years	4.4 mg/kg	12 or 24	PO/IV
Tetracycline			
Adult	2 g	6	PO/IV
Child ≥8 years	25–50 mg/kg	6	PO/IV
Chloramphenicol			
Adult	50 mg/kg	6	PO/IV
Child ≥1 year	50 mg/kg	6	PO/IV

[a]The dose must be adjusted in cases of reduced renal function. There are no published trial data for once-daily gentamicin as therapy for plague in adults or children, but this regimen is efficacious in sepsis of other gram-negative etiologies and has been successful in a recent outbreak of pneumonic plague in the Democratic Republic of the Congo. Neonates up to 1 week of age and premature infants should receive 2.5 mg/kg IV bid.

Source: TV Inglesby et al: JAMA 283:2281, 2000.

also effective and can be given by mouth but are not recommended for children under age 7 years because of tooth discoloration. Doxycycline is the tetracycline of choice; at an oral dosage of 100 mg twice daily, this drug was as effective as intramuscular gentamicin (2.5 mg/kg twice daily) in a trial in Tanzania.

Although *Y. pestis* is sensitive to β-lactam drugs in vitro and these drugs have been efficacious against plague in some animal models, the response to penicillins has been poor in some clinical cases; thus β-lactams and macrolides are not generally recommended as first-line therapy. Chloramphenicol, alone or in combination, is recommended for some focal complications of plague (e.g., meningitis, endophthalmitis, myocarditis) because of its tissue penetration properties. Fluoroquinolones, which have been effective in vitro and in animal models, are recommended in guidelines for possible bioterrorism-associated pneumonic plague and are increasingly used in therapy, although the only human efficacy data available so far are from a case report. Animal and in vitro studies suggest that fluoroquinolones at doses used in systemic gram-negative sepsis should be effective as therapy for plague: e.g., ciprofloxacin (400 mg twice daily IV, 500 mg twice daily by mouth), levofloxacin (500 mg/d IV or by mouth), ofloxacin (400 mg twice daily IV or by mouth), or moxifloxacin (400 mg/d IV or by mouth).

PREVENTION

In endemic areas, the control of plague in humans is based on reduction of the likelihood of being bitten by infected fleas or exposed to infected droplets from either humans or animals with plague pneumonia. In the United States, residence and outdoor activity in rural areas of western states where epizootics occur are the main risk factors for infection. To assess potential risks to humans in specific areas, surveillance for *Y. pestis* infection among animal plague hosts and vectors is carried out regularly as well as in response to observed animal die-offs. Personal protective measures include avoidance of areas where a plague epizootic has been identified and publicized (e.g., by warning signs or closure of campsites). Sick or dead animals should not be handled by the general public. Hunters and zoologists should wear gloves when handling wild animal carcasses in endemic areas. General measures to avoid rodent fleabite during outdoor activity are appropriate and include the use of insect repellant, insecticide, and protective clothing. General measures to reduce peridomestic and occupational human contact with rodents are advised and include rodent-proofing of buildings and food waste stores and removal of potential rodent habitats (e.g., woodpiles and junk heaps). Flea control by insecticide treatment of wild rodents is an effective means of minimizing human contact with plague if an epizootic is identified in an area close to human habitation. Any attempt to reduce rodent numbers must be preceded by flea suppression to reduce the migration of infected fleas to human hosts.

Patients in whom pneumonic plague is suspected should be managed in isolation, with droplet precautions observed until pneumonia is excluded or effective antimicrobial therapy has been given for 48 h. Review of the literature published before the advent of antimicrobial agents suggests that the main infective risk is posed by patients in the final stages of disease who are coughing up sputum with plentiful visible blood and/or pus. Cotton and gauze masks were protective in these circumstances. Current surgical masks capable of barrier protection against droplets, including large respiratory particles, are considered protective; a particulate respirator (e.g., N95 or greater) is not required.

Antimicrobial prophylaxis

Postexposure antimicrobial prophylaxis lasting 7 days is recommended following household, hospital, or other close contact with persons with untreated pneumonic plague.

(*Close contact* is defined as contact with a patient at <2 m.) Doxycycline is probably the first choice for prophylaxis **(Table 64-3)**.

Immunization

Studies with candidate plague vaccines in animal models show that neutralizing antibody provides protection against exposure but that cell-mediated immunity is critical for protection and clearance of *Y. pestis* from the host. A killed whole-cell vaccine used in humans required multiple doses, caused significant local and systemic reactions, and was not protective against pneumonic plague; this vaccine is not currently available in the United States. A live attenuated vaccine based on strain EV76 is still used in countries of the former Soviet Union but has significant side effects. Most research to date has focused on a subunit vaccine of recombinant F1 (rF1) and V (rV) proteins produced in *Escherichia coli*, combined either as a fusion protein or as a mixture, purified, and adsorbed to aluminum hydroxide for injection. This combination protects mice against both bubonic and pneumonic plague and has been evaluated in phase 2 clinical trials. Phase 3 trials are planned, but special ethical considerations with controlled clinical studies involving plague in humans make field efficacy studies unlikely. In the United States, the FDA is therefore prepared to assess this vaccine for human use under the Animal Rule, using efficacy data and other results from animal studies *(www.fda.gov/BiologicsBloodVaccines/ScienceResearch/BiologicsResearchAreas/ucm127288.htm)*. Future developments may include noninvasive vaccines (with intranasal administration or inhalation of dry powder incorporating these or other antigens) and mucosal delivery of microencapsulated proteins. Other antigens that could be added to this type of subunit vaccine are being investigated. Providing impetus for exploration of these antigens are (1) the recovery of F1-negative *Y. pestis* strains from natural sources and (2) the observation that F1 antigen is not required for virulence in primate models of pneumonic plague.

TABLE 64-3

GUIDELINES FOR PLAGUE PROPHYLAXIS

DRUG	DAILY DOSE	INTERVAL, h	ROUTE
Doxycycline			
Adult	200 mg	12 or 24	PO
Child ≥8 y	If weight is ≥45 kg, give adult dosage; if <45 kg, give 2.2 mg/kg PO bid (maximum, 200 mg/d)	12	PO
Tetracycline			
Adult	1–2 g	6 or 12	PO
Child ≥8 y	25–50 mg/kg	6 or 12	PO
Ciprofloxacin			
Adult	1 g	12	PO
Child	40 mg/kg	12	PO
Trimethoprim-sulfamethoxazole			
Adult	320 mg[a]	12	PO
Child ≥2 months	8 mg/kg[a]	12	PO

[a]Trimethoprim component.

Source: DT Dennis, GL Campbell: Plague and other *Yersinia* infections, in *Harrison's Principles of Internal Medicine,* 17th ed, AS Fauci et al (eds). New York, McGraw-Hill, Chap. 152, 2008.

YERSINIOSIS

Yersiniosis is a zoonotic infection with an enteropathogenic *Yersinia* species, usually *Y. enterocolitica* or *Y. pseudotuberculosis*. The usual hosts for these organisms are pigs and other wild and domestic animals; humans are usually infected by the oral route, and outbreaks from contaminated food occur. Yersiniosis is most common in childhood and in colder climates. Patients present with abdominal pain and sometimes with diarrhea (which may not occur in up to 50% of cases). *Y. enterocolitica* is more closely associated with terminal ileitis and *Y. pseudotuberculosis* with mesenteric adenitis, but both organisms may cause mesenteric adenitis and symptoms of abdominal pain and tenderness that result in pseudoappendicitis, with the surgical removal of a normal appendix. Diagnosis is based on culture of the organism or convalescent serology. *Y. pseudotuberculosis* and some rarer strains of *Y. enterocolitica* are especially likely to cause systemic infection, which is also more likely in patients with diabetes or iron overload. Systemic sepsis is treatable with antimicrobial agents, but postinfective arthropathy responds poorly to such therapy. Ten other *Yersinia* species are now recognized, but all lack the virulence plasmid pYV common to *Y. pestis*, *Y. pseudotuberculosis*, and *Y. enterocolitica* and are generally considered to be, at most, opportunistic pathogens of humans (*Y. aldovae*, *Y. bercovieri*, *Y. frederiksenii*, *Y. intermedia*, *Y. kristensenii*, *Y. massiliensis*, *Y. mollaretii*, *Y. rohdei*, *Y. similis*, and *Y. ruckeri*).

EPIDEMIOLOGY

Y. enterocolitica

Y. enterocolitica is found worldwide and has been isolated from a wide variety of wild and domestic animals and environmental samples, including samples of food and water. Strains are differentiated by combined biochemical reactions (biovar) and serogroup. Most clinical infections are associated with serogroups O:3, O:9, and O:5,27, with a declining number of O:8 infections in North America. Yersiniosis, mostly due to *Y. enterocolitica*, is the third commonest zoonosis reported in Europe; most reports come from northern Europe, especially Germany and Scandinavia. The incidence is highest among children; children

under the age of 4 years are more likely to present with diarrhea than are older children. Abdominal pain with mesenteric adenitis and terminal ileitis is more prominent among older children and adults. Septicemia is more likely in patients with preexisting conditions such as diabetes mellitus, liver disease, any condition involving iron overload (including thalassemia and hemochromatosis), advanced age, malignancy, or HIV/AIDS. As in enteritis of other bacterial etiologies, postinfective complications such as reactive arthritis occur mainly in individuals who are HLA-B27 positive. Erythema nodosum (Fig. 11-40) following *Yersinia* infection is not associated with HLA-B27 and is more common among women than among men.

Consumption or preparation of raw pork products (such as chitterlings) and some processed pork products is strongly linked with infection because a high percentage of pigs carry pathogenic *Y. enterocolitica* strains. Outbreaks of *Y. enterocolitica* infection have been associated with consumption of milk (pasteurized, unpasteurized, and chocolate-flavored) and various foods contaminated with springwater. Person-to-person transmission is suspected in a few cases (e.g., in nosocomial and familial outbreaks) but is much less likely with *Y. enterocolitica* than with other causes of gastrointestinal infection, such as *Salmonella*. A multivariate analysis indicates that contact with companion animals is a risk factor for *Y. enterocolitica* infection among children in Sweden, and low-level colonization of dogs and cats with *Y. enterocolitica* has been reported. Transfusion-associated septicemia due to *Y. enterocolitica*, while recognized as a rare but frequently fatal event for nearly 30 years, has been difficult to eradicate.

Y. pseudotuberculosis

Y. pseudotuberculosis is less frequently reported as a cause of human disease than *Y. enterocolitica*, and infection with *Y. pseudotuberculosis* is more likely to present as fever and abdominal pain due to mesenteric lymphadenitis. This organism is associated with wild mammals (rodents, rabbits, and deer), birds, and domestic pigs. Strains are differentiated by combined biochemical reactions (biovar) and serogroup. Although outbreaks are generally rare, several have recently occurred in Finland and have been associated with lettuce and raw carrots.

PATHOGENESIS

The usual route of infection is oral. Studies with both *Y. enterocolitica* and *Y. pseudotuberculosis* in animal models suggest that initial replication in the small intestine is followed by invasion of Peyer's patches of the distal ileum via M cells, with onward spread to mesenteric lymph nodes. The liver and spleen can also be involved after oral infection. The characteristic histologic appearance of enteropathogenic *Yersinia* after invasion of host tissues is as extracellular microabscesses surrounded by an epithelioid granulomatous lesion.

Experiments involving oral infection of mice with tagged *Y. enterocolitica* show that only a very small proportion of bacteria in the gut invade tissues. Individual bacterial clones from an orally inoculated pool give rise to each microabscess in a Peyer's patch, and the host restricts the invasion of previously infected Peyer's patches. A prior model positing progressive bacterial spread from Peyer's patches and mesenteric lymph nodes to the liver and spleen appears to be inaccurate: spread of individually tagged clones of *Y. pseudotuberculosis* to the liver and spleen of mice occurs independently of regional lymph node colonization and in mice lacking Peyer's patches.

Invasion requires the expression of several nonfimbrial adhesins, such as invasin (Inv) and—in *Y. pseudotuberculosis*—*Yersinia* adhesin A (YadA). Inv interacts directly with β1 integrins, which are expressed on the apical surfaces of M cells but not enterocytes. YadA of *Y. pseudotuberculosis* interacts with extracellular matrix proteins such as collagen and fibronectin to facilitate host cell integrin association and invasion. YadA of *Y. enterocolitica* lacks a crucial N-terminal region and binds collagen and laminin, but not fibronectin, and does not cause invasion. Inv is chromosomally encoded, whereas YadA is encoded on the virulence plasmid pYV. YadA helps to confer serum resistance by binding host complement regulators such as factor H and C4-binding protein. Another chromosomal gene, *ail* (attachment and invasion locus), encodes the extracellular protein Ail, which also confers serum resistance by binding these complement regulators.

By binding to host cell surfaces, YadA allows targeting of immune effector cells by the pYV plasmid–encoded type III secretion system (injectisome). As a consequence, the host's innate immune response is altered; toxins (*Yersinia* outer proteins, or Yops) are injected into host macrophages, neutrophils, and dendritic cells, affecting signal transduction pathways, resulting in reduced phagocytosis and inhibited production of reactive oxygen species by neutrophils, and triggering apoptosis of macrophages. Other factors functional in invasive disease include yersiniabactin (Ybt), a siderophore produced by some strains of *Y. pseudotuberculosis* and *Y. enterocolitica* as well as other Enterobacteriaceae. Yersiniabactin allows bacteria to access iron from saturated lactoferrin during infection and reduces production of reactive oxygen species by innate immune effector cells, thereby decreasing bacterial killing.

CLINICAL MANIFESTATIONS

Self-limiting diarrhea is the most common reported presentation in infection with pathogenic *Y. enterocolitica*, especially in children under the age of 4, who form the single largest group in most case series. Blood may be detected in diarrheal stool. Older children and adults are more likely than younger children to present with abdominal pain, which can be localized to the right iliac fossa—a situation that often leads to laparotomy

for presumed appendicitis (pseudoappendicitis). Appendectomy is not indicated for *Yersinia* infection causing pseudoappendicitis. Thickening of the terminal ileum and cecum is seen on endoscopy and ultrasound, with elevated round or oval lesions that may overlie Peyer's patches. Mesenteric lymph nodes are enlarged. Ulcerations of the mucosa are noted on endoscopy. Gastrointestinal complications include granulomatous appendicitis, a chronic inflammatory condition affecting the appendix that is responsible for ≥2% of cases of appendicitis; *Yersinia* is involved in a minority of cases. *Y. enterocolitica* infection can present as acute pharyngitis with or without other gastrointestinal symptoms. Fatal *Y. enterocolitica* pharyngitis has been recorded. Mycotic aneurysm can follow *Y. enterocolitica* bacteremia, as can focal infection (abscess) in many other sites and body compartments (liver, spleen, kidney, bone, meninges, endocardium).

In all age groups, *Y. pseudotuberculosis* is more likely to present as abdominal pain and fever than as diarrhea. A superantigenic toxin—*Y. pseudotuberculosis* mitogen (YPM)—is produced by strains seen in eastern Russia in association with Far Eastern scarlet-like fever, a childhood illness with desquamating rash, arthralgia, and toxic shock. A similar illness is recognized in Japan (Izumi fever) and Korea. Similarities have been noted with Kawasaki's disease, the idiopathic acute systematic vasculitis of childhood. There is an epidemiologic link between exposure of populations to superantigen-positive *Y. pseudotuberculosis* and an elevated incidence of Kawasaki's disease.

Y. enterocolitica or *Y. pseudotuberculosis* septicemia presents as a severe illness with fever and leukocytosis, often without localizing features, and is significantly associated with predisposing conditions such as diabetes mellitus, liver disease, and iron overload. Hemochromatosis combines several of these risk factors. Administration of iron chelators like desferrioxamine, which provide iron accessible to *Yersinia* (and have an inhibitory effect on neutrophil function), may result in *Yersinia* septicemia in patients with iron overload who presumably have an otherwise mild gastrointestinal infection. HIV/AIDS has been associated with *Y. pseudotuberculosis* septicemia. The unusual phenomenon of transfusion-associated septicemia is linked to the ability of *Y. enterocolitica* to multiply at refrigerator temperature (psychrotrophy). Typically, the transfused unit has been stored for >20 days, and it is believed that small numbers of yersiniae from an apparently healthy donor with subclinical bacteremia are amplified to very high numbers by growth inside the bag at ≥4°C, with consequent septic shock after transfusion. A method for preventing this very rare event (i.e., a range of 1 case in 500,000 to 1 case in several million transfused units in countries such as the United States and France) without unacceptable restriction in the blood supply has not yet been devised.

POSTINFECTIVE PHENOMENA

As in other invasive intestinal infections (salmonellosis, shigellosis), reactive arthritis (articular arthritis of multiple joints developing within 2–4 weeks of a preceding infection) occurs as a result of autoimmune activity initiated by the deposition of bacterial components (not viable bacteria) in joints in combination with the immune response to invading bacteria. The majority of individuals affected by reactive arthritis due to *Yersinia* are HLA-B27 positive. Myocarditis with electrocardiographic ST-segment abnormalities may occur with *Yersinia*-associated reactive arthritis. Most *Yersinia*-associated cases follow *Y. enterocolitica* infection (presumably because it is more common than infection with other species), but *Y. pseudotuberculosis*–associated reactive arthritis is also well documented in Finland, where sporadic and outbreak infections with *Y. pseudotuberculosis* are more common than in other countries. Of infected individuals identified in a recent *Y. pseudotuberculosis* serotype O:3 outbreak in Finland, 12% developed reactive arthritis affecting the small joints of the hands and feet, knees, ankles, and shoulders and lasting >6 months in most cases. Erythema nodosum (Fig. 11-40) occurs after *Yersinia* infection (more commonly in women) with no evidence of HLA-B27 linkage.

There is a long-standing association between antithyroid and anti-*Yersinia* antibodies. Antibody evidence of prior *Y. enterocolitica* infection in Graves' disease and increased levels of antithyroid antibody in patients with *Y. enterocolitica* antibodies were first noted in the 1970s. *Y. enterocolitica* contains a thyroid-stimulating hormone (TSH)–binding site that is recognized by anti-TSH antibodies from Graves' disease patients. Raised titers of antibodies to *Y. enterocolitica* whole cells and Yops have been found in some series of Graves' disease patients but not in others. One Danish study of twins found no evidence of an association between asymptomatic *Yersinia* infection (as evidenced by anti-Yop antibody titers) and antithyroid antibodies in euthyroid individuals, while another Danish study of twins with and without Graves' disease found that increased anti-Yop antibody titers were associated with Graves' disease. It remains unclear whether this cross-reactivity is significant in the etiology of Graves' disease.

LABORATORY DIAGNOSIS

Standard laboratory culture methods can be used to isolate enteropathogenic *Yersinia* species from sterile samples, including blood and cerebrospinal fluid. Culture on specific selective media (CIN agar), with or without preenrichment in broth or phosphate-buffered saline at either 4°C or 16°C, is the basis of most schema for isolation of yersiniae from stool or other nonsterile samples. Outside known high-incidence areas, specific culture may be carried out by laboratories only upon request. Virulence plasmid–negative strains of *Y. enterocolitica* can be isolated from cultures of stool

from asymptomatic individuals, especially after cold enrichment. These strains usually differ in biotype (typically biovar 1a) from virulence plasmid–possessing strains; although some display apparent pathogenicity in a mouse model, virulence plasmid–negative strains are not commonly accepted as human pathogens. Because of the frequency with which the virulence plasmid is lost on laboratory subculture, combined biochemical identification (with biotyping according to a standard schema) and serologic identification are usually required to interpret the significance of an isolate of *Y. enterocolitica* from a nonsterile site. Most pathogenic *Y. enterocolitica* strains currently isolated from humans are of serogroup O:3/biovar 4 or serogroup O:9/biovar 2; this pattern holds even in the United States, where serogroup O:8/biovar 1B strains were previously predominant. Many self-validated multiplex PCR screens for detection of *Y. enterocolitica* in clinical samples—and rather more for its detection in food—have been described, but none of these assays is widely used outside its originating laboratory. A standard for PCR detection in food samples is being prepared by the International Organization for Standardization.

Agglutinating or ELISA antibody titers to specific O-antigen types are used in the retrospective diagnosis of both *Y. enterocolitica* and *Y. pseudotuberculosis* infections. IgA and IgG antibodies persist in patients with reactive arthritis. Serologic cross-reactions between *Y. enterocolitica* serogroup O:9 and *Brucella* are due to the similarity of their lipopolysaccharide structures. Multiple assays are required to cover even the predominant serogroups (*Y. enterocolitica* O:3, O5,27, and O:9; *Y. pseudotuberculosis* O:1a, O:1b, and O:3), and these assays are generally available only in reference laboratories. ELISA and western blot tests for antibodies to Yops, which are expressed by all pathogenic strains of *Y. enterocolitica* and *Y. pseudotuberculosis*, are also available; most of the positivity in these assays probably relates to previous infection with *Y. enterocolitica*.

TREATMENT **Yersiniosis**

Most cases of diarrhea caused by enteropathogenic *Yersinia* are self-limiting. Data from clinical trials do not support antimicrobial treatment for adults or children with *Y. enterocolitica* diarrhea. Systemic infections with bacteremia or focal infections outside the gastrointestinal tract generally require antimicrobial therapy. Infants <3 months of age with documented *Y. enterocolitica* infection may require antimicrobial treatment because of the increased likelihood of bacteremia in this age group. *Y. enterocolitica* strains nearly always express β-lactamases. Because of the relative rarity of systemic *Y. enterocolitica* infection, there are no clinical trial data to guide antimicrobial choice or to suggest the optimal dose and duration of therapy. On the basis of retrospective case series and in vitro sensitivity data, fluoroquinolone therapy is effective for bacteremia in adults; for example, ciprofloxacin is given at a typical dose of 500 mg twice daily by mouth or 400 mg twice daily IV for at least 2 weeks (longer if positive blood cultures persist). A third-generation cephalosporin is an alternative—e.g., cefotaxime (typical dose, 6–8 g/d in 3 or 4 divided doses). In children, third-generation cephalosporins are effective; for example, cefotaxime is given to children ≥1 month of age at a typical dose of 75–100 mg/kg per day in 3 or 4 divided doses, with an increase to 150–200 mg/kg per day in severe cases (maximal daily dose, 8–10 g). Amoxicillin and amoxicillin/clavulanate have shown poor efficacy in case series. Trimethoprim-sulfamethoxazole, gentamicin, and imipenem are all active in vitro. *Y. pseudotuberculosis* strains do not express β-lactamase but are intrinsically resistant to polymyxin. Because human infection with *Y. pseudotuberculosis* is less common than that with *Y. enterocolitica*, less case information is available; however, studies in mice suggest that ampicillin is ineffective. Drugs similar to those used against *Y. enterocolitica* should be used. The best results have been obtained with a quinolone.

Some trials of treatment for reactive arthritis (with a large proportion of cases due to *Yersinia*) found that 3 months of oral ciprofloxacin therapy did not affect outcome. One trial in which the same therapy was given specifically for *Y. enterocolitica*–reactive arthritis found that, while outcome indeed was not affected, there was a trend toward faster remission of symptoms in the treated group. Follow-up 4–7 years after initial antibiotic treatment of reactive arthritis (predominantly following *Salmonella* and *Yersinia* infections) demonstrated apparent efficacy in the prevention of chronic arthritis in HLA-B27-positive individuals. A trial showing that azithromycin therapy did not affect outcome in reactive arthritis included cases believed to follow yersiniosis, although no breakdown of cases was provided. A Cochrane review evaluating the use of antibiotics for reactive arthritis is in progress.

PREVENTION AND CONTROL

Current control measures are similar to those used against other enteric pathogens like *Salmonella* and *Campylobacter*, which colonize the intestine of food animals. The focus is on safe handling and processing of food. No vaccine is effective in preventing intestinal colonization of food animals by enteropathogenic *Yersinia*. Consumption of food made from raw pork (which is popular in Germany and Belgium) should be discouraged at present because it is not possible to eliminate contamination with the enteropathogenic *Yersinia* strains found worldwide in pigs. Exposure of infants to raw pig intestine during domestic preparation of chitterlings is inadvisable. Modification of abattoir technique in Scandinavian countries from the 1990s onward included the removal of pig intestines in a closed plastic bag; levels of carcass contamination with *Y. enterocolitica* were reduced, but such contamination was not eliminated.

Experimental pig herds free of pathogenic *Y. enterocolitica* O:3 (and also of *Salmonella*, *Toxoplasma*, and *Trichinella*) have been established in Norway and may be commercialized in the future because of their enhanced safety. In the food industry, vigilance is required because of the potential for large outbreaks if small numbers of enteropathogenic yersiniae contaminate any ready-to-eat food whose safe preservation is based on refrigeration before consumption.

The rare phenomenon of contamination of blood for transfusion has proved impossible to eradicate. However, leukodepletion is now practiced in most blood transfusion centers, primarily to prevent nonhemolytic febrile transfusion reactions and alloimmunization against HLA antigens. This measure reduces but does not eliminate the risk of *Yersinia* blood contamination.

Notification of yersiniosis is now obligatory in some countries.

CHAPTER 65

BARTONELLA INFECTIONS, INCLUDING CAT-SCRATCH DISEASE

Michael Giladi ■ Moshe Ephros

Bartonella species are fastidious, facultative intracellular, slow-growing, gram-negative bacteria that cause a broad spectrum of diseases in humans. This genus includes at least 27 distinct species or subspecies, of which at least 13 have been recognized as confirmed or potential human pathogens; *B. bacilliformis*, *B. quintana*, and *B. henselae* are most commonly identified **(Table 65-1)**. Most *Bartonella* species have successfully adapted to survival in specific domestic or wild mammals. Prolonged intraerythrocytic infection in these animals creates a reservoir for human infections. *B. bacilliformis* and *B. quintana*, which are not zoonotic, are exceptions to this rule. Arthropod vectors are often involved. Isolation and characterization of *Bartonella* species are difficult and require special techniques. Clinical presentation generally depends on both the infecting *Bartonella* species and the immune status of the infected individual. *Bartonella* species are susceptible to many antibiotics in vitro; however, clinical responses to therapy and studies in animal models suggest that the minimal inhibitory concentrations of many antimicrobial agents correlate poorly with the drugs' in vivo efficacies in patients with *Bartonella* infections.

CAT-SCRATCH DISEASE

DEFINITION AND ETIOLOGY

Usually a self-limited illness, cat-scratch disease (CSD) has two general clinical presentations. *Typical* CSD, the more common, is characterized by subacute regional lymphadenopathy; *atypical* CSD is the collective designation for numerous extranodal manifestations involving various organs. *B. henselae* is the principal etiologic agent of CSD. Rare cases have been associated with *Afipia felis* and *B. quintana*; *B. clarridgeiae* may occasionally be involved as well.

EPIDEMIOLOGY

CSD occurs worldwide, favoring warm and humid climates. In temperate climates, incidence peaks during fall and winter; in the tropics, disease occurs year-round. Adults are affected nearly as frequently as children. Intrafamilial clustering is rare, and person-to-person transmission does not occur. Apparently healthy cats constitute the major reservoir of *B. henselae*, and cat fleas (*Ctenocephalides felis*) may be responsible for cat-to-cat transmission. CSD usually follows contact with cats (especially kittens), but other animals (e.g., dogs) have been implicated as possible reservoirs in rare instances. In the United States, the estimated disease incidence is ~10 cases per 100,000 population. About 10% of patients are hospitalized.

PATHOGENESIS

Inoculation of *B. henselae*, possibly via contaminated flea feces, usually results from a cat scratch or bite. Exposure to mucous membranes or conjunctivae via droplets

TABLE 65-1

***BARTONELLA* SPECIES KNOWN OR SUSPECTED TO BE HUMAN PATHOGENS**

BARTONELLA SPECIES[a]	DISEASE	RESERVOIR HOST[b]	ARTHROPOD VECTOR
B. henselae	Cat-scratch disease, bacillary angiomatosis, bacillary peliosis, bacteremia, endocarditis	Cats, other felines	Cat fleas (*Ctenocephalides felis*): associated with cat-to-cat, but not with cat-to-human, transmission
B. quintana	Trench fever, chronic bacteremia, bacillary angiomatosis, endocarditis	Humans	Human body lice (*Pediculus humanus corporis*)
B. bacilliformis	Bartonellosis (Carrión's disease)	Humans	Sandflies (*Lutzomyia verrucarum*)
B. elizabethae	Endocarditis	Rats, dogs	Unknown
B. grahamii	Retinitis	Mice, voles	Fleas
B. vinsonii subsp. *arupensis*	Endocarditis	Mice	Ticks
B. vinsonii subsp. *berkhoffii*	Endocarditis	Domestic dogs, coyotes, gray foxes	Ticks
B. washoensis	Myocarditis, meningitis	Squirrels, possibly other rodents	Fleas
B. alsatica	Endocarditis	Rabbits	Unknown
B. koehlerae	Endocarditis	Cats	Unknown
B. clarridgeiae	Possibly cat-scratch disease	Cats	Unknown
B. rochalimae	Bacteremia, fever, splenomegaly	Unknown	Possibly fleas
B. tamiae	Bacteremia, fever, myalgia, rash	Unknown	Unknown

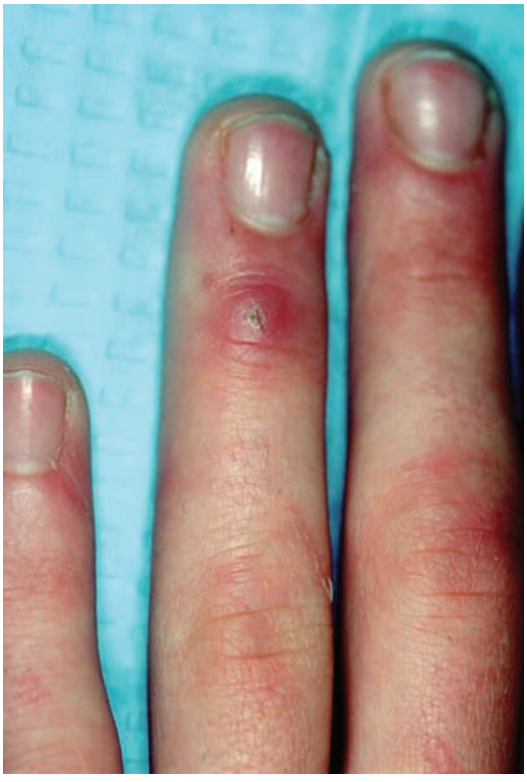
[a]Many other *Bartonella* species exist but are not recognized as human pathogens.
[b]Animals are implicated when existing evidence supports their infection with *Bartonella* species. Data supporting animal-to-human transmission may be lacking.

or licking may possibly be involved as well. With lymphatic drainage to one or more regional lymph nodes in immunocompetent hosts, a T_H1 response can result in necrotizing granulomatous lymphadenitis. Dendritic cells, along with their associated chemokines, play a role in the host inflammatory response and granuloma formation.

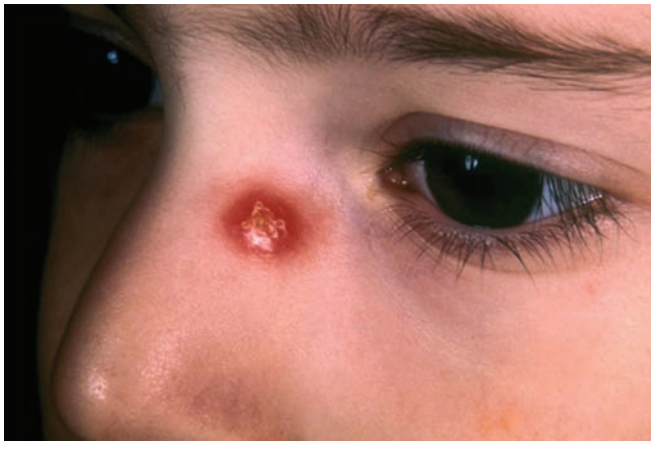
CLINICAL MANIFESTATIONS AND PROGNOSIS

Of patients with CSD, 85–90% have typical disease. The primary lesion, a small (0.3- to 1-cm) painless erythematous papule or pustule, develops at the inoculation site (usually the site of a scratch or a bite) within days to 2 weeks in about two-thirds of patients (**Fig. 65-1** *A*, *B*). Lymphadenopathy develops ≥1–3 weeks after cat contact. The affected lymph node(s) are enlarged and usually painful, sometimes have overlying erythema, and suppurate in 10–15% of cases (Fig. 65-1 *C*, *D*, and *E*). Axillary/epitrochlear nodes are most commonly involved; next in frequency are head/neck nodes and then inguinal/femoral nodes. Approximately 50% of patients have fever, malaise, and anorexia. A smaller proportion experience weight loss and night sweats mimicking the presentation of lymphoma. Fever is usually low-grade but infrequently rises to ≥39°C. Resolution is slow, requiring weeks (for fever, pain, and accompanying signs and symptoms) to months (for node shrinkage).

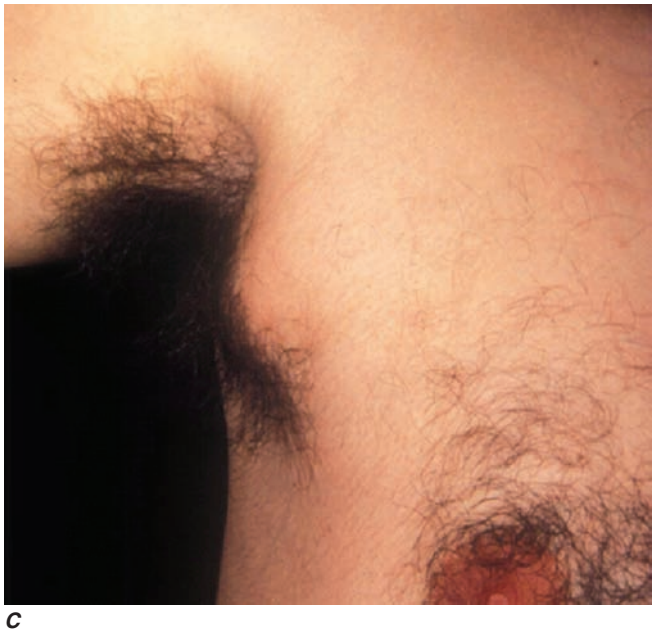
Atypical CSD occurs in 10–15% of patients as extranodal or complicated disease in the absence or presence of lymphadenopathy. Atypical disease includes Parinaud's oculoglandular syndrome (granulomatous conjunctivitis with ipsilateral preauricular lymphadenitis; Fig. 65-1, *E*), granulomatous hepatitis/splenitis, neuroretinitis (often presenting as unilateral deterioration of vision; Fig. 65-1*F*), and other ophthalmologic manifestations. In addition, neurologic involvement (encephalopathy, seizures, myelitis, radiculitis, cerebellitis, facial and other cranial or peripheral palsies), fever of unknown origin (FUO), debilitating myalgia, arthritis or arthralgia (affecting mostly women >20 years old), osteomyelitis (including multifocal disease), tendinitis, neuralgia, and dermatologic manifestations (including erythema nodosum [see Fig. 11-40], sometimes accompanying arthropathy) occur. Other manifestations and syndromes (pneumonitis, pleural effusion, idiopathic thrombocytopenic purpura, Henoch-Schönlein purpura, erythema multiforme [see Fig. 11-25], hypercalcemia, glomerulonephritis, myocarditis) have also been associated with CSD. In elderly patients (>60 years old), lymphadenopathy is most often absent, but encephalitis and FUO are more common than in younger patients. In immunocompetent individuals, CSD—whether typical or atypical—usually resolves without treatment and without sequelae. Lifelong immunity is the rule.



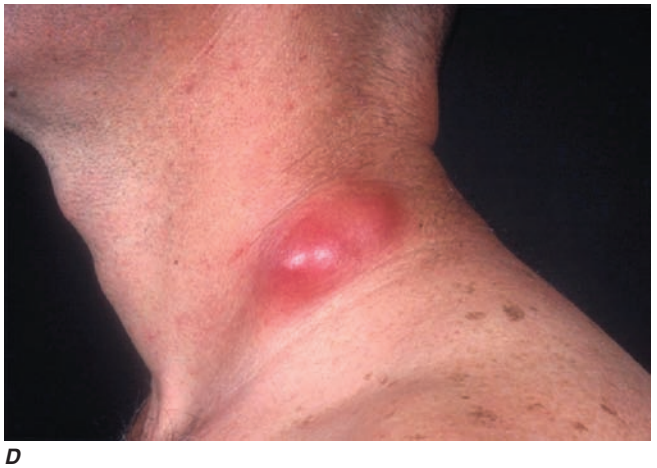
A



B



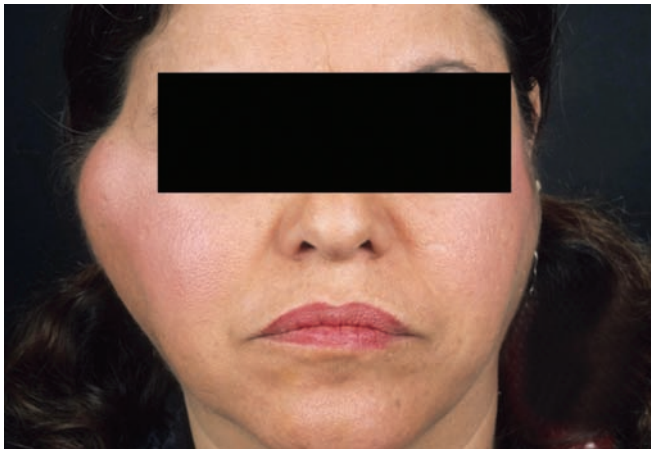
C



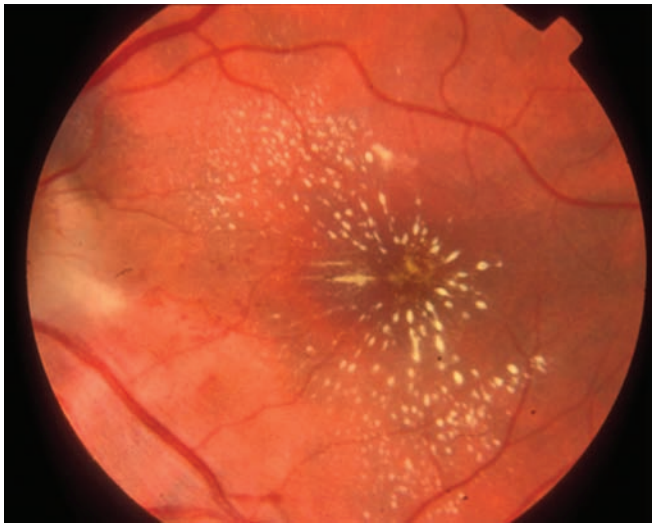
D

FIGURE 65-1

Manifestations of cat-scratch disease. ***A:*** Primary inoculation lesion. Axillary and epitrochlear lymphadenitis appeared 2 weeks later. ***B:*** Primary inoculation lesion. Submental lymphadenitis appeared 10 days later. ***C:*** Axillary lymphadenopathy of 2 weeks' duration. The overlying skin appears normal. ***D:*** Cervical lymphadenopathy of 6 weeks' duration. The overlying skin is red. Thick, odorless pus (12 mL) was aspirated. ***E:*** Preauricular lymphadenopathy. ***F:*** Left-eye neuroretinitis. Note papilledema and stellate macular exudates ("macular star").



E



F

FIGURE 65-1
(*Continued*)

DIAGNOSIS

Routine laboratory tests usually yield normal or nonspecific results. Histopathology initially shows lymphoid hyperplasia and later demonstrates stellate granulomata with necrosis, coalescing microabscesses, and occasional multinucleated giant cells, findings which, although nonspecific, may narrow the differential diagnosis. Serologic testing (immunofluorescence or enzyme immunoassay) is the most commonly used laboratory diagnostic approach, with variable sensitivity and specificity. Seroconversion may take a few weeks. Other tests are of low sensitivity (culture, Warthin-Starry silver staining), of low specificity (cytology, histopathology), or of limited availability in routine diagnostic laboratories (PCR, immunohistochemistry). PCR of lymph node tissue, pus, or the primary inoculation lesion is highly sensitive and specific and is particularly useful for definitive and rapid diagnosis in seronegative patients.

APPROACH TO THE PATIENT Cat-Scratch Disease

A history of cat contact, a primary inoculation lesion, and regional lymphadenopathy are highly suggestive of CSD. A characteristic clinical course and corroborative laboratory tests make the diagnosis very likely. Conversely, when acute- and convalescent-phase sera are negative (as is the case in 10–20% of CSD patients), when spontaneous regression of lymph node size does not occur, and particularly when constitutional symptoms persist, malignancy must be ruled out. Pyogenic lymphadenitis, mycobacterial infection, brucellosis, syphilis, tularemia, plague, toxoplasmosis, sporotrichosis, and histoplasmosis should also be considered. In clinically suspected CSD in a seronegative individual, fine-needle aspiration may be adequate and PCR can confirm the diagnosis. When data are less supportive of CSD, lymph node biopsy rather than fine-needle aspiration is preferred. In seronegative CSD patients with lymphadenopathy and severe complications (e.g., encephalitis or neuroretinitis), early biopsy is important to establish a specific diagnosis.

TREATMENT Cat-Scratch Disease

(Table 65-2) Treatment regimens are based on only minimal data. Suppurative nodes should be drained by large-bore needle aspiration and not by incision and drainage in order to avoid chronic draining tracts. Immunocompromised patients must always be treated with systemic antimicrobials.

PREVENTION

Avoiding cats (especially kittens) and instituting flea control are options for immunocompromised patients and for patients with valvular heart disease.

TRENCH FEVER AND CHRONIC BACTEREMIA

DEFINITION AND ETIOLOGY

Trench fever, also known as *5-day fever* or *quintan fever*, is a febrile illness caused by *B. quintana*. It was first described as an epidemic in the trenches of World War I and recently reemerged as chronic bacteremia seen most often in homeless people (also referred to as *urban* or *contemporary trench fever*).

TABLE 65-2

ANTIMICROBIAL THERAPY FOR DISEASE CAUSED BY *BARTONELLA* SPECIES IN ADULTS

DISEASE	ANTIMICROBIAL THERAPY
Typical cat-scratch disease	Not routinely indicated; for patients with extensive lymphadenopathy, consider azithromycin (500 mg PO on day 1, then 250 mg PO qd for 4 days)
Cat-scratch disease retinitis	Doxycycline (100 mg PO bid) *plus* rifampin (300 mg PO bid) for 4–6 weeks
Other atypical cat-scratch disease manifestations[a]	As per retinitis; treatment duration should be individualized
Trench fever or chronic bacteremia with *B. quintana*	Gentamicin (3 mg/kg IV qd for 14 days) *plus* doxycycline (200 mg PO qd or 100 mg PO bid for 6 weeks)
Suspected *Bartonella* endocarditis	Gentamicin[b] (1 mg/kg IV q8h for ≥14 days) *plus* doxycycline (100 mg PO/IV bid for 6 weeks[c]) *plus* ceftriaxone (2 g IV qd for 6 weeks)
Confirmed *Bartonella* endocarditis	As for suspected *Bartonella* endocarditis *minus* ceftriaxone
Bacillary angiomatosis	Erythromycin[d] (500 mg PO qid for 3 months) *or* Doxycycline (100 mg PO bid for 3 months)
Bacillary peliosis	Erythromycin[d] (500 mg PO qid for 4 months) *or* Doxycycline (100 mg PO bid for 4 months)
Bartonellosis (Carrión's disease)	
Oroya fever	Chloramphenicol (500 mg PO/IV qid for 14 days) *plus* another antibiotic (β-lactam preferred) *or* Ciprofloxacin (500 mg PO bid for 10 days)
Verruga peruana	Rifampin (10 mg/kg PO qd, to a maximum of 600 mg, for 14 days) *or* Streptomycin (15–20 mg/kg IM qd for 10 days)

[a]Data on treatment efficacy for encephalitis and hepatosplenic CSD are lacking. Therapy similar to that given for retinitis is reasonable.
[b]Some experts recommend gentamicin at 3 mg/kg IV qd. If gentamicin is contraindicated, rifampin (300 mg PO bid) can be added to doxycycline for documented *Bartonella* endocarditis.
[c]Some experts recommend extending oral doxycycline therapy for 3–6 months.
[d]Other macrolides are probably effective and may be substituted for erythromycin or doxycycline.
Source: Recommendations are modified from JM Rolain et al: Antimicrob Agents Chemother 48:1921, 2004.

EPIDEMIOLOGY

In addition to epidemics during World Wars I and II, sporadic outbreaks of trench fever have been reported in many regions of the world. The human body louse (*Pediculus humanus corporis*) has been identified as the vector and humans as the only known reservoir. After a hiatus of several decades during which trench fever was almost forgotten, small clusters of cases of *B. quintana* chronic bacteremia were reported sporadically, primarily from the United States and France, in HIV-uninfected homeless people. Alcoholism and louse infestation were identified as risk factors.

CLINICAL MANIFESTATIONS

The typical incubation period is 15–25 days (range, 3–38 days). "Classical" trench fever, as described in 1919, ranges from a mild febrile illness to a recurrent or protracted and debilitating disease. Onset may be abrupt or preceded by a prodrome of several days. Fever is often periodic, lasting 4–5 days with 5-day (range, 3- to 8-day) intervals between episodes. Other symptoms and signs include headache, back and limb pain, profuse sweating, shivering, myalgia, arthralgia, splenomegaly, a maculopapular rash in occasional cases, and nuchal rigidity in some cases. Untreated, the disease usually lasts 4–6 weeks. Death is rare. The clinical spectrum of *B. quintana* bacteremia in homeless people ranges from asymptomatic infection to a febrile illness with headache, severe leg pain, and thrombocytopenia. Endocarditis sometimes develops.

DIAGNOSIS

Definitive diagnosis requires isolation of *B. quintana* by blood culture. Some patients have positive blood cultures for several weeks. Patients with acute trench fever typically develop significant titers of antibody to *Bartonella*, whereas those with chronic *B. quintana* bacteremia may be seronegative. Patients with high titers of IgG antibodies should be evaluated for endocarditis. In epidemics, trench fever should be differentiated from epidemic louse-borne typhus and relapsing fever, which occur under similar conditions and share many features.

TREATMENT Bacteremia

(Table 65-2) In a small, randomized, placebo-controlled trial involving homeless people with *B. quintana* bacteremia, therapy with gentamicin and doxycycline was superior to administration of placebo in eradicating bacteremia. Treatment of bacteremia is important even in clinically mild cases to prevent endocarditis. Optimal therapy for trench fever without documented bacteremia is uncertain.

BARTONELLA ENDOCARDITIS

DEFINITION AND ETIOLOGY

Coxiella burnetii (Chap. 79) and *Bartonella* species are the most common pathogens in culture-negative endocarditis (Chap. 20). In France, for example, *Bartonella* species were identified as the etiologic agents in 28% of 348 cases of culture-negative endocarditis. Prevalence, however, varies by geographic location and epidemiologic setting. In addition to *B. quintana* and *B. henselae* (the most common *Bartonella* species implicated in endocarditis, with the former more commonly involved than the latter), other *Bartonella* species have reportedly caused rare cases (Table 65-1).

EPIDEMIOLOGY

Bartonella endocarditis has been reported worldwide. Most patients are adults; more are male than female. Risk factors associated with *B. quintana* endocarditis include homelessness, alcoholism, and body louse infestation; however, individuals with no risk factors have had *Bartonella* endocarditis diagnosed as well. *B. henselae* endocarditis is associated with exposure to cats. Most cases involve native rather than prosthetic valves; the aortic valve accounts for ~60% of cases. Patients with *B. henselae* endocarditis usually have preexisting valvulopathy, whereas *B. quintana* often infects normal valves.

CLINICAL MANIFESTATIONS

Clinical manifestations are usually characteristic of subacute endocarditis of any etiology. However, a substantial number of patients have a prolonged, minimally febrile or even afebrile indolent illness, with mild nonspecific symptoms lasting weeks or months before the diagnosis is made. Initial echocardiography may not show vegetations. Acute, aggressive disease is rare.

DIAGNOSIS

Blood cultures, even with use of special techniques (lysis centrifugation or EDTA-containing tubes), are positive in only ~25% of cases—mostly those caused by *B. quintana* and only rarely those caused by *B. henselae*. Prolonged incubation of cultures (up to 6 weeks) is required. Serologic tests—either immunofluorescence or enzyme immunoassay—usually demonstrate high-titer IgG antibodies to *Bartonella*. Because of cross-antigenicity, serology does not distinguish between *B. quintana* and *B. henselae* and may also be low-titer cross-reactive with other pathogens, such as *C. burnetii* and *Chlamydia* species. Identification of *Bartonella* to the species level is usually accomplished by application of PCR-based methods to valve tissue.

TREATMENT *Bartonella* Endocarditis

(Table 65-2) For patients with culture-negative endocarditis suspected to be due to *Bartonella* species, empirical treatment consists of gentamicin, doxycycline, and ceftriaxone; the major role of ceftriaxone in this regimen is to adequately treat other potential causes of culture-negative endocarditis, including members of the HACEK group. Once a diagnosis of *Bartonella* endocarditis has been established, ceftriaxone is discontinued. Aminoglycosides, the only antibiotics known to be bactericidal against *Bartonella*, should be included in the regimen for ≥2 weeks. Indications for valvular surgery are the same as in subacute endocarditis due to other pathogens; however, the proportion of patients who undergo surgery (~60%) is high, probably as a consequence of delayed diagnosis.

BACILLARY ANGIOMATOSIS AND PELIOSIS

DEFINITION AND ETIOLOGY

Bacillary angiomatosis (sometimes called *bacillary epithelioid angiomatosis* or *epithelioid angiomatosis*) is a disease of severely immunocompromised patients, is caused by *B. henselae* or *B. quintana*, and is characterized by neovascular proliferative lesions involving the skin and other organs. Both species cause cutaneous lesions; hepatosplenic lesions are caused only by *B. henselae*, while subcutaneous and lytic bone lesions are more frequently associated with *B. quintana*. Bacillary peliosis is a closely related angioproliferative disorder caused by *B. henselae* and involving primarily the liver (peliosis hepatis) but also the spleen and lymph nodes. Bacillary peliosis is characterized by blood-filled cystic structures whose size ranges from microscopic to several millimeters.

EPIDEMIOLOGY

Bacillary angiomatosis and bacillary peliosis occur primarily in HIV-infected persons (Chap. 93) with CD4+ T cell counts <100/μL but also affect other immunosuppressed patients and, in rare instances, immunocompetent patients. The previously reported incidence of ~1

case per 1000 HIV-infected persons is now lower; the recent decrease is most likely attributable to effective antiretroviral therapy and the routine use of rifabutin and macrolides to prevent *Mycobacterium avium* complex infection in AIDS patients. Contact with cats or cat fleas elevates the risk of *B. henselae* infection. Risk factors for *B. quintana* infection are low income, homelessness, and body louse infestation.

CLINICAL MANIFESTATIONS

Bacillary angiomatosis presents most commonly as one or more cutaneous lesions that are not painful and that may be tan, red, or purple in color. Subcutaneous masses or nodules, superficial ulcerated plaques **(Fig. 65-2)**, and verrucous growths are also seen. Nodular forms resemble those seen in fungal or mycobacterial infections. Subcutaneous nodules are often tender. Painful osseous lesions, most often involving long bones, may underlie cutaneous lesions and occasionally develop in their absence. In rare cases, other organs are involved in bacillary angiomatosis. Patients usually have constitutional symptoms, including fever, chills, malaise, headache, anorexia, weight loss, and night sweats. In osseous disease, lytic lesions are generally seen on radiography, and technetium scan shows focal uptake. The differential diagnosis of cutaneous bacillary angiomatosis includes Kaposi's sarcoma, pyogenic granuloma, subcutaneous tumors, and verruga peruana. In bacillary peliosis, hypodense hepatic areas are usually evident on imaging. In patients with advanced immunodeficiency, *B. henselae* and *B. quintana* are important causes of FUO. Intermittent bacteremia with positive blood cultures can occur with or without endocarditis.

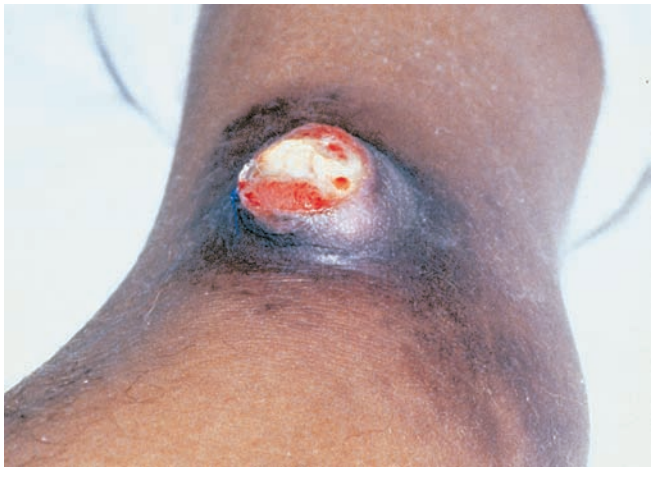


FIGURE 65-2
Nodular lesion of bacillary angiomatosis with superficial ulceration in an AIDS patient with advanced immunodeficiency. (*Reprinted with permission from DH Spach and E Darby: Bartonella Infections, Including Cat-Scratch Disease, in Harrison's Principles of Internal Medicine, 17th ed, AF Fauci et al [eds]. New York, McGraw-Hill, 2008, p 989.*)

PATHOLOGY

Bacillary angiomatosis consists of lobular proliferations of small blood vessels lined by enlarged endothelial cells interspersed with mixed infiltrates of neutrophils and lymphocytes, with predominance of the former. Histologic examination of organs with bacillary peliosis reveals small blood-filled cystic lesions partially lined by endothelial cells that can be several millimeters in size. Peliotic lesions are surrounded by fibromyxoid stroma containing inflammatory cells, dilated capillaries, and clumps of granular material. Warthin-Starry silver staining of bacillary angiomatosis and peliosis lesions reveals clusters of bacilli. Cultures are usually negative.

DIAGNOSIS

Bacillary angiomatosis and bacillary peliosis are diagnosed on histologic grounds. Blood cultures may be positive.

TREATMENT **Bacillary Angiomatosis and Peliosis**

(Table 65-2) Prolonged therapy with a macrolide or doxycycline is recommended for both bacillary angiomatosis and bacillary peliosis.

PREVENTION

Control of cat-flea infestation and avoidance of cat scratches (for prevention of *B. henselae*) and avoidance and treatment of body louse infestation (for prevention of *B. quintana*) are reasonable strategies for HIV-infected persons. Primary prophylaxis is not recommended, but suppressive therapy with a macrolide or doxycycline is indicated in HIV-infected patients with bacillary angiomatosis or bacillary peliosis until CD4+ T cell counts are >200/μL. Relapse may necessitate lifelong suppressive therapy in individual cases.

BARTONELLOSIS (CARRIÓN'S DISEASE)

DEFINITION AND ETIOLOGY

Bartonellosis is a biphasic disease caused by *B. bacilliformis*. *Oroya fever* is the initial, bacteremic, systemic form, and *verruga peruana* is its late-onset, eruptive manifestation.

EPIDEMIOLOGY AND PREVENTION

Infection is endemic to the geographically restricted Andes valleys of Peru, Ecuador, and Colombia (~500–3200 m above sea level). Sporadic epidemics occur. The disease is transmitted by the phlebotomine sandfly *Lutzomyia verrucarum*. Humans are the only known reservoir of *B. bacilliformis*. Sandfly control measures (e.g., insecticides) as well as personal

protection measures (e.g., repellents, screening, bednets) may decrease the risk of infection.

PATHOGENESIS

After inoculation by the sandfly, bacteria invade the blood vessel endothelium and proliferate; the reticuloendothelial system and various organs may also be involved. Upon re-entry into blood vessels, *B. bacilliformis* invades, replicates, and ultimately destroys erythrocytes, with consequent massive hemolysis and sudden, severe anemia. Microvascular thrombosis results in end-organ ischemia. Survivors sometimes develop cutaneous hemangiomatous lesions characterized by various inflammatory cells, endothelial proliferation, and the presence of *B. bacilliformis*.

CLINICAL MANIFESTATIONS

The incubation period is 3 weeks (range, 2–14 weeks). Oroya fever may present as a nonspecific bacteremic febrile illness without anemia or as an acute, severe hemolytic anemia with hepatomegaly and jaundice of rapid onset leading to vascular collapse and clouded sensorium. Myalgia, arthralgia, lymphadenopathy, and abdominal pain may develop. Temperature is elevated but not extremely so; high fever may suggest intercurrent infection. Subclinical asymptomatic infection also occurs. In verruga peruana, red, hemangioma-like, cutaneous vascular lesions of various sizes appear either weeks to months after systemic illness or with no previous suggestive history. These lesions persist for months up to 1 year. Mucosal and internal lesions may also develop.

DIAGNOSIS AND APPROACH TO THE PATIENT

Systemic illness (with or without anemia) or the development of cutaneous lesions in a person who has been to an endemic area raises the possibility of *B. bacilliformis* infection. Severe anemia with exuberant reticulocytosis—and sometimes thrombocytopenia—can occur. In systemic illness, Giemsa-stained blood films show typical intraerythrocytic bacilli, and blood and bone marrow cultures are positive. Serologic assays may be helpful. Biopsy may be required to confirm the diagnosis of verruga peruana. Differential diagnosis includes the spectrum of coendemic systemic febrile illnesses (e.g., typhoid fever, malaria, brucellosis) as well as diseases producing cutaneous vascular lesions (e.g., hemangiomata, bacillary angiomatosis, Kaposi's sarcoma).

TREATMENT Bartonellosis

(Table 65-2) Antibiotic therapy for systemic *B. bacilliformis* infection usually results in rapid defervescence. Additional antibiotic treatment of intercurrent infection (particularly salmonellosis) is often required. Blood transfusion may be necessary. Treatment of verruga peruana usually is not required, although large lesions or those interfering with function may require excision. Patients with numerous lesions, especially lesions that have been present for only a short period, may respond well to antibiotic therapy.

COMPLICATIONS AND PROGNOSIS

Mortality rates associated with Oroya fever have been reported to be as high as 40% without treatment but are considerably lower (~10%) with treatment. Complications such as bacterial superinfection and neurologic and cardiac manifestations occur frequently. Generalized massive edema (anasarca) and petechiae are associated with poor outcome. Permanent immunity usually develops.

CHAPTER 66

DONOVANOSIS

Nigel O'Farrell

Donovanosis is a chronic, progressive bacterial infection that usually involves the genital region. The condition is generally regarded as a sexually transmitted infection of low infectivity. This infection has been known by many other names, the most common being *granuloma inguinale*.

ETIOLOGY

The causative organism has been reclassified as *Klebsiella granulomatis comb nov* on the basis of phylogenetic analysis, although there is ongoing debate about this decision. Some authorities consider the original nomenclature (*Calymmatobacterium granulomatis*), which is based on analysis of 16S rRNA gene sequences, to be more appropriate.

Donovanosis was first described in Calcutta in 1882, and the causative organism was recognized by Charles Donovan in Madras in 1905. He identified the characteristic Donovan bodies, measuring 1.5 × 0.7 μm, in macrophages and the stratum malpighii. The organism was not reproducibly cultured until the mid-1990s, when its isolation in peripheral blood monocytes and human epithelial cell lines was reported.

EPIDEMIOLOGY

Donovanosis has an unusual geographic distribution that includes Papua New Guinea, parts of southern Africa, India, French Guyana, Brazil, and aboriginal communities in Australia. In Australia, donovanosis has virtually been eliminated through a sustained program backed by strong political commitment and resources at the primary health care level. Although few cases are now reported in the United States, donovanosis was once prevalent in this country, with 5000–10,000 cases recorded in 1947. The largest epidemic recorded was in Dutch South Guinea, where 10,000 cases were identified in a population of 15,000 (the Marind-anim people) between 1922 and 1952.

Donovanosis is associated with poor hygiene and is more common in lower socioeconomic groups than in those who are better off and in men than in women. Infection in sexual partners of index cases occurs to a limited extent. Donovanosis is a risk factor for HIV infection (Chap. 93).

Globally, the incidence of donovanosis has decreased significantly in recent times. This decline probably reflects a greater focus on effective management of genital ulcers because of their role in facilitating HIV transmission.

CLINICAL FEATURES

A lesion starts as a papule or subcutaneous nodule that later ulcerates after trauma. The incubation period is uncertain, but experimental infections in humans indicate that it lasts ~50 days. Four types of lesions have been described: (1) the classic ulcerogranulomatous lesion **(Fig. 66-1)**, a beefy red ulcer that bleeds readily when touched; (2) a hypertrophic or verrucous ulcer with a raised irregular edge; (3) a necrotic, offensive-smelling ulcer causing tissue destruction; and (4) a sclerotic or cicatricial lesion with fibrous and scar tissue.

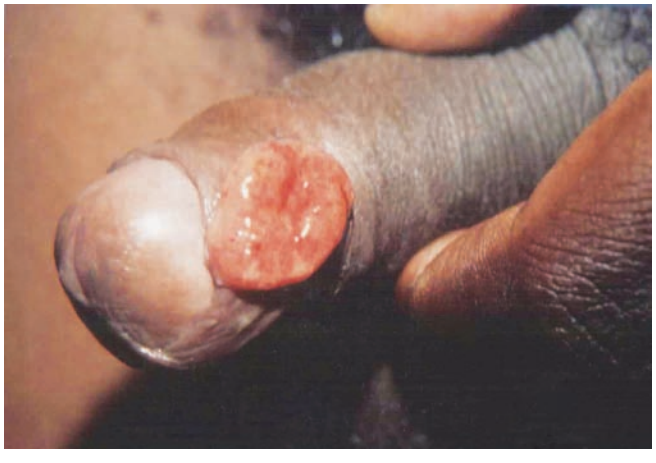


FIGURE 66-1
Ulcerogranulomatous penile lesion of donovanosis, with some hypertrophic features.

The genitals are affected in 90% of patients and the inguinal region in 10%. The most common sites of infection are the prepuce, coronal sulcus, frenum, and glans in men and the labia minora and fourchette in women. Cervical lesions may mimic cervical carcinoma. In men, lesions are associated with lack of circumcision. Lymphadenitis is uncommon. Extragenital lesions occur in 6% of cases and may involve the lip, gums, cheek, palate, pharynx, larynx, and chest. Hematogenous spread of *K. granulomatis comb nov* to liver and bone has been reported. During pregnancy, lesions tend to develop more quickly and respond more slowly to treatment. Polyarthritis and osteomyelitis are rare complications. In newborn infants, donovanosis may present with ear infection. Cases in children have been attributed to sitting on the laps of infected adults. As the incidence of donovanosis has decreased, the number of unusual case reports has appeared to be increasing.

Complications include neoplastic changes, pseudoelephantiasis, and stenosis of the urethra, vagina, or anus.

DIAGNOSIS

A clinical diagnosis of donovanosis is made by an experienced practitioner on the basis of the lesion's appearance and usually has a high positive predictive value. The diagnosis is confirmed by microscopic identification of Donovan bodies **(Fig. 66-2)** in tissue smears. Preparation of a good-quality smear is important. If donovanosis is suspected on clinical grounds, the smear for Donovan bodies should be taken before swab samples to be tested for other causes of genital ulceration so that enough material can be collected from the ulcer. A swab should be rolled firmly over an ulcer previously cleaned with a dry swab to remove debris. Smears can be examined in a clinical setting by direct microscopy with a rapid Giemsa or Wright's stain. Alternatively, a piece of granulation tissue crushed and spread between two slides can be used. Donovan bodies can be seen in large, mononuclear (Pund) cells as gram-negative intracytoplasmic cysts filled with deeply staining bodies that may have a safety-pin appearance. These cysts eventually rupture and release the infective organisms. Histologic changes include chronic inflammation with infiltration of plasma cells and neutrophils. Epithelial changes include ulceration, microabscesses, and elongation of rete ridges.

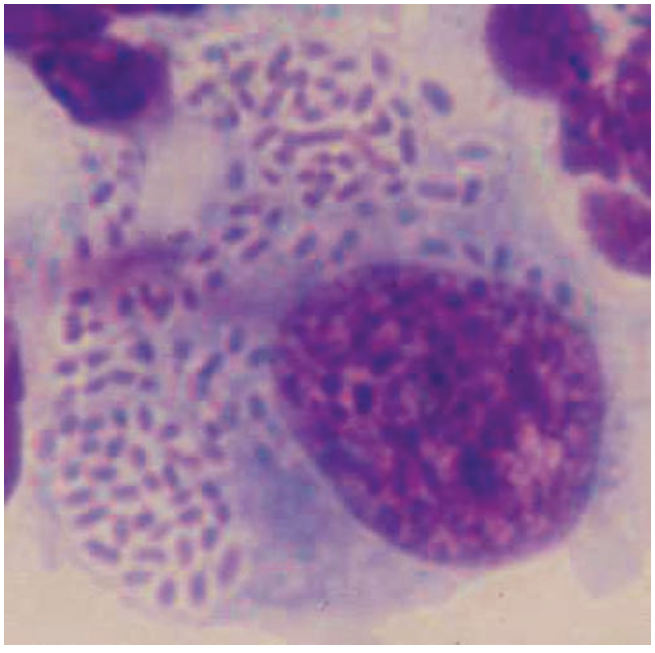


FIGURE 66-2
Pund cell stained by rapid Giemsa (RapiDiff) technique, showing numerous Donovan bodies.

A diagnostic polymerase chain reaction (PCR) test was developed in light of the observation that two unique base changes in the *phoE* gene eliminate Hae111 restriction sites, enabling differentiation of *K. granulomatis comb nov* from related *Klebsiella* species. PCR analysis with a colorimetric detection system can now be used in routine diagnostic laboratories. A genital ulcer multiplex PCR that includes *K. granulomatis* has been developed. Serologic tests are only poorly specific and are not used currently.

The differential diagnosis includes primary syphilitic chancres, secondary syphilis (condylomata lata), chancroid, lymphogranuloma venereum, genital herpes, neoplasm, and amebiasis. Mixed infections are common. Histologic appearances should be distinguished from those of rhinoscleroma, leishmaniasis, and histoplasmosis.

TREATMENT Donovanosis

Many patients with donovanosis present quite late with extensive ulceration. They may be embarrassed and have low self-esteem related to their disease. Reassurance that they have a treatable condition is important, as is the need to administer antibiotics and monitor patients for an adequate interval (see next). Epidemiologic treatment of sexual partners and advice about how to improve genital hygiene are recommended.

The recommended drug regimens for donovanosis are shown in Table 66-1. Gentamicin can be added if the response is slow. Ceftriaxone, chloramphenicol, and

TABLE 66-1
EFFECTIVE ANTIBIOTICS FOR THE TREATMENT OF DONOVANOSIS

ANTIBIOTIC	ORAL DOSE
Azithromycin	1 g on day 1, then 500 mg daily for 7 days or 1 g weekly for 4 weeks
Trimethoprim-sulfamethoxazole	960 mg bid for 14 days
Doxycycline	100 mg bid for 14 days
Erythromycin	500 mg qid for 14 days (in pregnant women)
Tetracycline	500 mg qid for 14 days

norfloxacin are also effective. Patients treated for 14 days should be monitored until lesions have healed completely. Those treated with azithromycin probably do not need such rigorous follow-up.

Surgery may be indicated for very advanced lesions.

CONTROL AND PREVENTION

Donovanosis is probably the cause of genital ulceration that is most readily recognizable clinically. Donovanosis is now limited to a few specific locations, and its global eradication is a distinct possibility.

CHAPTER 67

NOCARDIOSIS

Gregory A. Filice

Nocardia species are saprophytic aerobic actinomycetes and are common worldwide in soil, where they contribute to the decay of organic matter. More than 50 species have been identified, mostly on the basis of 16S rRNA gene sequences. More than 30 species have been associated with human disease. Until recently, isolates from the majority of cases of pneumonia and systemic disease were identified as *Nocardia asteroides*, but human disease involving *N. asteroides* proper is actually rare. Nocardiae are relatively inactive in standard biochemical tests, and speciation is difficult or impossible without molecular phylogenetic techniques. Most clinical laboratories cannot speciate isolates accurately and may identify them simply as *N. asteroides* or *Nocardia* species.

Nine species or species complexes are most commonly associated with human disease **(Table 67-1)**. Most systemic disease involves *N. cyriacigeorgica*, *N. farcinica*, *N. pseudobrasiliensis*, and species in the *N. transvalensis* and *N. nova* complexes. *N. brasiliensis* is usually associated with disease limited to the skin. Actinomycetoma—an indolent, slowly progressive disease of skin and underlying tissues with nodular swellings and draining sinuses—is often associated with *N. brasiliensis*, *N. otitidiscaviarum*, *N. transvalensis* complex strains, or other actinomycetes.

EPIDEMIOLOGY

Nocardiosis occurs worldwide. The annual incidence has been estimated on three continents (North America, Europe, and Australia) and is ~0.375 cases per 100,000 persons. The disease is more common among adults than among children and among males than among females. Nearly all cases are sporadic, but outbreaks have been associated with contamination of the hospital environment, solutions, or drug injection equipment. Person-to-person spread is not well documented. There is no known seasonality.

More than 90% of cases of pulmonary or disseminated disease occur in people with a host defense defect. Most have deficient cell-mediated immunity, especially that associated with lymphoma, transplantation, glucocorticoid therapy, or AIDS. The incidence is ~140-fold greater among patients with AIDS and ~340-fold greater among bone marrow transplant recipients than in general populations. In AIDS, nocardiosis usually affects persons with <250 CD4+ T lymphocytes/μL. Nocardiosis has also been associated with pulmonary alveolar proteinosis, tuberculosis and other mycobacterial diseases, chronic granulomatous disease, interleukin 12 deficiency, and treatment with monoclonal antibodies to tumor necrosis factor. Any child with nocardiosis and no known cause of immunosuppression should undergo tests to determine the adequacy of the phagocytic respiratory burst.

Cases of actinomycetoma occur mainly in tropical and subtropical regions, especially those of Mexico, Central and South America, Africa, and India. The most important risk factor is frequent contact with soil or vegetable matter, especially in laborers.

PATHOLOGY AND PATHOGENESIS

Pneumonia and disseminated disease are both thought to follow inhalation of fragmented bacterial mycelia. The characteristic histologic feature of nocardiosis is an abscess with extensive neutrophil infiltration and prominent necrosis.

TABLE 67-1

***NOCARDIA* SPECIES MOST COMMONLY ASSOCIATED WITH HUMAN DISEASE AND THEIR IN VITRO SUSCEPTIBILITY PATTERNS**

SPECIES	SUSCEPTIBLE TO	RESISTANT TO
N. abscessus	Amikacin, amoxicillin/clavulanic acid, ampicillin, cefotaxime, ceftriaxone, gentamicin, linezolid, minocycline, sulfamethoxazole	Ciprofloxacin, clarithromycin, erythromycin, imipenem (v)[a]
N. brevicatena/paucivorans complex (*N. brevicatena, N. paucivorans, N. carnea,* others)	Amikacin, amoxicillin/clavulanic acid, ampicillin, cefotaxime, ceftriaxone, ciprofloxacin, linezolid, minocycline, tobramycin, sulfamethoxazole	Ciprofloxacin, clarithromycin, erythromycin, gentamicin, imipenem (v)
N. nova complex (*N. nova, N. veterana, N. africana, N. kruczakiae, N. elegans,* others)	Amikacin, ampicillin, ceftriaxone, clarithromycin, erythromycin, imipenem, linezolid, minocycline, sulfamethoxazole	Amoxicillin/clavulanic acid, ciprofloxacin, gentamicin
N. transvalensis complex (*N. blacklockiae, N. wallacei,* others)	Cefotaxime (v), ceftriaxone (v), ciprofloxacin, imipenem, linezolid, sulfamethoxazole	Amikacin, ampicillin, clarithromycin, erythromycin, gentamicin
N. farcinica	Amikacin, ciprofloxacin, imipenem, linezolid, sulfamethoxazole	Ampicillin, cefotaxime, ceftriaxone, clarithromycin, erythromycin, gentamicin, tobramycin
N. cyriacigeorgica	Amikacin, cefotaxime, ceftriaxone, imipenem, linezolid, minocycline (v), sulfamethoxazole	Amoxicillin/clavulanic acid, ampicillin (v), ciprofloxacin, erythromycin, gentamicin
N. brasiliensis	Amikacin, amoxicillin/clavulanic acid, cefotaxime, ceftriaxone, minocycline, sulfamethoxazole	Ampicillin, ciprofloxacin, clarithromycin, imipenem
N. pseudobrasiliensis	Amikacin, cefotaxime (v), ceftriaxone (v), ciprofloxacin, clarithromycin, sulfamethoxazole	Amoxicillin/clavulanic acid, ampicillin, imipenem, minocycline
N. otitidiscaviarum complex	Amikacin, ciprofloxacin, gentamicin, sulfamethoxazole	Amoxicillin/clavulanic acid, ampicillin, ceftriaxone, imipenem

[a](v), variable.

Source: Adapted from BA Brown-Elliott et al: Clin Microbiol Rev 19:259, 2006.

Granulation tissue usually surrounds the lesions, but extensive fibrosis or encapsulation is uncommon.

Actinomycetoma is characterized by suppurative inflammation with sinus tract formation. Granules—microcolonies composed of dense masses of bacterial filaments extending radially from a central core—are occasionally observed in histologic preparations. They are frequently found in discharges from lesions of actinomycetoma but almost never in discharges from lesions in other forms of nocardiosis. Infrequently, nocardiae and other indolent pathogens, including fungi or mycobacteria, are isolated from the same patient.

Nocardiae have evolved a number of properties that enable them to survive within phagocytes, including neutralization of oxidants, prevention of phagosome-lysosome fusion, and prevention of phagosome acidification. Neutrophils phagocytose the organisms and limit their growth but do not kill them efficiently. Cell-mediated immunity is important for definitive control and elimination of nocardiae.

CLINICAL MANIFESTATIONS

Respiratory tract disease

Pneumonia, the most common form of nocardial disease in the respiratory tract, is typically subacute; symptoms have usually been present for days or weeks at presentation. The onset is occasionally more acute in immunosuppressed patients. Cough is prominent and produces small amounts of thick, purulent sputum that is not malodorous. Fever, anorexia, weight loss, and malaise are common; dyspnea, pleuritic pain, and hemoptysis are less common. Remissions and exacerbations over several weeks are frequent. Roentgenographic patterns vary, but some are highly suggestive of nocardial pneumonia. Infiltrates vary in size and are typically dense. Single or multiple nodules are common **(Figs. 67-1 and 67-2)**, sometimes suggesting tumors or metastases. Infiltrates and nodules tend to cavitate (Fig. 67-2). Empyema is present in one-quarter of cases.

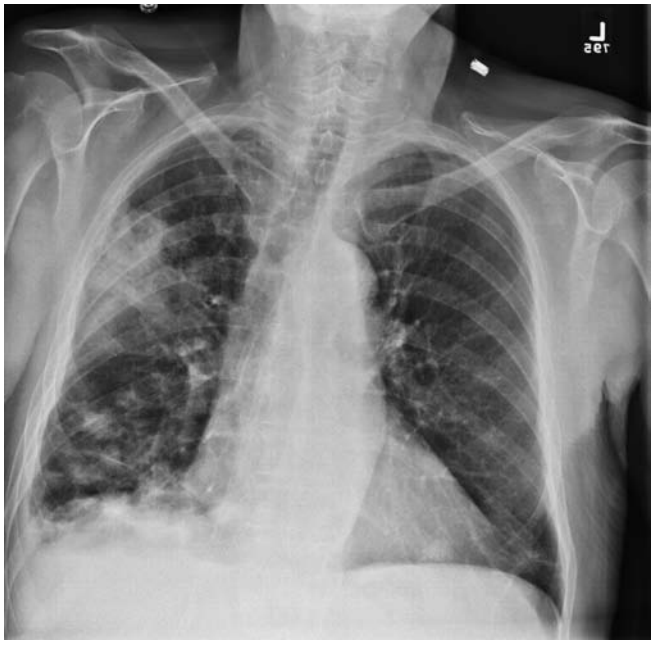


FIGURE 67-1
Nocardial pneumonia. A dense infiltrate with a possible cavity and several nodules are apparent in the right lung.

Nocardiosis may spread directly from the lungs to adjacent tissues. Pericarditis, mediastinitis, and the superior vena cava syndrome have all been reported. Nocardial laryngitis, tracheitis, bronchitis, and sinusitis are much less common than pneumonia. In the major airways, disease often presents as a nodular or granulomatous mass. Nocardiae are sometimes isolated from respiratory secretions of persons without apparent nocardial disease, usually individuals who have underlying lung or airway abnormalities.

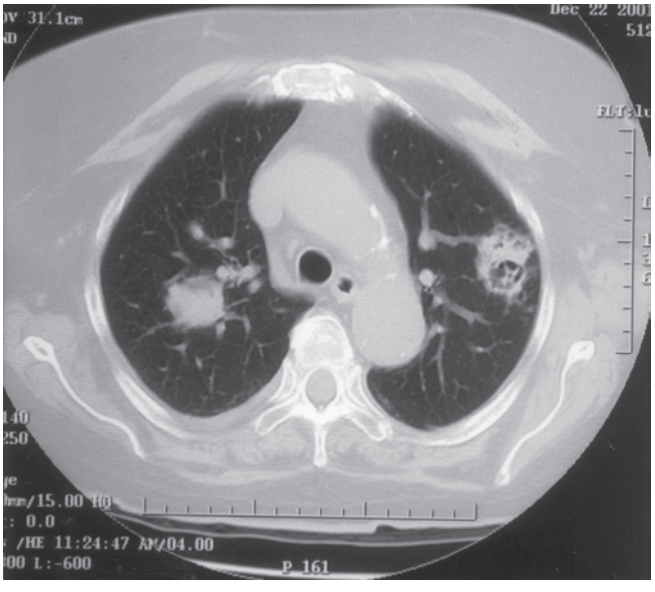


FIGURE 67-2
Nocardial pneumonia. A CT scan shows bilateral nodules, with cavitation in the nodule in the left lung.

Extrapulmonary disease

In half of all cases of pulmonary nocardiosis, disease appears outside the lungs. In one-fifth of cases of disseminated disease, lung disease is not apparent. The most common site of dissemination is the brain. Other common sites include the skin and supporting structures, kidneys, bone, and muscle, but almost any organ can be involved. Peritonitis has been reported in patients undergoing peritoneal dialysis. Nocardiae have been recovered from blood in a few cases of pneumonia, disseminated disease, or central venous catheter infection. Nocardial endocarditis occurs rarely and can affect either native or prosthetic valves.

The typical manifestation of extrapulmonary dissemination is a subacute abscess. A minority of abscesses outside the lungs or central nervous system (CNS) form fistulas and discharge small amounts of pus. In CNS infections, brain abscesses are usually supratentorial, are often multiloculated, and may be single or multiple **(Fig. 67-3)**. Brain abscesses tend to burrow into the ventricles or extend out into the subarachnoid space. The symptoms and signs are somewhat more indolent than those of other types of bacterial brain abscess. Meningitis is uncommon and is usually due to spread from a nearby brain abscess. Nocardiae are not easily recovered from cerebrospinal fluid (CSF).

Disease following transcutaneous inoculation

Disease that follows transcutaneous nocardial inoculation usually takes one of three forms: cellulitis, lymphocutaneous syndrome, or actinomycetoma.

Cellulitis generally begins 1–3 weeks after a recognized breach of the skin, often with soil contamination. Subacute cellulitis, with pain, swelling, erythema, and

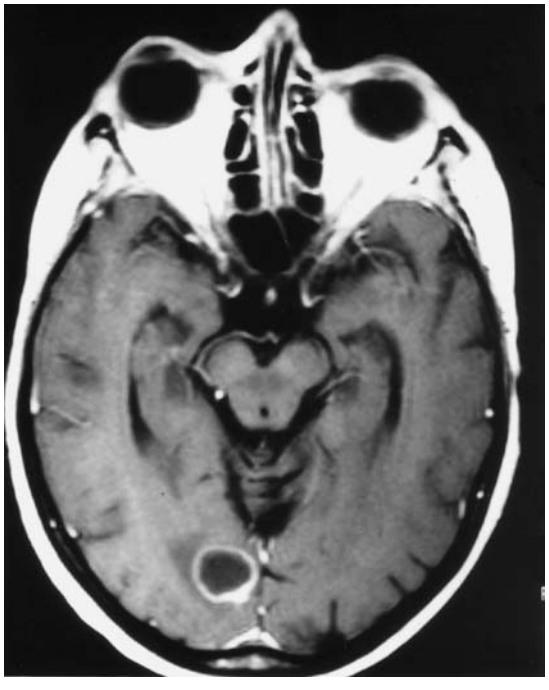


FIGURE 67-3
Nocardial abscesses in the right occipital lobe.

warmth, develops over days to weeks. The lesions are usually firm and not fluctuant. Disease may progress to involve underlying muscles, tendons, bones, or joints. Dissemination is rare. *N. brasiliensis* and species in the *N. otitidiscaviarum* complex are most common in cellulitis cases.

Lymphocutaneous disease usually begins as a pyodermatous nodule at the site of inoculation, with central ulceration and purulent or honey-colored drainage. Subcutaneous nodules often appear along lymphatics that drain the primary lesion. Most cases of nocardial lymphocutaneous syndrome are associated with *N. brasiliensis*. Similar disease occurs with other pathogens, most notably *Sporothrix schenckii* (sporotrichosis, Chap. 113).

Actinomycetoma **(Fig. 67-4)** usually begins with a nodular swelling, sometimes at a site of local trauma. Lesions typically develop on the feet or hands but may involve the posterior part of the neck, the upper back, the head, and other sites. The nodule eventually breaks down, and a fistula appears, typically followed by others. The fistulas tend to come and go, with new ones forming as old ones disappear. The discharge is serous or purulent, may be bloody, and often contains 0.1- to 2-mm white granules consisting of masses of mycelia. The lesions spread slowly along fascial planes to involve adjacent areas of skin, subcutaneous tissue, and bone. Over months or years, there may be extensive deformation of the affected part. Lesions involving soft tissues are only mildly painful; those affecting bones or joints are more so. Systemic symptoms are absent or minimal. Infection rarely disseminates from actinomycetoma, and lesions on the hands and feet usually cause only local disability. Lesions on the head, neck, and trunk can invade locally to involve deep organs, with consequent severe disability or death.

Eye infections

Nocardia species are uncommon causes of subacute keratitis, usually following eye trauma. Nocardial endophthalmitis can develop after eye surgery. In one series, nocardiae accounted for more than half of culture-proved cases of endophthalmitis after cataract surgery. Endophthalmitis can also occur during disseminated disease. Nocardial infection of lachrymal glands has been reported.

DIAGNOSIS

The first step in diagnosis is examination of sputum or pus for crooked, branching, beaded, gram-positive filaments 1 μm wide and up to 50 μm long **(Fig. 67-5)**. Most nocardiae are acid-fast in direct smears if a weak acid is used for decolorization (e.g., in the modified Kinyoun, Ziehl-Neelsen, and Fite-Faraco methods). The organisms often take up silver stains. Recovery from specimens containing a mixed flora can be improved with selective media (colistin–nalidixic acid agar, modified Thayer-Martin agar, or buffered charcoal–yeast extract agar). Nocardiae grow well on most fungal and mycobacterial media, but procedures used for decontamination of specimens for mycobacterial culture can kill nocardiae and thus should not be used when these organisms are suspected. Nocardiae grow relatively slowly; colonies may take up to 2 weeks to appear and may not develop their characteristic appearance—white, yellow, or orange, with aerial mycelia and delicate, dichotomously branched substrate mycelia—for up to 4 weeks. Several blood culture systems support nocardial growth, although nocardiae may not be detected for up to 2 weeks. The growth of nocardiae is so different from that of more common pathogens that the laboratory should be alerted when nocardiosis is suspected in order to maximize the likelihood of isolation.

In nocardial pneumonia, sputum smears are often negative. Unless the diagnosis can be made in smear-negative cases by sampling lesions in more accessible sites, bronchoscopy or lung aspiration is usually necessary.

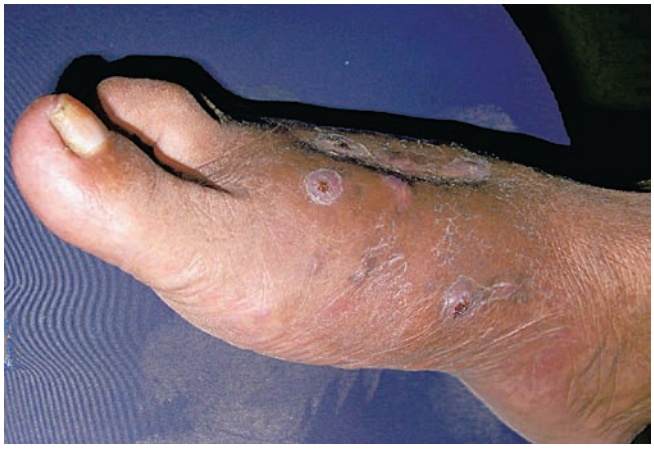


FIGURE 67-4
Common features of nocardial actinomycetoma include swelling, multiple sinus tracts, and involvement of the foot. (*Image provided by Amor Khachemoune and Ronald O. Perelman, New York University School of Medicine.*)

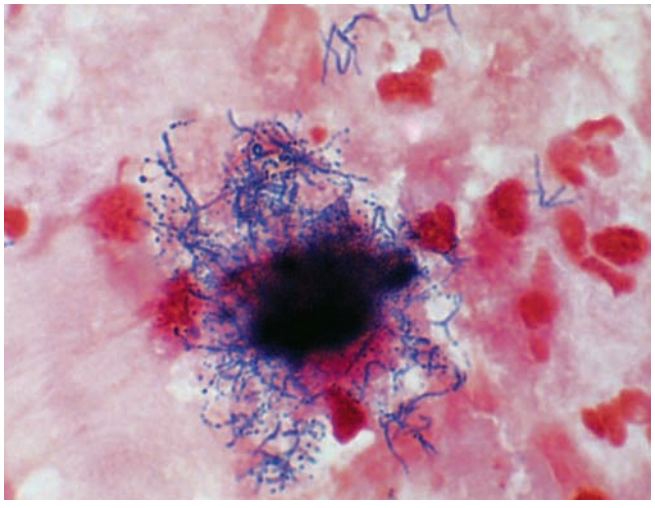


FIGURE 67-5
Gram-stained sputum from a patient with nocardial pneumonia. (*Image provided by Charles Cartwright and Susan Nelson, Hennepin County Medical Center, Minneapolis, MN.*)

To evaluate the possibility of dissemination in patients with nocardial pneumonia, a careful history should be obtained and a thorough physical examination performed. Suggestive symptoms or signs should be pursued with further diagnostic tests. CT or MRI of the head, with and without contrast material, should be undertaken if signs or symptoms suggest brain involvement. Some authorities recommend brain imaging in all cases of pulmonary or disseminated disease. When clinically indicated, CSF or urine should be concentrated and then cultured. Actinomycetoma, eumycetoma (cases involving fungi; Chap. 113), and botryomycosis (cases involving cocci or bacilli, often *Staphylococcus aureus*) are difficult to distinguish clinically but are readily distinguished with microbiologic testing. Granules should be sought in any discharge. Suspect particles should be washed in saline, examined microscopically, and cultured. Granules in actinomycetoma cases are usually white, pale yellow, pink, or red. Viewed microscopically, they consist of tight masses of fine filaments (0.5–1 μm wide) radiating outward from a central core. Granules from eumycetoma cases are white, yellow, brown, black, or green. Under the microscope, they appear as masses of broader filaments (2–5 μm wide) encased in a matrix. Granules of botryomycosis consist of loose masses of cocci or bacilli. Organisms can also be seen in wound discharge or histologic specimens. The most reliable way to differentiate among the various organisms associated with mycetoma is by culture.

Isolation of nocardiae from sputum or blood occasionally represents colonization, transient infection, or contamination. In typical cases of respiratory tract colonization, Gram-stained specimens are negative and cultures are only intermittently positive. A positive sputum culture in an immunosuppressed patient usually reflects disease. When nocardiae are isolated from sputum of an immunocompetent patient without apparent nocardial disease, the patient should be observed carefully without treatment. A patient with a host-defense defect that increases the risk of nocardiosis should usually receive antimicrobial treatment.

TREATMENT Nocardiosis

The Clinical Laboratory Standards Institute has approved a broth dilution antimicrobial susceptibility test protocol for use with human nocardial isolates. Procedures differ from those used with common human bacterial pathogens, and most clinical laboratories will not be sufficiently experienced with *Nocardia* to produce reliable results. Because nocardiosis is uncommon, data on the relation between susceptibility test results for specific drugs and clinical outcomes in patients treated with these drugs are meager. Empirical therapy with the drugs discussed next is recommended for newly diagnosed cases. When possible, and especially in severe cases or cases that do not improve promptly with empirical therapy, clinicians should arrange for susceptibility tests at a laboratory with experience in nocardial microbiology, such as the Mycobacteria/Nocardia Laboratory at the University of Texas Health Science Center (11937 US Highway 271, Tyler, TX 75708-3154; phone, 903-877-7685; fax, 903-877-7652).

Sulfonamides are the drugs of choice (Tables 67-1 and 67-2). The combination of sulfamethoxazole (SMX) and trimethoprim (TMP) is probably equivalent to a sulfonamide alone; some authorities believe that the combination may in fact be more effective, but it also poses a modestly greater risk of hematologic toxicity. At the outset, 10–20 mg of TMP per kg and 50–100 mg of SMX per kg are given each day in two divided doses. Later, daily doses can be decreased to as little as 5 mg/kg and 25 mg/kg, respectively. In persons with sulfonamide allergies, desensitization usually allows continuation of therapy with these effective and inexpensive drugs.

Clinical experience with other oral drugs is limited. Minocycline (100–200 mg twice a day) is often effective; other tetracyclines are usually less effective. Linezolid is active against all species in vitro and has been effective in a few clinical cases, but adverse effects are common with long-term use. Tigecycline appears to be active in vitro against some species, but no relevant clinical experience has been reported. Amoxicillin (875 mg) combined with clavulanic acid (125 mg), given twice a day, has been effective in some cases but should be avoided in cases involving strains of the *N. nova* complex, in which clavulanate induces β-lactamase production. Among quinolones, ciprofloxacin has been studied most often, but moxifloxacin and gemifloxacin now appear to be more active.

TABLE 67-2

TREATMENT DURATION FOR NOCARDIOSIS

DISEASE	DURATION
Pulmonary or systemic	
Intact host defenses	6–12 months
Deficient host defenses	12 months[a]
CNS disease	12 months[b]
Cellulitis, lymphocutaneous syndrome	2 months
Osteomyelitis, arthritis, laryngitis, sinusitis	4 months
Actinomycetoma	6–12 months after clinical cure
Keratitis	Topical: until apparent cure Systemic: until 2–4 months after apparent cure

[a]In some patients with AIDS and CD4+ T lymphocyte counts of <200/μL or with chronic granulomatous disease, therapy for pulmonary or systemic disease must be continued indefinitely.
[b]If all apparent CNS disease has been excised, the duration of therapy may be reduced to 6 months.

Amikacin, the best-established parenteral drug except in cases involving the *N. transvalensis* complex, is given in doses of 5–7.5 mg/kg every 12 h or 15 mg/kg every 24 h. Serum drug levels should be monitored during prolonged therapy in patients with diminished renal function and in the elderly. Cefotaxime, ceftriaxone, and imipenem are usually effective except as indicated in Table 67-1.

Patients with severe disease are initially treated with a combination including TMP-SMX, amikacin, and ceftriaxone or imipenem. Clinical improvement is usually noticeable after 1–2 weeks of therapy but may take longer, especially with CNS disease. After definite clinical improvement, therapy can be continued with a single drug (usually one that can be taken by mouth) in most cases. Some experts use two or more drugs for the entire course of therapy in some cases, but whether multiple drugs are better than a single agent is not known, and additional drugs increase the risk of toxicity. In patients with nocardiosis who need immunosuppressive therapy for an underlying disease or prevention of transplant rejection, immunosuppressive therapy should be continued.

Use of SMX and TMP in high-risk populations to prevent *Pneumocystis* disease or urinary tract infections appears to reduce but not eliminate the risk of nocardiosis. The incidence of nocardiosis is low enough that prophylaxis solely to prevent this disease is not recommended.

Surgical management of nocardial disease is similar to that of other bacterial diseases. Brain abscesses should be aspirated, drained, or excised if the diagnosis is unclear, if an abscess is large and accessible, or if an abscess fails to respond to chemotherapy. Small or inaccessible brain abscesses should be treated medically; clinical improvement should be noticeable within 1–2 weeks. Brain imaging should be repeated to document the resolution of lesions, although abatement on images often lags behind clinical improvement.

Antimicrobial therapy usually suffices for nocardial actinomycetoma. In deep or extensive cases, drainage or excision of heavily involved tissue may facilitate healing, but structure and function should be preserved whenever possible. Keratitis is treated with topical sulfonamide or amikacin drops plus a sulfonamide or an alternative drug given by mouth.

Nocardial infections tend to relapse (particularly in patients with chronic granulomatous disease), and long courses of antimicrobial therapy are necessary (Table 67-2). If disease is unusually extensive or if the response to therapy is slow, the recommendations in Table 67-2 should be exceeded.

With appropriate treatment, the mortality rate for pulmonary or disseminated nocardiosis outside the CNS should be <5%. CNS disease carries a higher mortality rate. Patients should be followed carefully for at least 6 months after therapy has ended.

CHAPTER 68

ACTINOMYCOSIS

Thomas A. Russo

Actinomycosis is an indolent, slowly progressive infection caused by anaerobic or microaerophilic bacteria, primarily of the genus *Actinomyces*, that colonize the mouth, colon, and vagina. Mucosal disruption may lead to infection at virtually any site in the body. In vivo growth of actinomycetes usually results in the formation of characteristic clumps called *grains* or *sulfur granules*. The clinical presentations of actinomycosis are myriad. Common in the preantibiotic era, actinomycosis has diminished in incidence, as has its timely recognition. Actinomycosis has been called the most misdiagnosed disease, and it has been said that no disease is so often missed by experienced clinicians. Thus this entity remains a diagnostic challenge.

Three clinical presentations that should prompt consideration of this unique infection are (1) the combination of chronicity, progression across tissue boundaries, and mass-like features (mimicking malignancy, with which it is often confused); (2) the development of a sinus tract, which may spontaneously resolve and recur;

and (3) a refractory or relapsing infection after a short course of therapy, since cure of established actinomycosis requires prolonged treatment. An awareness of the full spectrum of the disease, prompting clinical suspicion, will expedite its diagnosis and treatment and will minimize the unnecessary surgical interventions, morbidity, and mortality that are reported all too often.

ETIOLOGIC AGENTS

Actinomycosis is most commonly caused by *A. israelii*. *A. naeslundii, A. odontolyticus, A. viscosus, A. meyeri*, and *A. gerencseriae* are established but less common causes. Most if not all actinomycotic infections are polymicrobial. *Aggregatibacter (Actinobacillus) actinomycetemcomitans, Eikenella corrodens*, Enterobacteriaceae, and species of *Fusobacterium, Bacteroides, Capnocytophaga, Staphylococcus*, and *Streptococcus* are commonly isolated with actinomycetes in various combinations, depending on the site of infection. The contribution of these other species to the pathogenesis of actinomycosis is uncertain.

Comparative 16S rRNA gene sequencing has led to the identification of an ever-expanding list of *Actinomyces* species and to the reclassification of some actinomycetes as *Arcanobacterium*. Increasing data support the *Actinomyces* species *A. europaeus, A. neuii, A. radingae, A. graevenitzii, A. turicensis, A. cardiffensis, A. houstonensis, A. hongkongensis, A. lingnae,* and *A. funkei* as well as two former *Actinomyces* species now classified as *Arcanobacterium* (*A. pyogenes* and *A. bernardiae*) as additional causes of human actinomycosis.

EPIDEMIOLOGY

Actinomycosis has no geographic boundaries and occurs throughout life, with a peak incidence in the middle decades. Males have a threefold higher incidence than females, possibly because of poorer dental hygiene and/or more frequent trauma. Factors that have probably contributed to the decrease in actinomycosis incidence since the advent of antibiotics include improved dental hygiene and the initiation of antimicrobial treatment before the disease develops fully. Individuals who do not seek or have access to health care, those who have an intrauterine contraceptive device (IUCD) in place for a prolonged period (see "Pelvic Disease," later in the chapter), and those who receive bisphosphonate treatment (see "Oral-Cervicofacial Disease," later) are probably at higher risk.

PATHOGENESIS AND PATHOLOGY

The etiologic agents of actinomycosis are members of the normal oral flora and are often cultured from the bronchi, the gastrointestinal tract, and the female genital tract. The critical step in the development of actinomycosis is disruption of the mucosal barrier. Local infection may ensue. Once established, actinomycosis spreads contiguously in a slow progressive manner, ignoring tissue planes. Although acute inflammation may initially develop at the infection site, the hallmark of actinomycosis is the characteristic chronic, indolent phase manifested by lesions that usually appear as single or multiple indurations. Central necrosis consisting of neutrophils and sulfur granules develops and is virtually diagnostic. The fibrotic walls of the mass are typically described as "wooden." The responsible bacterial and/or host factors have not been identified. Over time, sinus tracts to the skin, adjacent organs, or bone may develop. In rare instances, distant hematogenous seeding may occur. As mentioned earlier, these unique features of actinomycosis mimic malignancy, with which it is often confused.

Foreign bodies appear to facilitate infection. This association most frequently involves IUCDs. Reports have described an association of actinomycosis with HIV infection; transplantation; treatment with infliximab, glucocorticoids, or bisphosphonates; and radio- or chemotherapy. Ulcerative mucosal infections (e.g., by herpes simplex virus or cytomegalovirus) may facilitate the development of actinomycosis.

CLINICAL MANIFESTATIONS

Oral-cervicofacial disease

Actinomycosis occurs most frequently at an oral, cervical, or facial site, usually as a soft tissue swelling, abscess, or mass lesion that is often mistaken for a neoplasm. The angle of the jaw is generally involved, but a diagnosis of actinomycosis should be considered with any mass lesion or relapsing infection in the head and neck (Chap. 17). Radiation therapy and especially bisphosphonate treatment have been recognized as contributing to an increasing incidence of actinomycotic infection of the mandible and maxilla **(Fig. 68-1)**. Otitis, sinusitis, and canaliculitis (most commonly due to *Propionibacterium propionicum*) also can develop. Pain, fever, and leukocytosis are

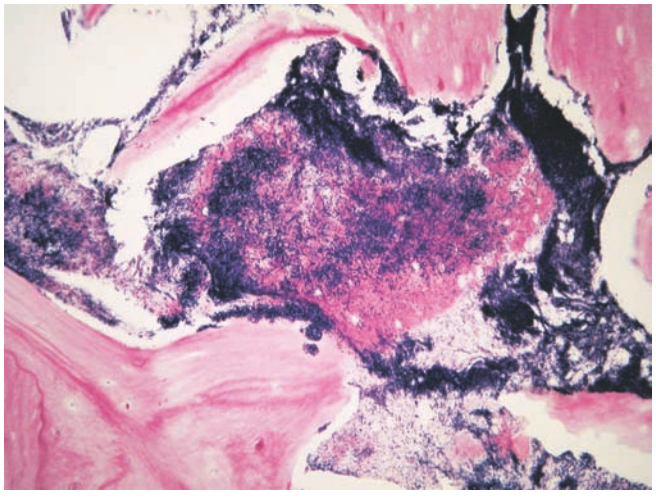


FIGURE 68-1
Bisphosphonate-associated maxillary osteomyelitis due to *A. viscosus*. A sulfur granule is seen within the bone. (*Reprinted with permission from NH Naik, TA Russo: Clin Infect Dis 49:1729, 2009. © 2009 University of Chicago Press.*)

variably reported. Contiguous extension to the cranium, cervical spine, or thorax is a potential sequela.

Thoracic disease

Thoracic actinomycosis usually follows an indolent progressive course, with involvement of the pulmonary parenchyma and/or the pleural space. Chest pain, fever, and weight loss are common. A cough, when present, is variably productive. The usual radiographic finding is either a mass lesion or pneumonia. On CT, central areas of low attenuation and ringlike rim enhancement may be seen. Cavitary disease or hilar adenopathy may develop. More than 50% of cases include pleural thickening, effusion, or empyema **(Fig. 68-2)**. Rarely, pulmonary nodules or endobronchial lesions occur. Pulmonary lesions suggestive of actinomycosis may cross fissures or pleura; may involve the mediastinum, contiguous bone, or chest wall; or may be associated with a sinus tract. In the absence of these findings, thoracic actinomycosis is usually mistaken for a neoplasm or for pneumonia due to more usual causes.

Mediastinal infection is uncommon, usually arising from thoracic extension but rarely resulting from perforation of the esophagus, from trauma, or from head and neck or abdominal disease. The structures within the mediastinum and the heart can be involved in various combinations; consequently, the possible presentations are diverse. Primary endocarditis and isolated disease of the breast have been described.

Abdominal disease

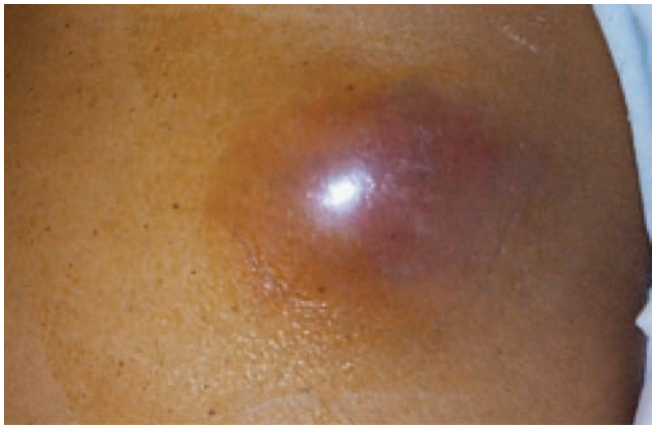
Abdominal actinomycosis poses a great diagnostic challenge. Months or years usually pass from the inciting event (e.g., appendicitis, diverticulitis, peptic ulcer disease, spillage of gall stones or bile during laparoscopic cholecystectomy, foreign-body perforation, bowel surgery, or ascension from IUCD-associated pelvic disease) to clinical recognition. Because of the flow of peritoneal fluid and/or the direct extension of primary disease, virtually any abdominal organ, region, or space can be involved. The disease usually presents as an abscess, a mass, or a mixed lesion that is often fixed to underlying tissue and mistaken for a tumor. On CT, enhancement is most often heterogeneous and adjacent bowel is thickened. Sinus tracts to the abdominal wall, to the perianal region, or between the bowel and other organs may develop and mimic inflammatory bowel disease. Recurrent disease or a wound or fistula that fails to heal suggests actinomycosis.

Hepatic infection usually presents as one or more abscesses or masses **(Fig. 68-3)**. Isolated disease presumably develops via hematogenous seeding from cryptic foci. Imaging and percutaneous techniques have resulted in improved diagnosis and treatment.

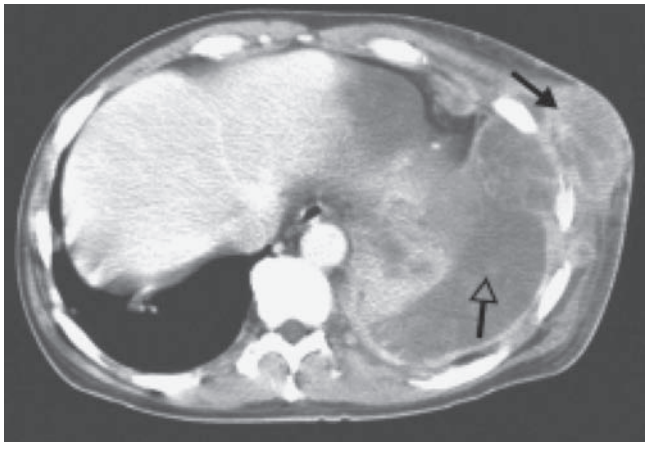
All levels of the urogenital tract can be infected. Renal disease usually presents as pyelonephritis and/or renal and perinephric abscess. Bladder involvement, usually due to extension of pelvic disease, may result in ureteral obstruction or fistulas to bowel, skin, or uterus. *Actinomyces* can be detected in urine with appropriate stains and cultures.

Pelvic disease

Actinomycotic involvement of the pelvis occurs most commonly in association with an IUCD. When an IUCD is in place or has recently been removed, pelvic symptoms should prompt consideration of actinomycosis. The risk, although not quantified, appears small. The disease rarely develops when the IUCD has been in place for <1 year, but the risk increases with time. Actinomycosis can also present months after IUCD removal. Symptoms are typically indolent; fever, weight loss, abdominal pain, and abnormal vaginal bleeding or discharge are the most common. The earliest stage of disease—often endometritis—commonly progresses



A



B

FIGURE 68-2

Thoracic actinomycosis. *A.* A chest wall mass from extension of pulmonary infection. ***B.*** Pulmonary infection is complicated by empyema (*open arrow*) and extension to the chest wall (*closed arrow*). (*Courtesy of Dr. C. B. Hsiao, Division of Infectious Diseases, Department of Medicine, State University of New York at Buffalo.*)

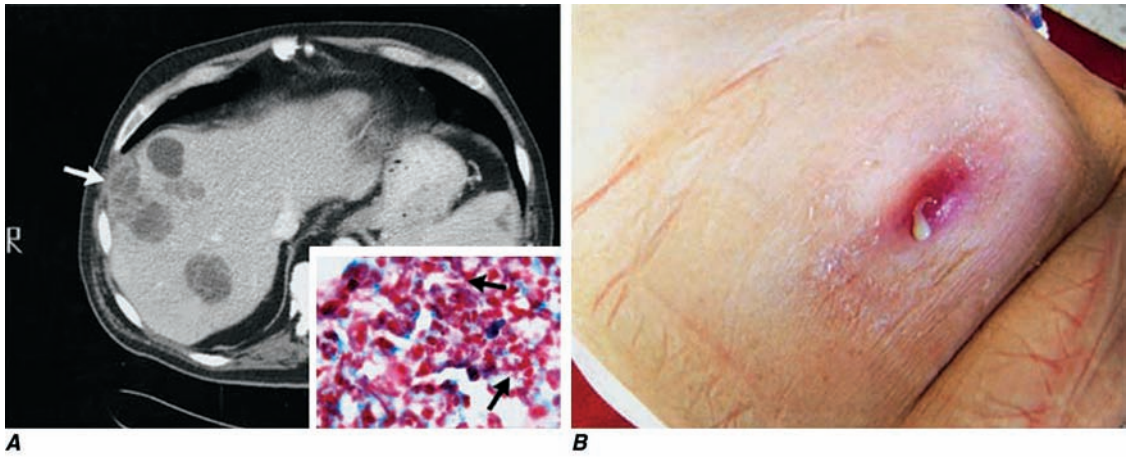


FIGURE 68-3
Hepatic-splenic actinomycosis. ***A.*** Computed tomogram showing multiple hepatic abscesses and a small splenic lesion due to *A. israelii.* Arrow indicates extension outside the liver. *Inset:* Gram's stain of abscess fluid demonstrating beaded filamentous gram-positive rods. ***B.*** Subsequent formation of a sinus tract. (*Reprinted with permission from M Saad: Actinomyces hepatic abscess with cutaneous fistula. N Engl J Med 353:e16, 2005. © 2005 Massachusetts Medical Society. All rights reserved.*)

to pelvic masses or a tuboovarian abscess **(Fig. 68-4)**. Unfortunately, because the diagnosis is often delayed, a "frozen pelvis" mimicking malignancy or endometriosis can develop by the time of recognition.

Identification of *Actinomyces*-like organisms (ALOs) on Papanicolaou-stained specimens, which occurs on average in 7% of women using an IUCD, has a low positive predictive value for a diagnosis of pelvic infection. Although the risk appears small, the consequences of infection are significant. Therefore, until more quantitative data become available, it seems prudent to remove the IUCD in the presence of symptoms that cannot be accounted for, regardless of whether ALOs are detected, and—if advanced disease is excluded—to initiate a 14-day course of empirical treatment for possible early pelvic actinomycosis. The detection of ALOs in the absence of symptoms warrants education of the patient and close follow-up but not removal of the IUCD unless a suitable contraceptive alternative is agreed on.

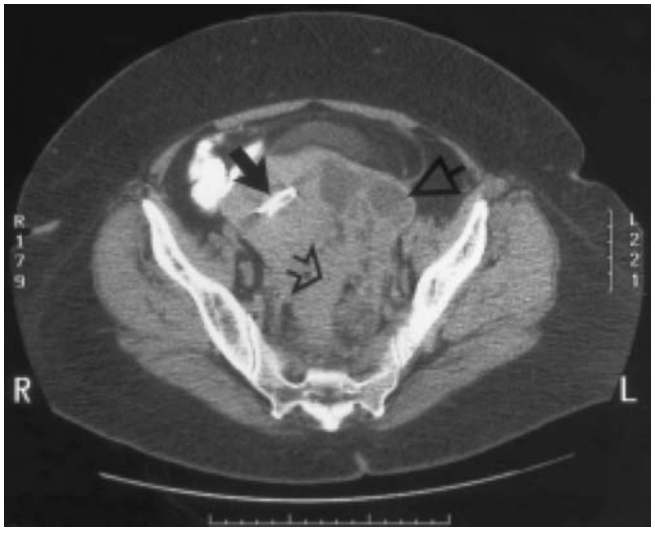


FIGURE 68-4
Computed tomogram showing pelvic actinomycosis associated with an intrauterine contraceptive device. The device is encased by endometrial fibrosis (*solid arrow*); also visible are paraendometrial fibrosis (*open triangular arrowhead*) and an area of suppuration (*open arrow*).

Central nervous system disease

Actinomycosis of the central nervous system (CNS) is rare. Single or multiple brain abscesses are most common. An abscess usually appears on CT as a ring-enhancing lesion with a thick wall that may be irregular or nodular. Magnetic resonance perfusion and spectroscopy findings have also been described, as have meningitis, epidural or subdural space infection, and cavernous sinus syndrome.

Musculoskeletal and soft tissue infection

Actinomycotic infection of bone is usually due to adjacent soft-tissue infection but may be associated with trauma (e.g., fracture of the mandible), osteoradionecrosis and bisphosphonate osteonecrosis (limited to mandibular and maxillary bones), or hematogenous spread. Because of slow disease progression, new bone formation and bone destruction are seen concomitantly. Infection of an extremity is uncommon and is usually a result of trauma. Skin, subcutaneous tissue, muscle, and bone (with periostitis or acute or chronic osteomyelitis) are involved alone or in various combinations. Cutaneous sinus tracts frequently develop.

Disseminated disease

Hematogenous dissemination of disease from any location rarely results in multiple-organ involvement. The lungs and liver are most commonly affected, with

the presentation of multiple nodules mimicking disseminated malignancy. The clinical presentation may be surprisingly indolent given the extent of disease.

DIAGNOSIS

The diagnosis of actinomycosis is rarely considered. All too often, the first mention of actinomycosis is by the pathologist after extensive surgery. Since medical therapy alone is frequently sufficient for cure, the challenge for the clinician is to consider the possibility of actinomycosis, to diagnose it in the least invasive fashion, and to avoid unnecessary surgery. The clinical and radiographic presentations that suggest actinomycosis are discussed above. Of note, hypermetabolism has been demonstrated by positive emission tomography in actinomycotic disease. Aspirations and biopsies (with or without CT or ultrasound guidance) are being used successfully to obtain clinical material for diagnosis, although surgery may be required. The diagnosis is most commonly made by microscopic identification of sulfur granules (an in vivo matrix of bacteria, calcium phosphate, and host material) in pus or tissues. Occasionally, these granules are identified grossly from draining sinus tracts or pus. Although sulfur granules are a defining characteristic of actinomycosis, granules are also found in mycetoma (Chaps. 67 and 113) and botryomycosis (a chronic suppurative bacterial infection of soft tissue or, in rare cases, visceral tissue that produces clumps of bacteria resembling granules). These entities can easily be differentiated from actinomycosis with appropriate histopathologic and microbiologic studies. Microbiologic identification of actinomycetes is often precluded by prior antimicrobial therapy or failure to perform appropriate microbiologic cultures. For optimal yield, the avoidance of even a single dose of antibiotics is mandatory. Primary isolation usually requires 5–7 days, but may take as long as 2–4 weeks. Although not routinely used, 16S rRNA gene amplification and sequencing have been successfully applied to increase diagnostic sensitivity. Because actinomycetes are components of the normal oral and genital-tract flora, their identification in the absence of sulfur granules in sputum, bronchial washings, and cervicovaginal secretions is of little significance.

TREATMENT Actinomycosis

Decisions about treatment are based on the collective clinical experience of the past 50 years. Actinomycosis requires prolonged treatment with high doses of antimicrobial agents. The need for intensive treatment is presumably due to the drugs' poor penetration of the thick-walled masses common in this infection and/or the sulfur granules themselves, which may represent a biofilm. Although therapy must be individualized, the IV administration of 18–24 million units of penicillin daily for 2–6 weeks, followed by oral therapy with penicillin or amoxicillin (total duration, 6–12 months), is a reasonable guideline for serious infections and bulky disease. Less extensive disease, particularly that involving the oral-cervicofacial region, may be cured with a shorter course. If therapy is extended beyond the resolution of measurable disease, the risk of relapse—a clinical hallmark of this infection—will be minimized; CT and MRI are generally the most sensitive and objective techniques by which to accomplish this goal. A similar approach is reasonable for immunocompromised patients, although refractory disease has been described in HIV-infected individuals. Suitable alternative antimicrobial agents and those deemed unreliable are listed in Table 68-1. Although the role played by "companion" microbes in actinomycosis is unclear, many

TABLE 68-1

APPROPRIATE AND INAPPROPRIATE ANTIBIOTIC THERAPY FOR ACTINOMYCOSIS[a]

CATEGORY	AGENT
Extensive successful clinical experience[b]	Penicillin: 3–4 million units IV q4h Amoxicillin: 500 mg PO q6h Erythromycin: 500–1000 mg IV q6h or 500 mg PO q6h Tetracycline: 500 mg PO q6h Doxycycline: 100 mg IV or PO q12h Minocycline: 100 mg IV or PO q12h Clindamycin: 900 mg IV q8h or 300–450 mg PO q6h
Anecdotal successful clinical experience	Ceftriaxone[c] Ceftizoxime Imipenem-cilastatin Piperacillin-tazobactam
Agents that should be avoided	Metronidazole Aminoglycosides Oxacillin Dicloxacillin Cephalexin
Agents predicted to be efficacious on the basis of in vitro activity	Moxifloxacin Vancomycin Linezolid Quinupristin-dalfopristin Ertapenem[c] Azithromycin[c]

[a]Additional coverage for concomitant "companion" bacteria may be required.
[b]Controlled evaluations have not been performed. Dose and duration require individualization depending on the host, site, and extent of infection. As a general rule, a maximal parenteral antimicrobial dose for 2–6 weeks followed by oral therapy, for a total duration of 6–12 months, is required for serious infections and bulky disease, whereas a shorter course may suffice for less extensive disease, particularly in the oral-cervicofacial region. Monitoring the impact of therapy with CT or MRI is advisable when appropriate.
[c]This agent can be considered for at-home parenteral therapy.

isolates are pathogens in their own right, and a regimen covering these organisms during the initial treatment course is reasonable.

Combined medical-surgical therapy is still advocated in some reports. However, an increasing body of literature now supports an initial attempt at cure with medical therapy alone, even in extensive disease. CT and MRI should be used to monitor the response to therapy. In most cases, either surgery can be avoided or a less extensive procedure can be used. This approach is particularly valuable in sparing critical organs, such as the bladder or the reproductive organs in women of child-bearing age. For a well-defined abscess, percutaneous drainage in combination with medical therapy is a reasonable approach. When a critical location is involved (e.g., the epidural space, the CNS) or when suitable medical therapy fails, surgical intervention may be appropriate.

CHAPTER 69

INFECTIONS DUE TO MIXED ANAEROBIC ORGANISMS

Dennis L. Kasper ■ Ronit Cohen-Poradosu

DEFINITIONS

Anaerobic bacteria are organisms that require reduced oxygen tension for growth, failing to grow on the surface of solid media in 10% CO_2 in air. (In contrast, *microaerophilic bacteria* can grow in an atmosphere of 10% CO_2 in air or under anaerobic or aerobic conditions, although they grow best in the presence of only a small amount of atmospheric oxygen, and *facultative bacteria* can grow in the presence or absence of air.) This chapter describes infections caused by nonsporulating anaerobic bacteria. Most clinically relevant anaerobes, such as *Bacteroides fragilis, Prevotella melaninogenica*, and *Fusobacterium nucleatum*, are relatively aerotolerant. Although they can survive for sustained periods in the presence of up to 2–8% oxygen, generally they do not multiply in this environment. A far smaller number of pathogenic anaerobic bacteria (which are also part of the normal flora) die after brief contact with oxygen, even in low concentrations.

Most human mucocutaneous surfaces harbor a rich indigenous flora composed of aerobic and anaerobic bacteria. These surfaces are dominated by anaerobic bacteria, which often account for 99.0–99.9% of the culturable flora and range in concentration from 10^9/mL in saliva to 10^{12}/mL in gingival scrapings and the colon. Most of the normal anaerobic flora cannot be grown or characterized by current laboratory methods. The major reservoirs of these bacteria are the mouth, lower gastrointestinal tract, skin, and female genital tract (Table 69-1). In the oral cavity, the ratio of anaerobic to aerobic bacteria ranges from 1:1 on the surface of a tooth to 1000:1 in the gingival crevices. Anaerobic bacteria are not found in appreciable numbers in the normal upper intestine until the distal ileum. In the colon, the proportion of anaerobes increases significantly, as does the overall bacterial count; for example, there are 10^{11}–10^{12} organisms per gram of stool, and >99% of these organisms are anaerobic, with an anaerobe-to-aerobe ratio of ~1000:1. In the female genital tract, there are ~10^9 organisms per milliliter of secretions, with an anaerobe-to-aerobe ratio of ~10:1.

Commensal anaerobes have been implicated as crucial mediators of physiologic, metabolic, and immunologic functions of the mammalian host. One of the most important roles that anaerobes serve as components of the normal colonic flora is colonization resistance, in which their presence effectively interferes with colonization by potentially pathogenic bacterial species through the depletion of oxygen and nutrients, the production of enzymes and toxic end products, and the modulation of the host's intestinal innate immune response. *Bacteroides* and other intestinal bacteria ferment carbohydrates and produce volatile fatty acids that are reabsorbed and used by the host as an

TABLE 69-1

ANAEROBIC HUMAN FLORA: AN OVERVIEW

ANATOMIC SITE	TOTAL BACTERIA[a]	ANAEROBIC/ AEROBIC RATIO	POTENTIAL PATHOGENS
Oral cavity			
Saliva	10^8–10^9	1:1	*Fusobacterium nucleatum, Prevotella melaninogenica, Prevotella oralis* group, *Bacteroides ureolyticus* group, *Peptostreptococcus* spp.
Tooth surface	10^{10}–10^{11}	1:1	
Gingival crevices	10^{11}–10^{12}	10^3:1	
Gastrointestinal tract			
Stomach	0–10^5	1:1	*Bacteroides* spp. (principally members of the *B. fragilis* group), *Prevotella* spp., *Clostridium* spp., *Peptostreptococcus* spp.
Jejunum/ileum	10^4–10^7	1:1	
Terminal ileum and colon	10^{11}–10^{12}	10^3:1	
Female genital tract	10^7–10^9	10:1	*Peptostreptococcus* spp., *Bacteroides* spp., *Prevotella bivia*

[a]Per gram or milliliter.

energy source. The anaerobic intestinal microflora is also responsible for the production of secreted products that promote human health (e.g., vitamin K and bile acids).

The anaerobic intestinal flora influences the development of an intact mucosa and of mucosa-associated lymphoid tissue. Colonization of germ-free mice with a single species, *Bacteroides thetaiotaomicron*, affects the expression of various host genes and corrects deficiencies of nutrient uptake, metabolism, angiogenesis, mucosal barrier function, and enteric nervous system development. The symbiosis factor polysaccharide A of *B. fragilis* influences the normal development and function of the mammalian immune system and protects mice against colitis in a model of inflammatory bowel disease.

Hundreds of species of anaerobic bacteria have been identified as part of the normal flora of humans. Despite the complex array of bacteria in the normal flora, relatively few species are isolated commonly from human infection. Anaerobic infections occur when the harmonious relationship between the host and the bacteria is disrupted. Any site in the body is susceptible to infection with these indigenous organisms when a mucosal barrier or the skin is compromised by surgery, trauma, tumor, ischemia, or necrosis, all of which can reduce local tissue redox potentials. Because the sites that are colonized by anaerobes contain many species of bacteria, disruption of anatomic barriers allows the penetration of many organisms, resulting in mixed infections involving multiple species of anaerobes combined with facultative or microaerophilic organisms. Such mixed infections are seen in the head and neck (chronic sinusitis, chronic otitis media, Ludwig's angina, and periodontal abscesses). Brain abscesses and subdural empyema are the most common anaerobic infections of the central nervous system (CNS). Anaerobes are responsible for pleuropulmonary diseases such as aspiration pneumonia, necrotizing pneumonia, lung abscess, and empyema. These organisms also play an important role in various intraabdominal infections, such as peritonitis and intraabdominal and hepatic abscesses (Chap. 25). They are isolated frequently in female genital tract infections, such as salpingitis, pelvic peritonitis, tuboovarian abscess, vulvovaginal abscess, septic abortion, and endometritis (Chap. 30). Anaerobic bacteria are also found often in bacteremia and in infections of the skin, soft tissues, and bones.

ETIOLOGY

The taxonomic classification of anaerobes is rapidly evolving, with frequent changes in nomenclature based on newly discovered relationships among bacterial species. Infections caused by anaerobic bacteria most frequently are due to more than one organism. These polymicrobial infections may be caused by one or several anaerobic species or by a combination of anaerobic organisms and microaerophilic or facultative bacteria acting synergistically. The major anaerobic gram-positive cocci that produce disease are *Peptostreptococcus* species; the major species of this genus that are involved in infections are *P. micros*, *P. magnus*, *P. asaccharolyticus*, *P. anaerobius*, and *P. prevotii*. Clostridia (Chap. 46) are spore-forming gram-positive rods that are isolated from wounds, abscesses, sites of abdominal infection, and blood. Gram-positive anaerobic non-spore-forming bacilli are uncommon as etiologic agents of human infection. *Propionibacterium acnes*, a component of the skin flora and a rare cause of foreign-body infections, is one of the few nonclostridial gram-positive rods associated with infections. The principal anaerobic gram-negative bacilli found in human infections are the *B. fragilis* group as well as *Fusobacterium*, *Prevotella*, and *Porphyromonas* species.

The most important potential anaerobic pathogens found in the upper airways and isolated from clinical specimens of oral and pleuropulmonary infections are the *Fusobacterium* species *F. necrophorum*, *F. nucleatum*, and *F. varium*; *P. melaninogenica*; the *Prevotella oralis* group; *Porphyromonas gingivalis*; *Porphyromonas asaccharolytica*; *Peptostreptococcus* species; and the *Bacteroides ureolyticus* group.

The *B. fragilis* group contains the anaerobic pathogens most frequently isolated from clinical infections. Members of this group are part of the normal bowel flora; they include several distinct species, such as *B. fragilis*, *B. thetaiotaomicron*, *B. vulgatus*, *B. uniformis*, *B. ovatus*, and *Parabacteroides distasonis*. *B. fragilis* is the most important clinical isolate, although it is isolated in lower numbers than some other *Bacteroides* species from cultures of commensal fecal flora.

In female genital tract infections, organisms normally colonizing the vagina (e.g., *Prevotella bivia* and *Prevotella disiens*) are the most common isolates. However, *B. fragilis* is not uncommon.

PATHOGENESIS

Anaerobic bacterial infections usually occur when an anatomic barrier is disrupted and constituents of the local flora enter a site that was previously sterile. Because of the specific growth requirements of anaerobic organisms and their presence as commensals on mucosal surfaces, conditions must arise that allow these organisms to penetrate mucosal barriers and enter tissue with a lowered oxidation-reduction potential. Therefore, tissue ischemia, trauma, surgery, perforated viscus, shock, and aspiration provide environments conducive to the proliferation of anaerobes. The introduction of many bacterial species into otherwise-sterile sites leads to a polymicrobial infection in which certain organisms predominate. Three major factors are involved in the pathogenesis of anaerobic infections: bacterial synergy, bacterial virulence factors, and mechanisms of abscess formation. The ability of different anaerobic bacteria to act synergistically during polymicrobial infection contributes to the pathogenesis of anaerobic infections. It has been postulated that facultative organisms function in part to lower the oxidation-reduction potential in the microenvironment, allowing the propagation of obligate anaerobes. Anaerobes can produce compounds such as succinic acid and short-chain fatty acids that inhibit the ability of phagocytes to clear facultative organisms. In experimental models, facultative and obligate anaerobes synergistically potentiate abscess formation. Virulence factors associated with anaerobes typically confer the ability to evade host defenses, adhere to cell surfaces, produce toxins and/or enzymes, or display surface structures such as capsular polysaccharides and lipopolysaccharide (LPS) that contribute to pathogenic potential. The ability of an organism to adhere to host tissues is important to the establishment of infection. Some oral species adhere to the epithelium in the oral cavity. *P. melaninogenica* actually attaches to other microorganisms. *P. gingivalis*, a common isolate in periodontal disease, has fimbriae that facilitate attachment. Some *Bacteroides* strains appear to be piliated, a characteristic that may account for their ability to adhere.

The most extensively studied virulence factor of the nonsporulating anaerobes is the capsular polysaccharide complex of *B. fragilis*. This organism is unique among anaerobes in its potential for virulence during growth at normally sterile sites. Although it constitutes only 0.5–1% of the normal colonic flora, *B. fragilis* is the anaerobe most commonly isolated from intraabdominal infections and bacteremia. One polysaccharide of *B. fragilis*, polysaccharide A, has a unique zwitterionic motif of charged sugars that confers distinct biologic properties, such as the ability to promote abscess formation. Intraabdominal abscess induction is related to the capacity of this polysaccharide to stimulate the release of cytokines and chemokines—in particular, interleukin (IL) 8, IL-17, and tumor necrosis factor α (TNF-α)—from resident peritoneal cells. The release of cytokines and chemokines results in the chemotaxis of polymorphonuclear neutrophils (PMNs) into the peritoneum, where they adhere to mesothelial cells induced by TNF-α to upregulate their expression of intercellular adhesion molecule 1 (ICAM-1). PMNs adherent to ICAM-1-expressing cells probably represent the nidus for an abscess. Polysaccharide A also activates T cells to produce certain cytokines, including IL-17 and interferon γ, that are necessary for abscess formation. Furthermore, when the same polysaccharide is administered to experimental animals prophylactically or therapeutically, it confers protection against abscess induction after challenge with microorganisms capable of inducing abscesses. This protection is mediated by IL-10-producing T cells.

Anaerobic bacteria produce a number of exoproteins that can enhance the organisms' virulence. The collagenase produced by *P. gingivalis* may enhance tissue destruction. An enterotoxin has been identified in *B. fragilis* strains associated with diarrheal disease in animals and young children. Exotoxins produced by clostridial species, including botulinum toxins, tetanus toxin, *C. difficile* toxins A and B, and five toxins produced by *C. perfringens*, are among the most virulent bacterial toxins in mouse lethality assays. Anaerobic gram-negative bacteria such as *B. fragilis* possess LPSs (endotoxins) that are 100–1000 times less biologically potent than endotoxins associated with aerobic gram-negative bacteria. This relative biologic inactivity may account for the lower frequency of disseminated intravascular coagulation and purpura in *Bacteroides* bacteremia than in facultative and aerobic gram-negative bacillary bacteremia. An exception is the LPS from *Fusobacterium*, which may account for the severity of Lemierre's syndrome.

APPROACH TO THE PATIENT — Infections Due to Mixed Anaerobic Organisms

The physician must consider several points when approaching the patient with presumptive infection due to anaerobic bacteria.

1. Most of the organisms colonizing mucosal sites are harmless commensals; very few cause disease. When these organisms do cause disease, it often occurs in proximity to the mucosal site they colonize.
2. For anaerobes to cause tissue infection, they must spread beyond the normal mucosal barriers.

3. Conditions favoring the propagation of these bacteria, particularly a lowered oxidation-reduction potential, are necessary. These conditions exist at sites of trauma, tissue destruction, compromised vascular supply, and complications of preexisting infection, which produce necrosis.
4. There is a complex array of infecting flora. For example, as many as 12 types of organisms can be isolated from a suppurative site.
5. Anaerobic organisms tend to be found in abscess cavities or in necrotic tissue. The failure of an abscess to yield organisms on routine culture is a clue that the abscess is likely to contain anaerobic bacteria. Often smears of this "sterile pus" are found to be teeming with bacteria when Gram's stain is applied. Although some facultative organisms (e.g., *Staphylococcus aureus*) are also capable of causing abscesses, abscesses in organs or deeper body tissues should call to mind anaerobic infection.
6. Gas is found in many anaerobic infections of deep tissues but is not diagnostic because it can be produced by aerobic bacteria as well.
7. Although a putrid-smelling infection site or discharge is considered diagnostic for anaerobic infection, this manifestation usually develops late in the course and is present in only 30–50% of cases.
8. Some species (the best example being the *B. fragilis* group) require specific therapy. However, many synergistic infections can be cured with antibiotics directed at some but not all of the organisms involved. Antibiotic therapy, combined with debridement and drainage, disrupts the interdependent relationship among the bacteria, and some species that are resistant to the antibiotic do not survive without the co-infecting organisms.
9. Manifestations of severe sepsis and disseminated intravascular coagulation are unusual in patients with purely anaerobic infection.

EPIDEMIOLOGY

Difficulties in the performance of appropriate cultures, contamination of cultures by components of the normal flora, and the lack of readily available, reliable culture techniques have made it impossible to obtain accurate data on incidence or prevalence. However, anaerobic infections are encountered frequently in hospitals with active surgical, trauma, and obstetric and gynecologic services. Depending on the institution, anaerobic bacteria account for 0.5–12% of all cases of bacteremia.

CLINICAL MANIFESTATIONS

Anaerobic infections of the mouth, head, and neck

(See also Chap. 17) Anaerobic bacteria are commonly involved in infections of the mouth, head, and neck. The predominant isolates are components of the normal flora of the upper airways—mainly the *Bacteroides oralis* group, pigmented *Prevotella* species, *P. asaccharolytica*, *Fusobacterium* species, peptostreptococci, and microaerophilic streptococci.

Soft tissue infections of the oral-facial area may or may not be odontogenic. Odontogenic infections—primarily dental caries and periodontal disease (gingivitis and periodontitis)—are common and have both local consequences (especially tooth loss) and the potential for life-threatening spread to the deep fascial spaces of the head and neck. Infections of the mouth can arise from either a supragingival or a subgingival dental plaque composed of bacteria colonizing the tooth surface. Supragingival plaque formation begins with the adherence of gram-positive bacteria to the tooth surface. This form of plaque is influenced by salivary and dietary components, oral hygiene, and local host factors. Supragingival plaque can lead to dental caries and, with further invasion, to pulpitis (endodontic infection) that can further perforate the alveolar bone, causing periapical abscess. Subgingival plaque is associated with periodontal infections (e.g., gingivitis, periodontitis, and periodontal abscess) that can further disseminate to adjacent structures such as the mandible, causing osteomyelitis of the maxillary sinuses. Periodontitis may also result in spreading infection that can involve adjacent bone or soft tissues. In the healthy periodontium, the sparse microflora consists mainly of gram-positive organisms such as *Streptococcus sanguinis* and *Actinomyces* species. In the presence of gingivitis, there is a shift to a greater proportion of anaerobic gram-negative bacilli in the subgingival flora, with predominance of *Prevotella intermedia*. In well-established periodontitis, the complexity of the flora increases further. The predominant isolates are *P. gingivalis*, *P. intermedia*, *Aggregatibacter* (formerly *Actinobacillus*) *actinomycetemcomitans*, *Treponema denticola*, and *Tannerella forsythensis*.

Necrotizing ulcerative gingivitis

Gingivitis may become a necrotizing infection (trench mouth, Vincent's stomatitis). The onset of disease is usually sudden and is associated with tender bleeding gums, foul breath, and a bad taste. The gingival mucosa, especially the papillae between the teeth, becomes ulcerated and may be covered by a gray exudate, which is removable with gentle pressure. Patients may become systemically ill, developing fever, cervical lymphadenopathy, and leukocytosis. Occasionally, ulcerative gingivitis can spread to the buccal mucosa, the teeth, and the mandible or maxilla, resulting in widespread destruction of bone and soft tissue. This infection is termed acute necrotizing ulcerative mucositis (cancrum oris, noma). It destroys tissue rapidly, causing the teeth to fall out and large areas of bone—or even the whole mandible—to be sloughed. A strong putrid odor is frequently detected, although the lesions are not painful. The gangrenous lesions eventually heal, leaving large disfiguring defects. This infection most commonly follows a debilitating illness or affects severely malnourished children. It has been known to complicate leukemia or to develop in individuals with a genetic deficiency of catalase.

Acute necrotizing infections of the pharynx

These infections usually occur in association with ulcerative gingivitis. Symptoms include an extremely sore throat, foul breath, and a bad taste accompanied by fever and a sensation of choking. Examination of the pharynx demonstrates that the tonsillar pillars are swollen, red, ulcerated, and covered with a grayish membrane that peels easily. Lymphadenopathy and leukocytosis are common. The disease may last for only a few days or, if not treated, may persist for weeks. Lesions begin unilaterally but may spread to the other side of the pharynx or the larynx. Aspiration of the infected material by the patient can result in lung abscesses.

Peripharyngeal space infections

These infections arise from the spread of organisms from the upper airways to potential spaces formed by the fascial planes of the head and neck. The etiology is typically polymicrobial and represents the normal flora of the mucosa of the originating site.

Peritonsillar abscess (*quinsy*) is a complication of acute tonsillitis caused mainly by a mixed flora containing anaerobes and group A *Streptococcus*. In submandibular space infection (*Ludwig's angina*), 80% of cases are caused by infection of the tissues surrounding the second and third molar teeth. This infection results in marked local swelling of tissues, with pain, trismus, and superior and posterior displacement of the tongue. Submandibular swelling of the neck can impair swallowing and cause respiratory obstruction. In some cases, tracheotomy may be life-saving. Cervicofacial actinomycosis (Chap. 68) is caused by a branching, gram-positive, non-spore-forming, strict/facultative anaerobe that is a part of the normal oral flora. This chronic disease is characterized by abscesses, draining sinus tracts, fistula, bone destruction, and fibrosis. It can easily be mistaken for malignancy or granulomatous disease. Actinomycosis less frequently involves the thorax, abdomen, pelvis, and CNS.

Sinusitis and otitis

Anaerobic bacteria have been implicated in chronic sinusitis but play little role in acute sinusitis. In several studies on chronic sinusitis, anaerobic bacteria were found in 12–93% of cases, depending on the method used to collect specimens. Predominant isolates were pigmented *Prevotella, Fusobacterium,* and *Peptostreptococcus* species. Aerobic gram-negative bacilli and *S. aureus* have also been implicated in chronic sinusitis. Polymicrobial infection is common and may be synergistic.

Anaerobic bacteria are much more easily implicated in chronic suppurative otitis media than in acute otitis media. Purulent exudate from chronically draining ears has been found to contain anaerobes, particularly *Bacteroides* species, in up to 50% of cases. *B. fragilis* has been isolated from up to 28% of patients with chronic otitis media.

Complications of anaerobic head and neck infections

Contiguous cranial spread of these infections may result in osteomyelitis of the skull or mandible or in intracranial infections such as brain abscess and subdural empyema. Caudal spread can produce mediastinitis or pleuropulmonary infection. Hematogenous complications may also result from anaerobic infections of the head and neck. Bacteremia, which occasionally is polymicrobial, can lead to endocarditis or other distant infections. Lemierre's syndrome, which has been uncommon in the antimicrobial era, is an acute oropharyngeal infection with secondary septic thrombophlebitis of the internal jugular vein and frequent metastasis, most commonly to the lung. *F. necrophorum* is the usual cause. This infection typically begins with pharyngitis, which is followed by local invasion in the lateral pharyngeal space with resultant internal jugular vein thrombophlebitis. A typical clinical triad seen in recent series is pharyngitis, a tender/swollen neck, and noncavitating pulmonary infiltrates.

CNS infections

CNS infections associated with anaerobic bacteria are brain abscess (Chap. 31), epidural abscess, and subdural empyema. Anaerobic meningitis is rare and is usually related to parameningeal collection or shunt infection. If optimal bacteriologic techniques are employed, as many as 85% of brain abscesses yield anaerobic bacteria, which usually originate from otorhinolaryngeal infection. However, intraabdominal or pelvic infections can occasionally lead to bacteremia with an anaerobic organism that seeds the cerebral cortex. Commonly isolated are *Peptostreptococcus*, *Fusobacterium*, *Bacteroides*, *Prevotella*, *Propionibacterium, Eubacterium, Veillonella,* and *Actinomyces* species. Facultative or microaerophilic streptococci and coliforms are often part of a mixed infecting flora in brain abscesses.

Pleuropulmonary infections

Anaerobic pleuropulmonary infections result from the aspiration of oropharyngeal contents, often in the context of an altered state of consciousness or an absent gag reflex. Four clinical syndromes are associated with anaerobic pleuropulmonary infection produced by aspiration: simple aspiration pneumonia, necrotizing pneumonia, lung abscess, and empyema. Many of these infections have an indolent course that may serve as a clinical clue differentiating them, for example, from pneumococcal pneumonia, which often presents with abrupt onset, shaking chills, and rapid progression.

Aspiration pneumonitis

Bacterial aspiration pneumonitis must be distinguished from two other clinical syndromes associated with aspiration that are not of bacterial etiology. One syndrome results from aspiration of solids, usually food. Obstruction of major airways typically results in atelectasis and

moderate nonspecific inflammation. Therapy consists of removal of the foreign body.

The second aspiration syndrome is more easily confused with bacterial aspiration. *Mendelson's syndrome,* a chemical pneumonitis, results from regurgitation of stomach contents and aspiration of chemical material, usually acidic gastric juices. Pulmonary inflammation—including the destruction of the alveolar lining, with transudation of fluid into the alveolar space—occurs with remarkable rapidity. Typically this syndrome develops within hours, often following anesthesia when the gag reflex is depressed. The patient becomes tachypneic, hypoxic, and febrile. The leukocyte count may rise, and the chest x-ray may evolve suddenly from normal to a complete bilateral "whiteout" within 8–24 h. Sputum production is minimal. The pulmonary signs and symptoms can resolve quickly with symptom-based therapy or can culminate in respiratory failure, with the subsequent development of bacterial superinfection over a period of days. Antibiotic therapy is not indicated unless bacterial infection supervenes.

In contrast to these syndromes, bacterial aspiration pneumonia develops over a period of several days or weeks rather than hours. It is seen in patients who are hospitalized and have a depressed gag reflex, impaired swallowing, or a tracheal or nasogastric tube; elderly patients; and patients with transiently impaired consciousness in the wake of seizures, cerebrovascular accidents, or alcoholic blackouts. Patients who enter the hospital with this syndrome typically have been ill for several days and generally report low-grade fever, malaise, and sputum production. In some patients, weight loss and anemia reflect a more chronic process. Usually the history reveals factors predisposing to aspiration, such as alcohol overdose or residence in a nursing home. Examination sometimes yields evidence of periodontal disease. Sputum characteristically is not malodorous unless the process has been under way for at least a week. A mixed bacterial flora with many PMNs is evident on Gram's staining of sputum. Expectorated sputum is unreliable for anaerobic cultures because of inevitable contamination by normal oral flora. Reliable specimens for culture can be obtained by transtracheal or transthoracic aspiration—techniques that are rarely used at present. Culture of protected-brush specimens or bronchoalveolar lavage fluid obtained by bronchoscopy is controversial.

Chest x-rays show consolidation in dependent pulmonary segments: in the basilar segments of the lower lobes if the patient has aspirated while upright and in either the posterior segment of the upper lobe (usually on the right side) or the superior segment of the lower lobe if the patient has aspirated while supine. The organisms isolated from the lungs reflect the pharyngeal flora; pigmented and nonpigmented *Prevotella* species, *Peptostreptococcus* species, *Bacteroides* species, *Fusobacterium* species, and anaerobic cocci are the most common isolates. While most patients with aspiration pneumonia acquired in the community have a mixed infection caused by anaerobes and aerobic or microaerophilic streptococci, the patient who aspirates in the hospital may also have a mixed infection involving enteric gram-negative rods. In a study on the microbiology of severe aspiration pneumonia in institutionalized elderly patients, gram-negative bacilli were cultured in 49% of cases (with an anaerobe also recovered in 14% of this group), anaerobes in 16%, and *S. aureus* in 12%.

Necrotizing pneumonitis

This form of anaerobic pneumonitis is characterized by numerous small abscesses that spread to involve several pulmonary segments. The process can be indolent or fulminating. This syndrome is less common than either aspiration pneumonia or lung abscess and includes features of both types of infection.

Anaerobic lung abscesses

These abscesses result from subacute anaerobic pulmonary infection. The clinical syndrome typically involves a history of constitutional signs and symptoms (including malaise, weight loss, fever, night sweats, and foul-smelling sputum), perhaps over a period of weeks (Chap. 18). Patients who develop lung abscesses characteristically have dental infection and periodontitis, but lung abscesses in edentulous patients have been reported. Abscess cavities may be single or multiple and generally occur in dependent pulmonary segments **(Fig. 69-1)**. Anaerobic abscesses must be distinguished from lesions associated with tuberculosis, neoplasia, and other conditions. Oral anaerobes predominate and are found in 60–80% of cases. There is also an important role for microaerophilic streptococci such as *S. milleri*. *S. aureus* and enteric gram-negative bacilli may be found as well. Septic pulmonary emboli may originate from intraabdominal or female genital tract infections and can produce anaerobic pneumonia and abscess.

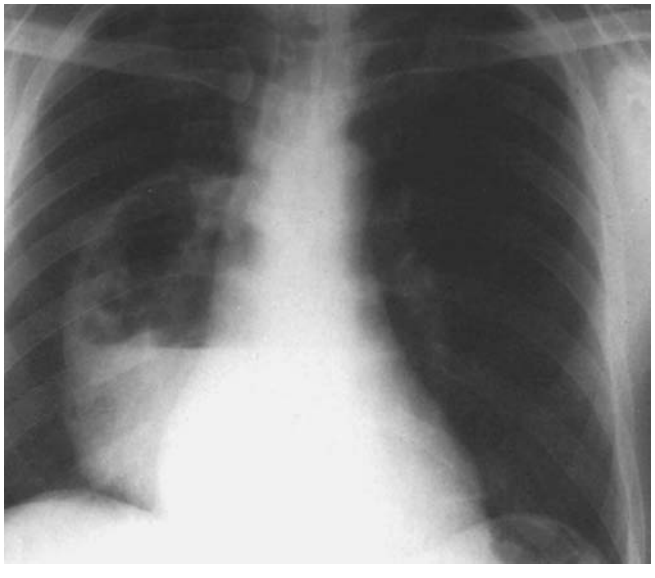


FIGURE 69-1

Chest radiograph of right-lower-lobe lung abscess in a 60-year-old alcoholic patient. (*From GL Mandell [ed]: Atlas of Infectious Diseases, Vol VI. Philadelphia, Current Medicine Inc, Churchill Livingstone, 1996; with permission.*)

Empyema

Empyema is a manifestation of long-standing anaerobic pulmonary infection. The clinical presentation, which includes foul-smelling sputum, resembles that of other anaerobic pulmonary infections. Patients may report pleuritic chest pain and marked chest-wall tenderness. Empyema may be masked by overlying pneumonitis and should be considered especially in cases of persistent fever despite antibiotic therapy. Diligent physical examination and the use of ultrasound to localize a loculated empyema are important diagnostic tools. The collection of a foul-smelling exudate by thoracentesis is typical. Cultures of infected pleural fluid yield an average of 3.5 anaerobic and 0.6 facultative or aerobic bacterial species. Drainage is required. Defervescence, a return to a feeling of well-being, and resolution of the process may require several months.

Extension from a subdiaphragmatic infection may also result in anaerobic empyema.

Intraabdominal infections

Intraabdominal infections—mainly peritonitis and abscesses—are usually polymicrobial and represent the normal intestinal (especially colonic) flora. These infections usually follow a breach in the mucosal barrier resulting from appendicitis, diverticulitis, neoplasm, inflammatory bowel disease, surgery, or trauma. On average, four to six bacterial species are isolated per specimen submitted to the microbiology laboratory, with a predominance of enteric aerobic/facultative gram-negative bacilli, anaerobes, and streptococci/enterococci. The most common isolates are *Escherichia coli* (found in ≤50% of patients) and *B. fragilis* (30–50%). Disease originating from proximal-bowel perforation reflects the flora of this site, with a predominance of aerobic and anaerobic gram-positive bacteria and *Candida*.

Enterotoxigenic *B. fragilis* has been associated with watery diarrhea in a few young children and adults. In case-control studies of children with undiagnosed diarrheal disease, enterotoxigenic *B. fragilis* was isolated from significantly more children with diarrhea than children in the control group. Neutropenic enterocolitis (typhlitis) has been associated with anaerobic infection of the cecum but—in the setting of neutropenia (Chap. 12)—may involve the entire bowel. Patients usually present with fever; abdominal pain, tenderness, and distention; and watery diarrhea. The bowel wall is edematous with hemorrhage and necrosis. The primary pathogen is thought by some authorities to be *Clostridium septicum*, but other clostridia and mixed anaerobes have also been implicated. More than 50% of patients developing early clinical signs can benefit from antibiotic therapy and bowel rest. Surgery is sometimes required to remove gangrenous bowel. See Chap. 25 for a complete discussion of intraabdominal infections.

Pelvic infections

The vagina of a healthy woman is a major reservoir of anaerobic and aerobic bacteria. In the normal flora of the female genital tract, anaerobes outnumber aerobes by a ratio of ~10:1 and include anaerobic gram-positive cocci and *Bacteroides* species (Table 69-1). Anaerobes are isolated from most women with genital tract infections that are not caused by a sexually transmitted pathogen. The major anaerobic pathogens are *B. fragilis*, *P. bivia*, *P. disiens*, *P. melaninogenica*, anaerobic cocci, and *Clostridium* species. Anaerobes are frequently encountered in Bartholin gland abscess, salpingitis, tuboovarian abscess, septic abortion, pyometra, endometritis, and postoperative wound infection, particularly following hysterectomy. These infections are often of mixed etiology, involving both anaerobes and coliforms; pure anaerobic infections without coliform or other facultative bacterial species occur more often in pelvic than in intraabdominal sites. Suppurative thrombophlebitis of the pelvic veins may complicate the infections and lead to repeated episodes of septic pulmonary emboli. See Chap. 30 for a complete discussion of pelvic inflammatory disease.

Anaerobic bacteria have been thought to be contributing factors in the etiology of bacterial vaginosis. This syndrome of unknown etiology is characterized by a profuse malodorous discharge and a change in the bacterial ecology that results in replacement of the *Lactobacillus*-dominated normal flora with an overgrowth of bacterial species including *Gardnerella vaginalis*, *Prevotella* species, *Mobiluncus* species, peptostreptococci, and genital mycoplasmas. A study based on 16S rRNA identification found other anaerobes that were predominant in cases but not in controls: *Atopobium, Leptotrichia, Megasphaera*, and *Eggerthella*. Pelvic infections due to *Actinomyces* species have been associated with the use of intrauterine devices (Chap. 68).

Skin and soft tissue infections

Injury to skin, bone, or soft tissue by trauma, ischemia, or surgery creates a suitable environment for anaerobic infections. These infections are most frequently found in sites prone to contamination with feces or with upper airway secretions—e.g., wounds associated with intestinal surgery, decubitus ulcers, or human bites. Moreover, anaerobes have been isolated from cutaneous abscesses, rectal abscesses, and axillary sweat gland infections (hidradenitis suppurativa). Anaerobes are also frequently cultured from foot ulcers of diabetic patients. The deep soft-tissue infections associated with anaerobic bacteria are crepitant cellulitis, synergistic cellulitis, gangrene, and necrotizing fasciitis (Chaps. 22 and 46).

These soft tissue or skin infections are usually polymicrobial. A mean of 4.8 bacterial species are isolated, with an anaerobe-to-aerobe ratio of ~3:2. The most frequently isolated organisms include *Bacteroides*, *Peptostreptococcus*, *Clostridium*, *Enterococcus*, and *Proteus* species. The involvement of anaerobes in these types of infections is associated with a higher frequency of fever, foul-smelling lesions, gas in the tissues, and visible foot ulcer.

Anaerobic bacterial synergistic gangrene (*Meleney's gangrene*), a rare infection of the superficial fascia, is

characterized by exquisite pain, redness, and swelling followed by induration. Erythema surrounds a central zone of necrosis. A granulating ulcer forms at the original center as necrosis and erythema extend outward. Symptoms are limited to pain; fever is not typical. These infections usually involve a combination of *Peptostreptococcus* species and *S. aureus*; the usual site of infection is an abdominal surgical wound or the area surrounding an ulcer on an extremity. Treatment includes surgical removal of necrotic tissue and antimicrobial administration.

Necrotizing fasciitis, a rapidly spreading destructive disease of the fascia, is usually attributed to group A streptococci (Chap. 39) but can also be a mixed infection involving anaerobes and aerobes, usually after surgeries and in patients with diabetes or peripheral vascular disease. The most frequently isolated anaerobes in these infections are *Peptostreptococcus* and *Bacteroides* species. Gas may be found in the tissues. Similarly, myonecrosis can be associated with mixed anaerobic infection. *Fournier's gangrene* consists of cellulitis involving the scrotum, perineum, and anterior abdominal wall, with mixed anaerobic organisms spreading along deep external fascial planes and causing extensive loss of skin.

Bone and joint infections

Although actinomycosis (Chap. 68) accounts on a worldwide basis for most anaerobic infections in bone, organisms including peptostreptococci or microaerophilic cocci, *Bacteroides* species, *Fusobacterium* species, and *Clostridium* species can also be involved. These infections frequently arise adjacent to soft tissue infections. Hematogenous seeding of bone is uncommon. *Prevotella* and *Porphyromonas* species are detected in infections involving the maxilla and mandible, whereas *Clostridium* species have been reported as anaerobic pathogens in cases of osteomyelitis of the long bones following fracture or trauma. Fusobacteria have been isolated in pure culture from sites of osteomyelitis adjacent to the perinasal sinuses. Peptostreptococci and microaerophilic cocci have been reported as significant pathogens in infections involving the skull, mastoid, and prosthetic implants placed in bone. In patients with osteomyelitis (Chap. 23), the most reliable culture specimen is a bone biopsy sample free of normal uninfected skin and subcutaneous tissue. In patients with anaerobic osteomyelitis, a mixed flora is frequently isolated from a bone biopsy specimen.

In cases of anaerobic septic arthritis, the most common isolates are *Fusobacterium* species. Most of the patients involved have uncontrolled peritonsillar infections progressing to septic cervical venous thrombophlebitis (Lemierre's syndrome) and resulting in hematogenous dissemination with a predilection for the joints. Unlike anaerobic osteomyelitis, anaerobic pyoarthritis in most cases is not polymicrobial and may be acquired hematogenously. Anaerobes are important pathogens in infections involving prosthetic joints; in these infections, the causative organisms (such as *Peptostreptococcus* species and *P. acnes*) are part of the normal skin flora.

Bacteremia

Transient bacteremia is a well-known event in healthy individuals whose anatomic mucosal barriers have been injured (e.g., during dental extractions or dental scaling). These bacteremic episodes, which are often due to anaerobes, have no pathologic consequences. However, anaerobic bacteria are found in cultures of blood from clinically ill patients when proper culture techniques are used. Anaerobes have accounted for 2–5% of all bacteremias, depending on the institution. *B. fragilis* is the single most common anaerobic isolate from the bloodstream, accounting for 35–80% of anaerobic bacteremias. The rate decreased from the 1970s through the early 1990s. This change may be related to the administration of antibiotic prophylaxis before intestinal surgery, the earlier recognition of localized infections, and the empirical use of broad-spectrum antibiotics for presumed infection. However, anaerobic bacteremia may be reemerging. Comparing two periods (1993–1996 and 2001–2004), investigators at the Mayo Clinics found a 74% increase in the incidence of anaerobic bacteremias per 100,000 patient-days; this finding contrasts with a 45% decrease in incidence from 1977 to 1988 at the same institution.

Once the organism in the blood has been identified, both the portal of bloodstream entry and the underlying problem that probably led to seeding of the bloodstream can often be deduced from an understanding of the organism's normal site of residence. For example, mixed anaerobic bacteremia including *B. fragilis* usually implies colonic pathology with mucosal disruption from neoplasia, diverticulitis, or some other inflammatory lesion. The initial manifestations are determined by the portal of entry and reflect the localized condition. When bloodstream invasion occurs, patients can become extremely ill, with rigors and hectic fevers. The clinical picture may be quite similar to that seen in sepsis involving aerobic gram-negative bacilli. Although complications of anaerobic bacteremia (e.g., septic thrombophlebitis and septic shock) have been reported, their incidence in association with anaerobic bacteremia is low. Anaerobic bacteremia is potentially fatal and requires rapid diagnosis and appropriate therapy. The mortality rate appears to increase with the age of the patient (with reported rates of >66% among patients >60 years old), with the isolation of multiple species from the bloodstream, and with the failure to surgically remove a focus of infection. The attributable mortality rate for bacteremia associated with the *B. fragilis* group was examined in a matched case-control study. Patients with *B. fragilis*–group bacteremia had a significantly higher mortality rate (28% vs 8%), with an attributable mortality rate of 19.3% and a mortality risk ratio of 3.2.

Endocarditis and pericarditis

(See also Chap. 20) Endocarditis due to anaerobes is uncommon. However, anaerobic streptococci, which

are often classified incorrectly, are responsible for this disease more frequently than is generally appreciated. Gram-negative anaerobes are unusual causes of endocarditis. Signs and symptoms of anaerobic endocarditis are similar to those of endocarditis due to facultative organisms. Mortality rates of 21–43% have been reported for anaerobic endocarditis.

Anaerobes, particularly *B. fragilis* and *Peptostreptococcus* species, are uncommonly found in infected pericardial fluids. Anaerobic pericarditis is associated with a mortality rate of >50%. Anaerobes can reach the pericardial space by hematogenous spread, by spread from a contiguous site of infection (e.g., heart or esophagus), or by direct inoculation arising from trauma or surgery.

DIAGNOSIS

There are three critical steps in the diagnosis of anaerobic infection: (1) proper specimen collection; (2) rapid transport of the specimens to the microbiology laboratory, preferably in anaerobic transport media; and (3) proper handling of the specimens by the laboratory. Specimens must be collected by meticulous sampling of infected sites, with avoidance of contamination by the normal flora. When such contamination is likely, the specimen is unacceptable. Examples of specimens unacceptable for anaerobic culture include sputum collected by expectoration or nasal tracheal suction, bronchoscopy specimens, samples collected directly through the vaginal vault, urine collected by voiding, and feces. Specimens appropriate for anaerobic culture include sterile body fluids such as blood, pleural fluid, peritoneal fluid, cerebrospinal fluid, and aspirates or biopsies from normally sterile sites. As a general rule, liquid or tissue specimens are preferred; swab specimens should be avoided.

Because even brief exposure to oxygen may kill some anaerobic organisms and result in failure to isolate them in the laboratory, air must be expelled from the syringe used to aspirate the abscess cavity, and the needle must be capped with a sterile rubber stopper. It is also important to remember that prior antibiotic therapy reduces cultivability of these bacteria. Specimens can be injected into transport bottles containing a reduced medium or taken immediately in syringes to the laboratory for direct culture on anaerobic media. Delays in transport may lead to a failure to isolate anaerobes due to exposure to oxygen or overgrowth of facultative organisms, which may eliminate or obscure any anaerobes that are present. All clinical specimens from suspected anaerobic infections should be Gram-stained and examined for organisms with characteristic morphology. It is not unusual for organisms to be observed on Gram's staining but not isolated in culture.

Because of the time and difficulty involved in the isolation of anaerobic bacteria, diagnosis of anaerobic infections must frequently be based on presumptive evidence. There are few clinical clues to the probable presence of anaerobic bacteria at infected sites. The involvement of certain sites with lowered oxidation-reduction potential (e.g., avascular necrotic tissues) and the presence of an abscess favor the diagnosis of an anaerobic infection. When infections occur in proximity to mucosal surfaces normally harboring an anaerobic flora, such as the gastrointestinal tract, female genital tract, or oropharynx, anaerobes should be considered as potential etiologic agents. A foul odor is often indicative of anaerobes, which produce certain organic acids as they proliferate in necrotic tissue. Although these odors are nearly pathognomonic for anaerobic infection, the absence of odor does not exclude an anaerobic etiology. Because anaerobes often coexist with other bacteria to cause mixed or synergistic infection, Gram's staining of exudate frequently reveals multiple morphotypes suggestive of anaerobes. Sometimes these organisms have morphologic characteristics associated with specific species.

The presence of gas in tissues is highly suggestive, but not diagnostic, of anaerobic infection. When cultures of obviously infected sites or purulent material yield no growth, streptococci only, or a single aerobic species (such as *E. coli*) and Gram's staining reveals a mixed flora, the involvement of anaerobes should be suspected; the implication is that the anaerobic microorganisms failed to grow because of inadequate transport and/or culture techniques. Failure of an infection to respond to antibiotics that are not active against anaerobes (e.g., aminoglycosides and—in some circumstances—penicillin, cephalosporins, or tetracyclines) suggests an anaerobic etiology.

TREATMENT Anaerobic Infections

Successful therapy for anaerobic infections requires the administration of a combination of appropriate antibiotics, surgical resection, debridement of devitalized tissues, and drainage either surgically or percutaneously (guided by an imaging technique such as CT, MRI, or ultrasound). Any anatomic breach must be closed promptly, closed spaces drained, tissue compartments decompressed, and an adequate blood supply established. Abscess cavities should be drained as soon as fluctuation or localization occurs.

ANTIBIOTIC THERAPY AND RESISTANCE

Decisions about the treatment of anaerobic infections with antibiotics are usually based on known resistance patterns in certain species, on the likelihood of encountering a given species in the case at hand, and on Gram's stain findings. Antibiotics active against clinically relevant anaerobes can be grouped into four categories on the basis of their predicted activity (Table 69-2). (Nearly all the drugs listed have toxic side effects, which are described in detail in Chap. 36.) In many infections, anaerobes are mixed with coliforms and other facultative organisms. The best therapeutic regimens, therefore, are usually those active against both aerobic and anaerobic bacteria. The choice of empirical antibiotics for the anaerobes in mixed infections can nearly always be made reliably, since patterns of antimicrobial susceptibility are usually predictable (Chap. 36 and Table 69-2).

TABLE 69-2

ANTIMICROBIAL THERAPY FOR INFECTIONS INVOLVING COMMONLY ENCOUNTERED ANAEROBIC GRAM-NEGATIVE RODS

CATEGORY 1 (<2% RESISTANCE)	CATEGORY 2 (<15% RESISTANCE)	CATEGORY 3 (VARIABLE RESISTANCE)	CATEGORY 4 (RESISTANCE)
Carbapenems (imipenem, meropenem, doripenem)	Tigecycline	Cephamycins	Aminoglycosides
Metronidazole[a]	High-dose antipseudomonal penicillins	Clindamycin	Monobactams
β-Lactam/β-lactamase inhibitor combinations (ampicillin/sulbactam, ticarcillin/clavulanic acid, piperacillin/tazobactam)		Penicillin	Trimethoprim-sulfamethoxazole
Chloramphenicol[b]		Cephalosporins	
		Tetracycline	
		Vancomycin	
		Erythromycin	
		Moxifloxacin	

[a]Usually needs to be given in combination with aerobic bacterial coverage. For infections originating below the diaphragm, aerobic gram-negative coverage is essential. For infections from an oral source, aerobic gram-positive coverage is added. Metronidazole also is not active against *Actinomyces*, *Propionibacterium*, or other gram-positive non-spore-forming bacilli (e.g., *Eubacterium*, *Bifidobacterium*) and is unreliable against peptostreptococci.

[b]Chloramphenicol is probably not as effective as other category 1 antimicrobial agents in treating anaerobic infections.

Antibiotic susceptibility testing of anaerobic bacteria has been difficult and controversial. Owing to the slow growth rate of many anaerobes, the lack of standardized testing methods and of clinically relevant standards for resistance, and the generally good results obtained with empirical therapy, there has been limited interest in testing these organisms for antibiotic susceptibility. However, one study of antibiotic-treated patients with *Bacteroides* isolates from blood found mortality rates of 45% among those whose isolates were deemed resistant to the agent used and 16% among those whose isolates were deemed sensitive. These figures suggest that in vitro susceptibility testing should be performed for *Bacteroides* isolates from hospitalized patients with bacteremia and that the results of this testing should guide treatment. In general, cure rates of >80% can be attained among *Bacteroides*-infected patients with appropriate antimicrobial therapy and drainage. Of the drugs active against most clinically relevant anaerobes, metronidazole, β-lactam/β-lactamase inhibitor combinations, and carbapenems are preferred.

Antibiotic resistance in anaerobic bacteria is an increasing problem. Resistance rates vary with the institution and the geographic region. In recent years, the activity of clindamycin, cefoxitin, cefotetan, and moxifloxacin has decreased against *B. fragilis* and related strains (*B. distasonis*, *B. ovatus*, *B. thetaiotaomicron*, *B. uniformis*, *B. vulgatus*). Nearly all organisms in the *B. fragilis* group (>97%) are resistant to penicillin G. Rates of resistance to β-lactam agents among anaerobes other than *Bacteroides* are lower but highly variable. β-Lactam/β-lactamase inhibitor combinations such as ampicillin/sulbactam, ticarcillin/clavulanic acid, and piperacillin/tazobactam are usually a good therapeutic option, but decreased susceptibility in up to 10% of *B. fragilis*–group isolates has been observed in a study from Belgium. Rates of resistance to the cephamycins (cefoxitin and cefotetan) have varied between 8% and 33% in different surveys. Metronidazole is active against gram-negative anaerobes, including the *B. fragilis* group; resistance is rare, but has been reported. Resistance to metronidazole is more common among gram-positive anaerobes, including *P. acnes*, *Actinomyces* species, lactobacilli, and anaerobic streptococci. In the United States, rates of clindamycin resistance among isolates of the *B. fragilis* group increased from 3% in 1982 to 16% in 1996 and 26% in 2000, with figures as high as 44% in some series. Rates of resistance to clindamycin among non-*Bacteroides* anaerobes are much lower (<10%). Carbapenems (ertapenem, doripenem, meropenem, and imipenem) are equally active against anaerobes, with <1% of *B. fragilis* strains showing resistance. Tigecycline is active against some anaerobic bacteria, including *Peptostreptococcus*, *Propionibacterium*, *Prevotella*, *Fusobacterium*, and most *Bacteroides* species. Its efficacy for treatment of intraabdominal infections was comparable to that of imipenem in two phase 2 clinical trials. Low resistance rates (~4%) have been observed. High rates of resistance to moxifloxacin among *Bacteroides* and *Prevotella* species have been reported, ranging up to 32% in a recent survey from Greece.

If a patient fails to respond to one of the category 1 or category 2 drugs (Table 69-2), consideration should be given to alternative therapy and to determination of the resistance patterns among *Bacteroides* isolates. Although in vitro resistance of *Bacteroides* species to chloramphenicol has not been reported, this drug may not be as effective as other category 1 drugs.

INFECTIONS AT SPECIFIC SITES In clinical situations, specific regimens must be tailored to the initial site of infection. The duration of therapy also depends on the infection site; the reader is referred to specific chapters on sites of infection for recommendations.

Infections above the diaphragm usually reflect the orodental flora, which does not include the *B. fragilis* group. β-Lactamase production has been reported in anaerobic

strains that are usually isolated from infections originating above the diaphragm. Up to 60% of clinical isolates classified as *Prevotella* or *Porphyromonas* species, non–*B. fragilis* species of *Bacteroides*, or *Fusobacterium* species reportedly produce β-lactamase; thus all β-lactam drugs (penicillins and cephalosporins) are poor options. Because most of these infections have a mixed etiology that includes microaerophilic and aerobic streptococci, antibiotics that cover both aerobic and anaerobic bacteria are recommended. The recommended regimens include clindamycin, a β-lactam/β-lactamase inhibitor combination, or metronidazole in combination with a drug active against microaerophilic and aerobic streptococci.

Although many oral anaerobic infections and most cases of anaerobic pneumonia still respond to penicillin therapy, some infections due to oral organisms fail to respond to this drug, and in these cases the use of a drug that is effective against penicillin-resistant anaerobes is recommended (Table 69-2). Life-threatening infections involving the anaerobic flora of the mouth, such as space infections of the head and neck, should be treated empirically as if penicillin-resistant anaerobes are involved. Less serious infections involving the oral microflora can be treated with penicillin alone; metronidazole can be added (or clindamycin can be substituted) if the patient responds poorly to penicillin therapy. Bronchoscopy in lung abscess is indicated only to rule out airway obstruction and does not enhance drainage; in any event, it should be delayed until the antimicrobial regimen has begun to affect the disease process so that the procedure does not spread the infection. Surgery is almost never indicated because of the danger of spilling the abscess contents into the lungs.

Chloramphenicol has been used successfully against anaerobic CNS infections at doses of 30–60 mg/kg per day, with the exact dose depending on the severity of illness. However, penicillin G and metronidazole also cross the blood-brain barrier and are bactericidal for many anaerobic organisms (Chap. 31).

Anaerobic infections arising below the diaphragm (e.g., colonic and intraabdominal infections) must be treated specifically with agents active against *Bacteroides* species (Table 69-2). In intraabdominal sepsis (Chap. 25), the use of antibiotics effective against penicillin-resistant anaerobes has clearly reduced the incidence of postoperative infections and serious infectious complications. Specifically, a drug from category 1 (Table 69-2) must be included for broad-spectrum coverage. Recommended doses for commonly used category 1 drugs are given in Table 69-3. Therapy for intraabdominal sepsis must also include drugs active against the gram-negative aerobic flora of the bowel. If the involvement of gram-positive bacteria such as enterococci is suspected, either ampicillin or vancomycin should be added. A meta-analysis of 40 randomized or quasi-randomized controlled trials of 16 antibiotic regimens for secondary peritonitis showed equivalent clinical success for all regimens.

TABLE 69-3

DOSES AND SCHEDULES FOR TREATMENT OF SERIOUS INFECTIONS DUE TO COMMONLY ENCOUNTERED ANAEROBIC GRAM-NEGATIVE RODS

FIRST-LINE THERAPY	DOSE	SCHEDULE[a]
Metronidazole[b]	500 mg	q6h
Ticarcillin/clavulanic acid	3.1 g	q4h
Piperacillin/tazobactam	3.375 g	q6h
Imipenem	0.5 g	q6h
Meropenem	1.0 g	q8h

[a]See disease-specific chapters for recommendations on duration of therapy.
[b]Should generally be used in conjunction with drugs active against aerobic or facultative organisms. Note: All drugs are given by the IV route.

Cases of anaerobic osteomyelitis in which a mixed flora is isolated from a bone biopsy specimen should be treated with a regimen that covers all the isolates. When an anaerobic organism is recognized as a major or sole pathogen infecting a joint, the duration of treatment should be similar to that used for arthritis caused by aerobic bacteria (Chap. 24). Therapy includes the management of underlying disease states, the administration of appropriate antimicrobial agents, temporary joint immobilization, percutaneous drainage of effusions, and (usually) the removal of infected prostheses or internal fixation devices. Surgical drainage and debridement procedures such as sequestrectomy are essential for the removal of necrotic tissue that can sustain anaerobic infections.

The outcome of anaerobic bacteremia is significantly better in patients either initially given or switched to appropriate therapy based on known antibiotic susceptibilities.

FAILURE OF THERAPY Anaerobic infections that fail to respond to treatment or that relapse should be reassessed. Consideration should be given to additional surgical drainage or debridement. Superinfections with resistant gram-negative facultative or aerobic bacteria should be ruled out. The possibility of drug resistance must be entertained; if resistance is involved, repeated cultures may yield the pathogenic organism.

SUPPORTIVE MEASURES Other supportive measures in the management of anaerobic infections include careful attention to fluid and electrolyte balance (since extensive local edema may lead to hypoalbuminemia), hemodynamic support for septic shock, immobilization of infected extremities, maintenance of adequate nutrition during chronic infections by parenteral hyperalimentation, relief of pain, and anticoagulation with heparin for thrombophlebitis. For patients with severe anaerobic infections of soft tissues, hyperbaric oxygen therapy is advocated by some experts, but its value has not been proven in controlled trials.

CHAPTER 70

TUBERCULOSIS

Mario C. Raviglione ■ Richard J. O'Brien

Tuberculosis (TB), which is one of the oldest diseases known to affect humans and is likely to have existed in prehominids, is a major cause of death worldwide. This disease is caused by bacteria of the *Mycobacterium tuberculosis* complex and usually affects the lungs, although other organs are involved in up to one-third of cases. If properly treated, TB caused by drug-susceptible strains is curable in virtually all cases. If untreated, the disease may be fatal within 5 years in 50–65% of cases. Transmission usually takes place through the airborne spread of droplet nuclei produced by patients with infectious pulmonary TB.

ETIOLOGIC AGENT

Mycobacteria belong to the family Mycobacteriaceae and the order Actinomycetales. Of the pathogenic species belonging to the *M. tuberculosis* complex, the most common and important agent of human disease is *M. tuberculosis*. The complex includes *M. bovis* (the bovine tubercle bacillus—characteristically resistant to pyrazinamide, once an important cause of TB transmitted by unpasteurized milk, and currently the cause of a small percentage of cases worldwide), *M. caprae* (related to *M. bovis*), *M. africanum* (isolated from cases in West, Central, and East Africa), *M. microti* (the "vole" bacillus, a less virulent and rarely encountered organism), *M. pinnipedii* (a bacillus infecting seals and sea lions in the Southern Hemisphere and recently isolated from humans), and *M. canetti* (a rare isolate from East African cases that produces unusual smooth colonies on solid media and is considered closely related to a supposed progenitor type).

M. tuberculosis is a rod-shaped, nonspore-forming, thin aerobic bacterium measuring 0.5 μm by 3 μm. Mycobacteria, including *M. tuberculosis*, are often neutral on Gram's staining. However, once stained, the bacilli cannot be decolorized by acid alcohol; this characteristic justifies their classification as acid-fast bacilli (AFB; Fig. 70-1). Acid fastness is due mainly to the organisms' high content of mycolic acids, long-chain cross-linked fatty acids, and other cell-wall lipids. Microorganisms other than mycobacteria that display some acid fastness include species of *Nocardia* and *Rhodococcus*, *Legionella micdadei*, and the protozoa *Isospora* and *Cryptosporidium*. In the mycobacterial cell wall, lipids (e.g., mycolic acids) are linked to underlying arabinogalactan and peptidoglycan. This structure confers very low permeability of the cell wall, thus reducing the effectiveness of most antibiotics. Another molecule in the mycobacterial cell wall, lipoarabinomannan, is involved in the pathogen-host interaction and facilitates the survival of *M. tuberculosis* within macrophages.

The complete genome sequence of *M. tuberculosis* comprises 4043 genes encoding 3993 proteins and 50 genes encoding RNAs; its high guanine-plus-cytosine content (65.6%) is indicative of an aerobic "lifestyle." A large proportion of genes are devoted to

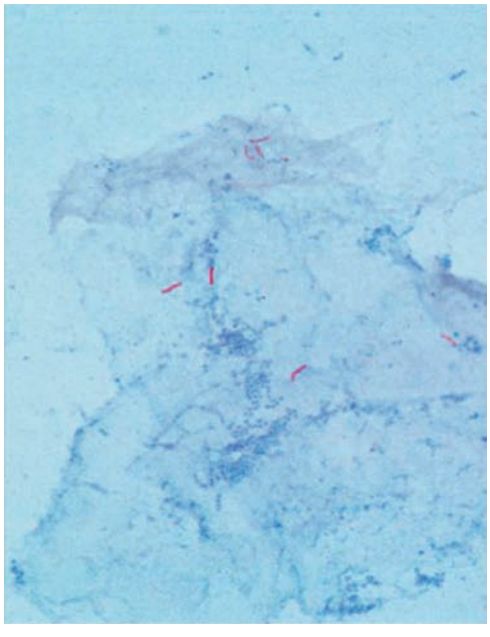


FIGURE 70-1
Acid-fast bacillus smear showing *M. tuberculosis* bacilli. (*Courtesy of the CDC, Atlanta.*)

the production of enzymes involved in cell wall metabolism.

EPIDEMIOLOGY

More than 5.8 million new cases of TB (all forms, both pulmonary and extrapulmonary) were reported to the World Health Organization (WHO) in 2009; 95% of cases were reported from developing countries. However, because of insufficient case detection and incomplete notification, reported cases represent only ~63% (range, 60–67%) of total estimated cases. The WHO estimated that 9.4 million (range, 8.9–9.9 million) new cases of TB occurred worldwide in 2009, 95% of them in developing countries of Asia (5.2 million), Africa (2.8 million), the Middle East (0.7 million), and Latin America (0.3 million). It is further estimated that 1.7 million (range, 1.5–1.9 million) deaths from TB, including 0.4 million among people living with HIV infection, occurred in 2008, 96% of them in developing countries. Estimates of TB incidence rates (per 100,000 population) and numbers of TB-related deaths in 2008 are depicted in **Figs. 70-2** and **70-3**, respectively. During the late 1980s and early 1990s, numbers of reported cases of TB increased in industrialized countries. These increases were related largely to immigration from countries with a high prevalence of TB; infection with HIV; social problems, such as increased urban poverty, homelessness, and drug abuse; and dismantling of TB services. During the past few years, numbers of reported cases have begun to decline again or stabilized in industrialized nations. In the United States, with the implementation of stronger control programs, the decrease resumed in 1993. In 2009, 11,540 cases of TB (3.8 cases per 100,000 population) were reported to the Centers for Disease Control and Prevention (CDC).

In the United States, TB is uncommon among young adults of European descent, who have only rarely been exposed to *M. tuberculosis* infection during recent decades. In contrast, because of a high risk of transmission in the past, the prevalence of *M. tuberculosis* infection is relatively high among elderly whites. Blacks, however, account for the highest proportion of cases (41.4% of 4499) among U.S.-born persons. TB in the United States is also a disease of adult members of the HIV-infected population, the foreign-born population (60% of all cases in 2009), and disadvantaged/marginalized populations. Overall, more TB cases were reported among Hispanics than among other ethnic groups; next in frequency were cases among Asians and blacks, with the highest rates per capita among Asians. Similarly, in Europe, TB has reemerged as an important public health problem, mainly as a result of cases among immigrants from high-prevalence countries and among marginalized populations. In many western European countries, there are currently more cases among foreign-born than native populations.

Recent data on global trends indicate that in 2009 TB incidence was stable or falling in most regions; this trend began in 2004 and appears to continue, with an average annual decline of <1% globally. This global decrease is due largely to a reduction (after a peak in 2004) in sub-Saharan Africa, where incidence had risen steeply since the 1980s as a result of the HIV epidemic and the weakness of health systems and services. In eastern Europe, incidence increased during the 1990s because of deterioration in socioeconomic conditions

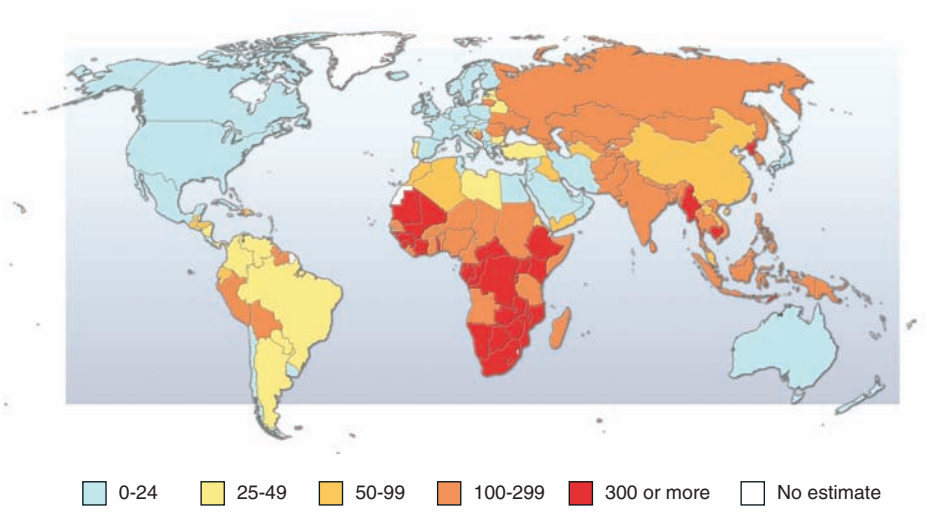


FIGURE 70-2
Estimated tuberculosis incidence rates (per 100,000 population) in 2008. The designations employed and the presentation of material on this map do not imply the expression of any opinion whatsoever on the part of the WHO concerning the legal status of any country, territory, city, or area or of its authorities or concerning the delimitation of its frontiers or boundaries. White lines on maps represent approximate border lines for which there may not yet be full agreement. (*Courtesy of the Stop TB Department, WHO; with permission.*)

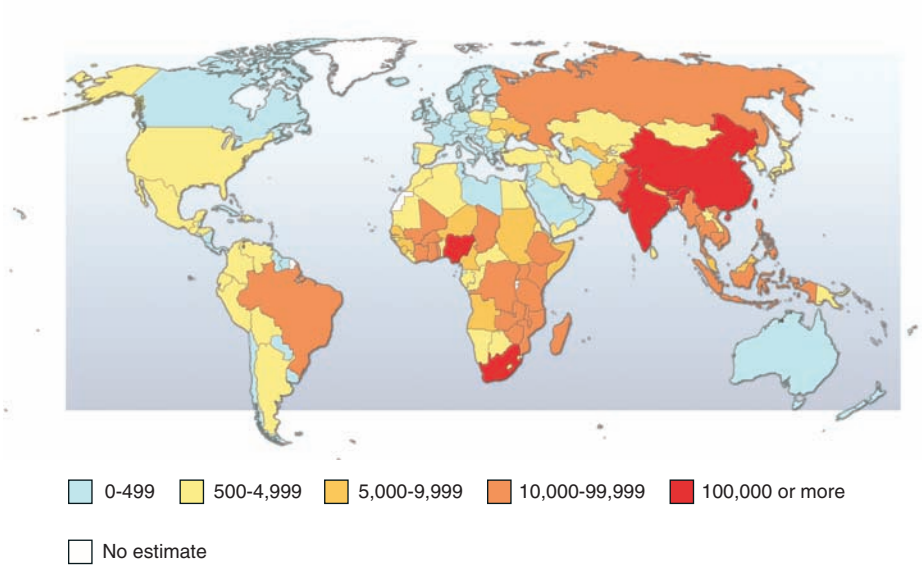


FIGURE 70-3
Estimated numbers of tuberculosis-related deaths in 2008. (*See disclaimer in* Fig. 70-2. *Courtesy of the Stop TB Department, WHO; with permission.*)

and the health care infrastructure; however, after peaking in 2001, incidence has since declined slowly.

Of the 9.4 million new cases estimated for 2009, 12% (1.1 million) were associated with HIV, and 80% of these HIV-associated cases occurred in Africa. An estimated 0.4 million deaths due to HIV-associated TB occurred in 2008. Furthermore, an estimated 440,000 cases of multidrug-resistant TB (MDR-TB), a form of disease caused by bacilli resistant at least to isoniazid and rifampin, may have emerged in 2008. At present, >90% of these cases are not identified because of a lack of culture and drug-susceptibility testing capacity in most settings worldwide. The independent states of the former Soviet Union have reported the highest rates of MDR-TB among new cases (up to 20% or even higher); several provinces of China follow, with peaks of 10%. Overall, 60% of all MDR-TB cases are in India, China, and the Russian Federation. Starting in 2006, 58 countries, including the United States, reported cases of extensively drug-resistant TB (XDR-TB), in which MDR-TB is compounded by additional resistance to the most powerful second-line anti-TB drugs (fluoroquinolones and at least one of the injectable drugs amikacin, kanamycin, and capreomycin). Probably ~10% of the MDR-TB cases worldwide are XDR-TB, but the vast majority of XDR cases remain undiagnosed.

FROM EXPOSURE TO INFECTION

M. tuberculosis is most commonly transmitted from a person with infectious pulmonary TB to others by droplet nuclei, which are aerosolized by coughing, sneezing, or speaking. The tiny droplets dry rapidly; the smallest (<5–10 μm in diameter) may remain suspended in the air for several hours and may reach the terminal air passages when inhaled. There may be as many as 3000 infectious nuclei per cough. Other routes of transmission of tubercle bacilli (e.g., through the skin or the placenta) are uncommon and of no epidemiologic significance. The probability of contact with a person who has an infectious form of TB, the intimacy and duration of that contact, the degree of infectiousness of the case, and the shared environment in which the contact takes place are all important determinants of the likelihood of transmission. Several studies of close-contact situations have clearly demonstrated that TB patients whose sputum contains AFB visible by microscopy are the most likely to transmit the infection. The most infectious patients have cavitary pulmonary disease or, much less commonly, laryngeal TB and produce sputum containing as many as 10^5–10^7 AFB/mL. Patients with sputum smear–negative/culture-positive TB are less infectious, although they have been responsible for up to 20% of transmission in some studies in the United States, and those with culture-negative pulmonary TB and extrapulmonary TB are essentially noninfectious. Because persons with both HIV infection and TB are less likely to have cavitations, they may be less infectious than persons without HIV co-infection. Crowding in poorly ventilated rooms is one of the most important factors in the transmission of tubercle bacilli, since it increases the intensity of contact with a case.

In short, the risk of acquiring *M. tuberculosis* infection is determined mainly by exogenous factors. Because of delays in seeking care and in making a diagnosis, it is generally believed that, in high-prevalence settings, up to 20 contacts may be infected by each AFB-positive case before the index case is found to have TB.

FROM INFECTION TO DISEASE

Unlike the risk of acquiring infection with *M. tuberculosis*, the risk of developing disease after being infected depends largely on endogenous factors, such as the

individual's innate immunologic and nonimmunologic defenses and level of function of cell-mediated immunity (CMI). Clinical illness directly following infection is classified as *primary TB* and is common among children in the first few years of life and among immunocompromised persons. Although primary TB may be severe and disseminated, it is not generally associated with high-level transmissibility. When infection is acquired later in life, the chance is greater that the mature immune system will contain it at least temporarily. Dormant bacilli, however, may persist for years before reactivating to produce *secondary* (or *postprimary*) *TB*, which, because of frequent cavitation, is more often infectious than is primary disease. Overall, it is estimated that up to 10% of infected persons will eventually develop active TB in their lifetime, with half of them doing so during the first year after infection. The risk is much higher among HIV-infected persons. Reinfection of a previously infected individual, which is common in areas with high rates of TB transmission, may also favor the development of disease. At the height of the TB resurgence in the United States in the early 1990s, molecular typing and comparison of strains of *M. tuberculosis* suggested that up to one-third of cases of active TB in some inner-city communities were due to recent transmission rather than to reactivation of latent infection. Age is an important determinant of the risk of disease after infection. Among infected persons, the incidence of TB is highest during late adolescence and early adulthood; the reasons are unclear. The incidence among women peaks at 25–34 years of age. In this age group rates among women may be higher than those among men, while at older ages the opposite is true. The risk increases in the elderly, possibly because of waning immunity and comorbidity.

A variety of diseases and conditions favor the development of active TB **(Table 70-1)**. In absolute terms, the most potent risk factor for TB among infected individuals is clearly HIV co-infection, which suppresses cellular immunity. The risk that latent *M. tuberculosis* infection will proceed to active disease is directly related to the patient's degree of immunosuppression. In a study of HIV-infected, tuberculin skin test (TST)–positive persons, this risk varied from 2.6 to 13.3 cases per 100 person-years and increased as the CD4+ T cell count decreased.

TABLE 70-1

RISK FACTORS FOR ACTIVE TUBERCULOSIS AMONG PERSONS WHO HAVE BEEN INFECTED WITH TUBERCLE BACILLI

FACTOR	RELATIVE RISK/ODDS[a]
Recent infection (<1 year)	12.9
Fibrotic lesions (spontaneously healed)	2–20
Comorbidity	
HIV infection	21–>30
Silicosis	30
Chronic renal failure/hemodialysis	10–25
Diabetes	2–4
IV drug use	10–30
Immunosuppressive treatment	10
Gastrectomy	2–5
Jejunoileal bypass	30–60
Posttransplantation period (renal, cardiac)	20–70
Tobacco smoking	2–3
Malnutrition and severe underweight	2

[a]Old infection = 1.

NATURAL HISTORY OF DISEASE

Studies conducted in various countries before the advent of chemotherapy showed that untreated TB is often fatal. About one-third of patients died within 1 year after diagnosis, and more than 50% died within 5 years. The 5-year mortality rate among sputum smear–positive cases was 65%. Of the survivors at 5 years, ~60% had undergone spontaneous remission, while the remainder were still excreting tubercle bacilli. With effective, timely, and proper chemotherapy, patients have a very high chance of being cured. However, improper use of anti-TB drugs, while reducing mortality rates, may also result in large numbers of chronic infectious cases, often with drug-resistant bacilli.

PATHOGENESIS AND IMMUNITY

INFECTION AND MACROPHAGE INVASION

The interaction of *M. tuberculosis* with the human host begins when droplet nuclei containing microorganisms from infectious patients are inhaled. While the majority of inhaled bacilli are trapped in the upper airways and expelled by ciliated mucosal cells, a fraction (usually <10%) reach the alveoli. There, alveolar macrophages that have not yet been activated phagocytize the bacilli. Adhesion of mycobacteria to macrophages results largely from binding of the bacterial cell wall with a variety of macrophage cell-surface molecules, including complement receptors, the mannose receptor, the immunoglobulin GFcγ receptor, and type A scavenger receptors. Phagocytosis is enhanced by complement activation leading to opsonization of bacilli with C3 activation products such as C3b. After a phagosome forms, the survival of *M. tuberculosis* within it seems to depend on reduced acidification due to lack of accumulation of vesicular proton-adenosine triphosphatase. A complex series of events is probably generated by the bacterial cell-wall glycolipid lipoarabinomannan. This glycolipid inhibits the intracellular increase of Ca^{2+}. Thus, the Ca^{2+}/calmodulin pathway (leading to phagosome-lysosome fusion) is impaired, and the bacilli may survive within the phagosomes. The *M. tuberculosis*

phagosome has been found to inhibit the production of phosphatidylinositol 3-phosphate (PI3P). Normally, PI3P earmarks phagosomes for membrane sorting and maturation including phagolysosome formation, which would destroy the bacteria. Bacterial factors have also been found to block the newly identified host defense of autophagy, in which the cell sequesters the phagosome in a double-membrane vesicle (*autophagosome*) that is destined to fuse with lysosomes. If the bacilli are successful in arresting phagosome maturation, then replication begins and the macrophage eventually ruptures and releases its bacillary contents. Other uninfected phagocytic cells are then recruited to continue the infection cycle by ingesting dying macrophages and their bacillary content, thus in turn becoming infected themselves and expanding the infection.

VIRULENCE OF TUBERCLE BACILLI

Since the elucidation of the *M. tuberculosis* genome in 1998, large mutant collections have been generated, and many bacterial genes that contribute to *M. tuberculosis* virulence have been found. Different patterns of virulence defects have been defined in various animal models, predominantly mice but also guinea pigs, rabbits, and nonhuman primates. The *katG* gene encodes for a catalase/peroxidase enzyme that protects against oxidative stress and is required for isoniazid activation and subsequent bactericidal activity. Region of difference 1 (RD1) is a 9.5-kb locus that encodes two key small protein antigens—early secretory antigen-6 (ESAT-6) and culture filtrate protein-10 (CFP-10)—as well as a putative secretion apparatus that may facilitate their egress; the absence of this locus in the vaccine strain *M. bovis* bacille Calmette-Guérin (BCG) has been shown to be a key attenuating mutation. A recent observation in *Mycobacterium marinum*, the validity of which needs to be confirmed in *M. tuberculosis*, showed that a mutation in the RD1 virulence locus encoding the ESX1 secretion system impairs the capacity of apoptotic macrophages to recruit uninfected cells for further rounds of infection. The results are less replication and fewer new granulomas. Mutants lacking key enzymes of bacterial biosynthesis become auxotrophic for the missing substrate and are often totally unable to proliferate in animals; these include the *leuD* and *panCD* mutants, which require leucine and pantothenic acid, respectively. The isocitrate lyase gene *icl1* encodes a key step in the glyoxylate shunt that facilitates bacterial growth on fatty acid substrates; this gene is required for long-term persistence of *M. tuberculosis* infection in mice with chronic TB. *M. tuberculosis* mutants in regulatory genes such as sigma factor C and sigma factor H (*sigC* and *sigH*) are associated with normal bacterial growth in mice, but they fail to elicit full tissue pathology. Finally, the recently identified mycobacterial protein CarD (expressed by the *carD* gene) seems essential for the control of rRNA transcription that is required for replication and persistence in the host cell. Its loss exposes mycobacteria to oxidative stress, starvation, DNA damage, and ultimately sensitivity to killing by a variety of host mutagens and defensive mechanisms.

INNATE RESISTANCE TO INFECTION

Several observations suggest that genetic factors play a key role in innate nonimmune resistance to infection with *M. tuberculosis* and the development of disease. The existence of this resistance, which is polygenic in nature, is suggested by the differing degrees of susceptibility to TB in different populations. In mice, a gene called *Nramp1* (natural resistance–associated macrophage protein 1) plays a regulatory role in resistance/susceptibility to mycobacteria. The human homologue NRAMP1, which maps to chromosome 2q, may play a role in determining susceptibility to TB, as is suggested by a study among West Africans. Recent studies of mouse genetics identified a novel host resistance gene, *ipr1*, that is encoded within the *sst1* locus; *ipr1* encodes an interferon (IFN)-inducible nuclear protein that interacts with other nuclear proteins in macrophages primed with IFNs or infected by *M. tuberculosis*. In addition, polymorphisms in multiple genes, such as those encoding for various histocompatibility leukocyte antigen (HLA) alleles, IFN-γ, T cell growth factor β, interleukin (IL) 10, mannose-binding protein, IFN-γ receptor, Toll-like receptor 2, vitamin D receptor, and IL-1, have been associated with susceptibility to TB.

THE HOST RESPONSE AND GRANULOMA FORMATION

In the initial stage of host-bacterium interaction, prior to the onset of an acquired CMI response, *M. tuberculosis* undergoes a period of extensive growth within naïve unactivated macrophages, and additional naïve macrophages are recruited to the early granuloma. Studies suggest that *M. tuberculosis* uses a specific virulence mechanism to subvert host cellular signaling and to elicit an early proinflammatory response that promotes granuloma expansion and bacterial growth during this key early phase. A recent study of *M. marinum* infection in zebrafish has delineated the likely molecular mechanism by which mycobacteria induce granuloma formation. The mycobacterial protein ESAT-6 induces secretion of matrix metalloproteinase 9 (MMP9) by nearby epithelial cells that are in contact with infected macrophages. MMP9 in turn stimulates recruitment of naïve macrophages, thus inducing granuloma maturation and bacterial growth. Disruption of MMP9 function results in reduced bacterial growth. Another study has shown that *M. tuberculosis*–derived cyclic AMP is secreted from the phagosome into host macrophages, subverting the cell's signal transduction pathways and stimulating an elevation in the secretion of tumor necrosis factor α (TNF-α) and further proinflammatory cell recruitment. Ultimately, the chemoattractants and bacterial products released during the repeated rounds of cell lysis and infection of newly arriving macrophages

enable dendritic cells to access bacilli; these cells migrate to the draining lymph nodes and present mycobacterial antigens to T lymphocytes. At this point, the development of CMI and humoral immunity begins. These initial stages of infection are usually asymptomatic.

About 2–4 weeks after infection, two host responses to *M. tuberculosis* develop: a macrophage-activating CMI response and a tissue-damaging response. The *macrophage-activating response* is a T cell–mediated phenomenon resulting in the activation of macrophages that are capable of killing and digesting tubercle bacilli. The *tissue-damaging response* is the result of a delayed-type hypersensitivity (DTH) reaction to various bacillary antigens; it destroys unactivated macrophages that contain multiplying bacilli but also causes caseous necrosis of the involved tissues (see next). Although both of these responses can inhibit mycobacterial growth, it is the balance between the two that determines the form of TB that will develop subsequently.

With the development of specific immunity and the accumulation of large numbers of activated macrophages at the site of the primary lesion, granulomatous lesions (tubercles) are formed. These lesions consist of accumulations of lymphocytes and activated macrophages that evolve toward epithelioid and giant cell morphologies. Initially, the tissue-damaging response can limit mycobacterial growth within macrophages. As stated earlier, this response, mediated by various bacterial products, not only destroys macrophages but also produces early solid necrosis in the center of the tubercle. Although *M. tuberculosis* can survive, its growth is inhibited within this necrotic environment by low oxygen tension and low pH. At this point, some lesions may heal by fibrosis, with subsequent calcification, whereas inflammation and necrosis occur in other lesions. Some observations have challenged the traditional view that any encounter between mycobacteria and macrophages results in chronic infection. It is possible that an immune response capable of eradicating early infection may sometimes develop as a consequence, for instance, of disabling mutations in mycobacterial genomes rendering their replication ineffective.

MACROPHAGE-ACTIVATING RESPONSE

CMI is critical at this early stage. In the majority of infected individuals, local macrophages are activated when bacillary antigens processed by macrophages stimulate T lymphocytes to release a variety of lymphokines. These activated macrophages aggregate around the lesion's center and effectively neutralize tubercle bacilli without causing further tissue destruction. In the central part of the lesion, the necrotic material resembles soft cheese (*caseous necrosis*)—a phenomenon that may also be observed in other conditions, such as neoplasms. Even when healing takes place, viable bacilli may remain dormant within macrophages or in the necrotic material for many years. These "healed" lesions in the lung parenchyma and hilar lymph nodes may later undergo calcification.

DELAYED-TYPE HYPERSENSITIVITY

In a minority of cases, the macrophage-activating response is weak, and mycobacterial growth can be inhibited only by intensified DTH reactions, which lead to lung tissue destruction. The lesion tends to enlarge further, and the surrounding tissue is progressively damaged. At the center of the lesion, the caseous material liquefies. Bronchial walls as well as blood vessels are invaded and destroyed, and cavities are formed. The liquefied caseous material, containing large numbers of bacilli, is drained through bronchi. Within the cavity, tubercle bacilli multiply, spill into the airways, and are discharged into the environment through expiratory maneuvers such as coughing and talking. In the early stages of infection, bacilli are usually transported by macrophages to regional lymph nodes, from which they gain access to the central venous return; from there they reseed the lungs and may also disseminate beyond the pulmonary vasculature throughout the body via the systemic circulation. The resulting extrapulmonary lesions may undergo the same evolution as those in the lungs, although most tend to heal. In young children with poor natural immunity, hematogenous dissemination may result in fatal miliary TB or tuberculous meningitis.

ROLE OF MACROPHAGES AND MONOCYTES

While CMI confers partial protection against *M. tuberculosis*, humoral immunity plays a less well-defined role in protection (although evidence is accumulating on the existence of antibodies to lipoarabinomannan, which may prevent dissemination of infection in children). In the case of CMI, two types of cells are essential: macrophages, which directly phagocytize tubercle bacilli, and T cells (mainly CD4+ T lymphocytes), which induce protection through the production of cytokines, especially IFN-γ. After infection with *M. tuberculosis*, alveolar macrophages secrete various cytokines responsible for a number of events (e.g., the formation of granulomas) as well as systemic effects (e.g., fever and weight loss). Monocytes and macrophages attracted to the site are key components of the immune response. Their primary mechanism is probably related to production of nitric oxide, which has antimycobacterial activity and increases the synthesis of cytokines such as TNF-α and IL-1, which in turn regulate the release of reactive nitrogen intermediates. In addition, macrophages can undergo apoptosis—a defensive mechanism to prevent release of cytokines and bacilli via their sequestration in the apoptotic cell.

ROLE OF T LYMPHOCYTES

Alveolar macrophages, monocytes, and dendritic cells are also critical in processing and presenting antigens to T lymphocytes, primarily CD4+ and CD8+ T cells; the result is the activation and proliferation of CD4+ T lymphocytes, which are crucial to the host's

defense against *M. tuberculosis*. Qualitative and quantitative defects of CD4+ T cells explain the inability of HIV-infected individuals to contain mycobacterial proliferation. Activated CD4+ T lymphocytes can differentiate into cytokine-producing T_H1 or T_H2 cells. T_H1 cells produce IFN-γ—an activator of macrophages and monocytes—and IL-2. T_H2 cells produce IL-4, IL-5, IL-10, and IL-13 and may also promote humoral immunity. The interplay of these various cytokines and their cross-regulation determine the host's response. The role of cytokines in promoting intracellular killing of mycobacteria, however, has not been entirely elucidated. IFN-γ may induce the generation of reactive nitrogen intermediates and regulate genes involved in bactericidal effects. TNF-α also seems to be important. Observations made originally in transgenic knockout mice and more recently in humans suggest that other T cell subsets, especially CD8+ T cells, may play an important role. CD8+ T cells have been associated with protective activities via cytotoxic responses and lysis of infected cells as well as with production of IFN-γ and TNF-α. Finally, natural killer cells act as co-regulators of CD8+ T cell lytic activities, and γ^{δ} T cells are increasingly thought to be involved in protective responses in humans.

MYCOBACTERIAL LIPIDS AND PROTEINS

Lipids have been involved in mycobacterial recognition by the innate immune system, and lipoproteins (such as 19-kDa lipoprotein) have been proven to trigger potent signals through Toll-like receptors present in blood dendritic cells. *M. tuberculosis* possesses various protein antigens. Some are present in the cytoplasm and cell wall; others are secreted. That the latter are more important in eliciting a T lymphocyte response is suggested by experiments documenting the appearance of protective immunity in animals after immunization with live, protein-secreting mycobacteria. Among the antigens that may play a protective role are the 30-kDa (or 85B) and ESAT-6 antigens. Protective immunity is probably the result of reactivity to many different mycobacterial antigens.

SKIN TEST REACTIVITY

Coincident with the appearance of immunity, DTH to *M. tuberculosis* develops. This reactivity is the basis of the TST, which is used primarily for the detection of *M. tuberculosis* infection in persons without symptoms. The cellular mechanisms responsible for TST reactivity are related mainly to previously sensitized CD4+ T lymphocytes, which are attracted to the skin-test site. There, they proliferate and produce cytokines. While DTH is associated with protective immunity (TST-positive persons being less susceptible to a new *M. tuberculosis* infection than TST-negative persons), it by no means guarantees protection against reactivation. In fact, cases of active TB are often accompanied by strongly positive skin-test reactions. There is also evidence of reinfection with a new strain of *M. tuberculosis* in patients previously treated for active disease. This evidence underscores the fact that previous latent or active TB may not confer fully protective immunity.

CLINICAL MANIFESTATIONS

TB is classified as pulmonary, extrapulmonary, or both. Before the advent of HIV infection, ~80% of all new cases of TB were limited to the lungs. However, up to two-thirds of HIV-infected patients with TB may have both pulmonary and extrapulmonary TB or extrapulmonary TB alone.

PULMONARY TB

Pulmonary TB can be conventionally categorized as primary or postprimary (adult-type, secondary). This distinction has been challenged by molecular evidence from TB-endemic areas indicating that a large percentage of cases of adult pulmonary TB result from recent infection (either primary infection or reinfection) and not from reactivation.

Primary disease

Primary pulmonary TB occurs soon after the initial infection with tubercle bacilli. It may be asymptomatic or present with fever and occasionally pleuritic chest pain. In areas of high TB transmission, this form of disease is often seen in children. Because most inspired air is distributed to the middle and lower lung zones, these areas of the lungs are most commonly involved in primary TB. The lesion forming after initial infection (the Ghon focus) is usually peripheral and accompanied by transient hilar or paratracheal lymphadenopathy, which may not be visible on standard chest radiography. Some patients develop erythema nodosum in the legs or phlyctenular conjunctivitis. In the majority of cases, the lesion heals spontaneously and only becomes evident as a small calcified nodule. Pleural reaction overlying a subpleural focus is also common. The Ghon focus, with or without overlying pleural reaction, thickening, and regional lymphadenopathy, is referred to as the *Ghon complex*.

In young children with immature CMI and in persons with impaired immunity (e.g., those with malnutrition or HIV infection), primary pulmonary TB may progress rapidly to clinical illness. The initial lesion increases in size and can evolve in different ways. Pleural effusion, which is found in up to two-thirds of cases, results from the penetration of bacilli into the pleural space from an adjacent subpleural focus. In severe cases, the primary site rapidly enlarges, its central portion undergoes necrosis, and cavitation develops (*progressive primary TB*). TB in young children is almost invariably accompanied by hilar or paratracheal lymphadenopathy due to the spread of bacilli from the lung parenchyma

through lymphatic vessels. Enlarged lymph nodes may compress bronchi, causing total obstruction with distal collapse, partial obstruction with large-airway wheezing, or a ball-valve effect with segmental/lobar hyperinflation. Lymph nodes may also rupture into the airway with development of pneumonia, often including areas of necrosis and cavitation, distal to the obstruction. Bronchiectasis may develop in any segment/lobe damaged by progressive caseating pneumonia. Occult hematogenous dissemination commonly follows primary infection. However, in the absence of a sufficient acquired immune response, which usually contains the infection, disseminated or miliary disease may result **(Fig. 70-4)**. Small granulomatous lesions develop in multiple organs and may cause locally progressive disease or result in tuberculous meningitis; this is a particular concern in very young children and immunocompromised persons (e.g., patients with HIV infection).

Postprimary (adult-type) disease

Also referred to as *reactivation* or *secondary TB*, postprimary TB is probably most accurately termed *adult-type TB*, since it may result from endogenous reactivation of distant latent infection or recent infection (primary infection or reinfection). It is usually localized to the apical and posterior segments of the upper lobes, where the substantially higher mean oxygen tension (compared with that in the lower zones) favors mycobacterial growth. The superior segments of the lower lobes are also more frequently involved. The extent of lung parenchymal involvement varies greatly, from small infiltrates to extensive cavitary disease. With cavity formation, liquefied necrotic contents are ultimately discharged into the airways and may undergo bronchogenic spread, resulting in satellite lesions within the lungs that may in turn undergo cavitation **(Figs. 70-5 and 70-6)**. Massive involvement of pulmonary segments or lobes, with coalescence of lesions, produces caseating pneumonia. While up to one-third of untreated patients reportedly succumb to severe pulmonary TB within a few months after onset (the classic "galloping consumption" of the past), others may undergo a process of spontaneous remission or proceed along a chronic, progressively debilitating course ("consumption" or *phthisis*). Under these circumstances, some pulmonary lesions become fibrotic and may later calcify, but cavities persist in other parts of the lungs. Individuals with such chronic disease continue to discharge tubercle bacilli into the environment. Most patients respond to treatment, with defervescence, decreasing cough, weight gain, and a general improvement in well-being within several weeks.

Early in the course of disease, symptoms and signs are often nonspecific and insidious, consisting mainly of diurnal fever and night sweats due to defervescence, weight loss, anorexia, general malaise, and weakness. However, in up to 90% of cases, cough eventually develops—often initially nonproductive and limited to the morning and subsequently accompanied by the production of purulent sputum, sometimes with blood streaking. Hemoptysis develops in 20–30% of cases, and massive hemoptysis may ensue as a consequence of the erosion of a blood vessel in the wall of a cavity.

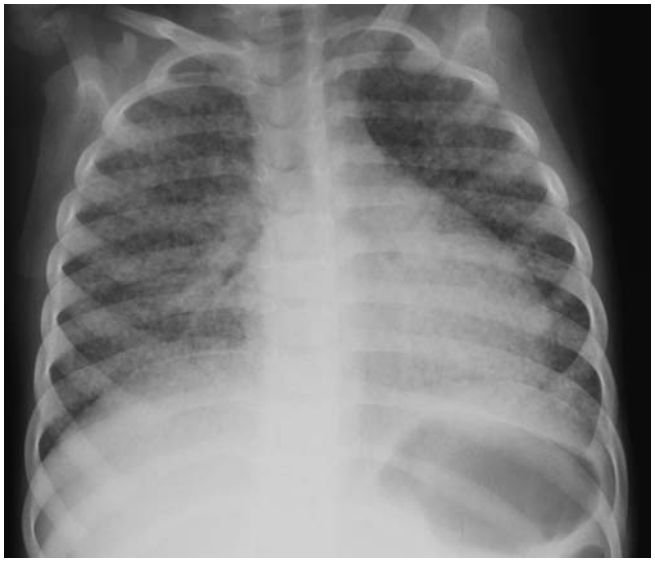


FIGURE 70-4
Chest radiograph showing bilateral miliary (millet-sized) infiltrates in a child. (*Courtesy of Prof. Robert Gie, Department of Paediatrics and Child Health, Stellenbosch University, South Africa; with permission.*)

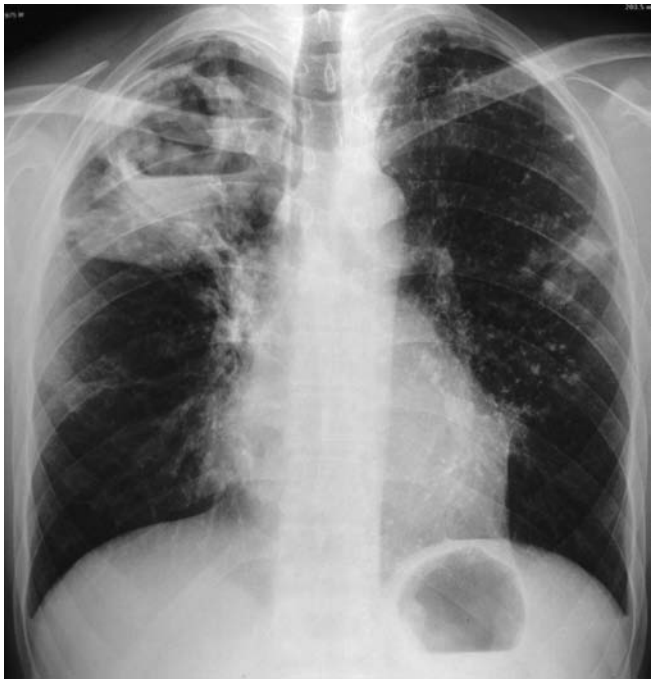


FIGURE 70-5
Chest radiograph showing a right-upper-lobe infiltrate and a cavity with an air-fluid level in a patient with active tuberculosis. (*Courtesy of Dr. Andrea Gori, Department of Infectious Diseases, S. Paolo University Hospital, Milan, Italy; with permission.*)

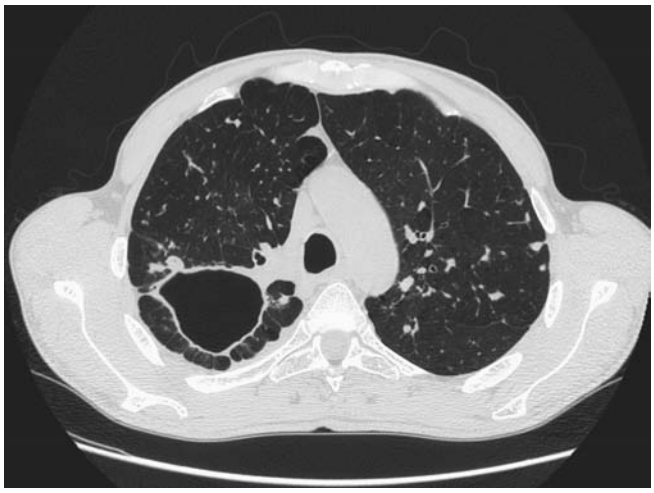


FIGURE 70-6
CT scan showing a large cavity in the right lung of a patient with active tuberculosis. (*Courtesy of Dr. Enrico Girardi, National Institute for Infectious Diseases, Spallanzani Hospital, Rome, Italy; with permission.*)

Hemoptysis, however, may also result from rupture of a dilated vessel in a cavity (*Rasmussen's aneurysm*) or from aspergilloma formation in an old cavity. Pleuritic chest pain sometimes develops in patients with subpleural parenchymal lesions or pleural disease. Extensive disease may produce dyspnea and, in rare instances, adult respiratory distress syndrome. Physical findings are of limited use in pulmonary TB. Many patients have no abnormalities detectable by chest examination, whereas others have detectable rales in the involved areas during inspiration, especially after coughing. Occasionally, rhonchi due to partial bronchial obstruction and classic amphoric breath sounds in areas with large cavities may be heard. Systemic features include fever (often low grade and intermittent) in up to 80% of cases and wasting. Absence of fever, however, does not exclude TB. In some cases, pallor and finger clubbing develop. The most common hematologic findings are mild anemia, leukocytosis, and thrombocytosis with a slightly elevated erythrocyte sedimentation rate and/or C-reactive protein level. None of these findings is consistent or sufficiently accurate for diagnostic purposes. Hyponatremia due to the syndrome of inappropriate secretion of antidiuretic hormone has also been reported.

EXTRAPULMONARY TB

In order of frequency, the extrapulmonary sites most commonly involved in TB are the lymph nodes, pleura, genitourinary tract, bones and joints, meninges, peritoneum, and pericardium. However, virtually all organ systems may be affected. As a result of hematogenous dissemination in HIV-infected individuals, extrapulmonary TB is seen more commonly today than in the past.

Lymph node TB (tuberculous lymphadenitis)

The most common presentation of extrapulmonary TB in both HIV-seronegative and HIV-infected patients (35% in general and >40% of cases in the United States in recent series), lymph node disease is particularly frequent among HIV-infected patients and in children. In the United States, besides children, women (particularly non-Caucasians) seem to be especially susceptible. Once caused mainly by *M. bovis*, tuberculous lymphadenitis is today due largely to *M. tuberculosis*. Lymph node TB presents as painless swelling of the lymph nodes, most commonly at posterior cervical and supraclavicular sites (a condition historically referred to as *scrofula*). Lymph nodes are usually discrete in early disease but develop into a matted nontender mass over time and may result in a fistulous tract draining caseous material. Associated pulmonary disease is present in <50% of cases, and systemic symptoms are uncommon except in HIV-infected patients. The diagnosis is established by fine-needle aspiration biopsy (with a yield of up to 80%) or surgical excision biopsy. Bacteriologic confirmation is achieved in the vast majority of cases, granulomatous lesions with or without visible AFBs are typically seen, and cultures are positive in 70–80% of cases. Among HIV-infected patients, granulomas are less well organized and are frequently absent entirely, but bacterial loads are heavier than in HIV-seronegative patients, with higher yields from microscopy and culture. Differential diagnosis includes a variety of infectious conditions, neoplastic diseases such as lymphomas or metastatic carcinomas, and rare disorders like Kikuchi's disease (necrotizing histiocytic lymphadenitis), Kimura's disease, and Castleman's disease.

Pleural TB

Involvement of the pleura accounts for ~20% of extrapulmonary cases in the United States and elsewhere. Isolated pleural effusion usually reflects recent primary infection, and the collection of fluid in the pleural space represents a hypersensitivity response to mycobacterial antigens. Pleural disease may also result from contiguous parenchymal spread, as in many cases of pleurisy accompanying postprimary disease. Depending on the extent of reactivity, the effusion may be small, remain unnoticed, and resolve spontaneously or may be sufficiently large to cause symptoms such as fever, pleuritic chest pain, and dyspnea. Physical findings are those of pleural effusion: dullness to percussion and absence of breath sounds. A chest radiograph reveals the effusion and, in up to one-third of cases, also shows a parenchymal lesion. Thoracentesis is required to ascertain the nature of the effusion and to differentiate it from manifestations of other etiologies. The fluid is straw colored and at times hemorrhagic; it is an exudate with a protein concentration >50% of that in serum (usually ~4–6 g/dL), a normal to low glucose concentration, a pH of ~7.3 (occasionally <7.2), and detectable white blood cells (usually 500–6000/μL). Neutrophils may predominate in the early stage, but lymphocyte predominance is the typical finding later. Mesothelial cells are generally

rare or absent. AFB are seen on direct smear in only 10–25% of cases, but cultures may be positive for *M. tuberculosis* in 25–75% of cases; positive cultures are more common among postprimary cases. Determination of the pleural concentration of adenosine deaminase (ADA) is a useful screening test: tuberculosis is virtually excluded if the value is very low. Lysozyme is also present in the pleural effusion. Measurement of IFN-γ, either directly or through stimulation of sensitized T cells with mycobacterial antigens, can be helpful. Needle biopsy of the pleura is often required for diagnosis and reveals granulomas and/or yields a positive culture in up to 80% of cases. This form of pleural TB responds rapidly to chemotherapy and may resolve spontaneously. Concurrent glucocorticoid administration may reduce the duration of fever and/or chest pain but is of not proven benefit.

Tuberculous empyema is a less common complication of pulmonary TB. It is usually the result of the rupture of a cavity, with spillage of a large number of organisms into the pleural space. This process may create a bronchopleural fistula with evident air in the pleural space. A chest radiograph shows hydropneumothorax with an air-fluid level. The pleural fluid is purulent and thick and contains large numbers of lymphocytes. Acid-fast smears and mycobacterial cultures are often positive. Surgical drainage is usually required as an adjunct to chemotherapy. Tuberculous empyema may result in severe pleural fibrosis and restrictive lung disease. Removal of the thickened visceral pleura (decortication) is occasionally necessary to improve lung function.

TB of the upper airways

Nearly always a complication of advanced cavitary pulmonary TB, TB of the upper airways may involve the larynx, pharynx, and epiglottis. Symptoms include hoarseness, dysphonia, and dysphagia in addition to chronic productive cough. Findings depend on the site of involvement, and ulcerations may be seen on laryngoscopy. Acid-fast smear of the sputum is often positive, but biopsy may be necessary in some cases to establish the diagnosis. Carcinoma of the larynx may have similar features but is usually painless.

Genitourinary TB

Genitourinary TB, which accounts for ~10–15% of all extrapulmonary cases in the United States and elsewhere, may involve any portion of the genitourinary tract. Local symptoms predominate, and up to 75% of patients have chest radiographic abnormalities suggesting previous or concomitant pulmonary disease. Urinary frequency, dysuria, nocturia, hematuria, and flank or abdominal pain are common presentations. However, patients may be asymptomatic and the disease discovered only after severe destructive lesions of the kidneys have developed. Urinalysis gives abnormal results in 90% of cases, revealing pyuria and hematuria. The documentation of culture-negative pyuria in acidic urine raises the suspicion of TB. IV pyelography, abdominal CT, or MRI **(Fig. 70-7)** may show deformities and obstructions, and calcifications and ureteral strictures are suggestive findings. Culture of three morning urine specimens yields a definitive diagnosis in nearly 90% of cases. Severe ureteral strictures may lead to hydronephrosis and renal damage. Genital TB is diagnosed more commonly in female than in male patients. In female patients, it affects the fallopian tubes and the endometrium and may cause infertility, pelvic pain, and menstrual abnormalities. Diagnosis requires biopsy or culture of specimens obtained by dilatation and curettage. In male patients, genital TB preferentially affects the epididymis, producing a slightly tender mass that may drain externally through a fistulous tract; orchitis and prostatitis may also develop. In almost half of cases of genitourinary TB, urinary tract disease is also present. Genitourinary TB responds well to chemotherapy.

Skeletal TB

In the United States, TB of the bones and joints is responsible for ~10% of extrapulmonary cases. In bone and joint disease, pathogenesis is related to reactivation of hematogenous foci or to spread from adjacent paravertebral lymph nodes. Weight-bearing joints (the spine in 40% of cases, the hips in 13%, and the knees in 10%) are most commonly affected. Spinal TB (Pott's disease or tuberculous spondylitis; **Fig. 70-8**) often involves two or more adjacent vertebral bodies. While the upper thoracic spine is the most common site of spinal TB in children, the lower thoracic and upper lumbar vertebrae

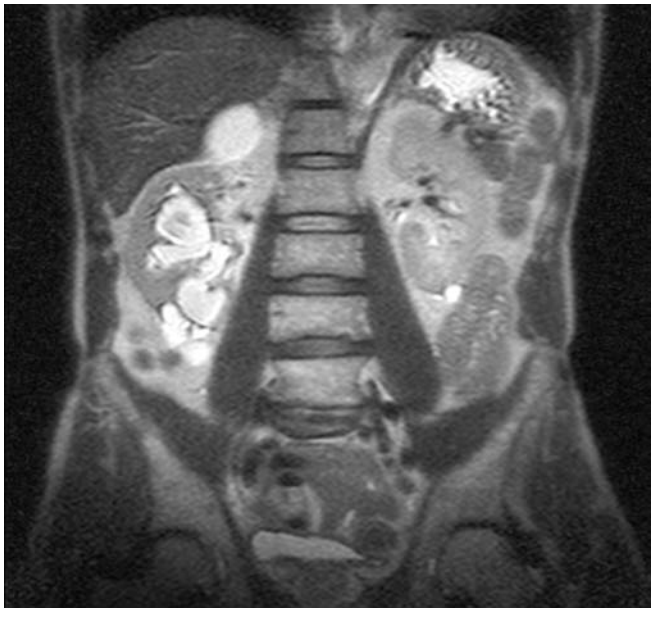


FIGURE 70-7
MRI of culture-confirmed renal tuberculosis. T2-weighted coronary plane: coronal sections showing several renal lesions in both the cortical and the medullary tissues of the right kidney. (*Courtesy of Dr. Alberto Matteelli, Department of Infectious Diseases, University of Brescia, Italy; with permission.*)

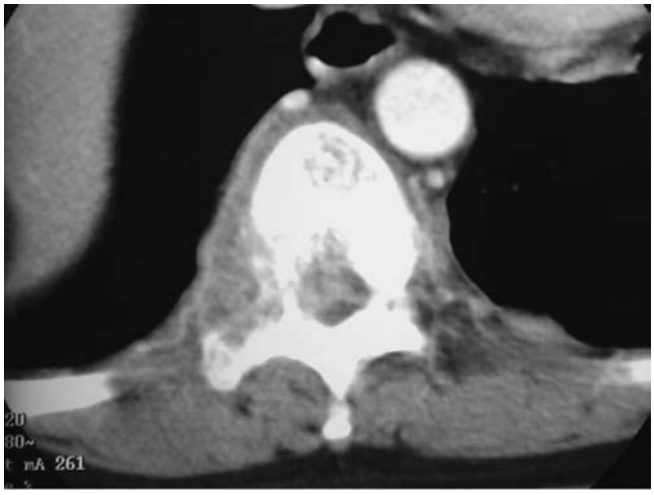


FIGURE 70-8
CT scan demonstrating destruction of the right pedicle of T10 due to Pott's disease. The patient, a 70-year-old Asian woman, presented with back pain and weight loss and had biopsy-proven tuberculosis. (*Courtesy of Charles L. Daley, MD, University of California, San Francisco; with permission.*)

are usually affected in adults. From the anterior superior or inferior angle of the vertebral body, the lesion slowly reaches the adjacent body, later affecting the intervertebral disk. With advanced disease, collapse of vertebral bodies results in kyphosis (*gibbus*). A paravertebral "cold" abscess may also form. In the upper spine, this abscess may track to and penetrate the chest wall, presenting as a soft tissue mass; in the lower spine, it may reach the inguinal ligaments or present as a psoas abscess. CT or MRI reveals the characteristic lesion and suggests its etiology. The differential diagnosis includes tumors and other infections. Pyogenic bacterial osteomyelitis, in particular, involves the disk very early and produces rapid sclerosis. Aspiration of the abscess or bone biopsy confirms the tuberculous etiology, as cultures are usually positive and histologic findings highly typical. A catastrophic complication of Pott's disease is paraplegia, which is usually due to an abscess or a lesion compressing the spinal cord. Paraparesis due to a large abscess is a medical emergency and requires rapid drainage. TB of the hip joints, usually involving the head of the femur, causes pain; TB of the knee produces pain and swelling. If the disease goes unrecognized, the joints may be destroyed. Diagnosis requires examination of the synovial fluid, which is thick in appearance, with a high protein concentration and a variable cell count. Although synovial fluid culture is positive in a high percentage of cases, synovial biopsy and tissue culture may be necessary to establish the diagnosis. Skeletal TB responds to chemotherapy, but severe cases may require surgery.

Tuberculous meningitis and tuberculoma

TB of the central nervous system accounts for ~5% of extrapulmonary cases in the United States. It is seen most often in young children but also develops in adults, especially those infected with HIV. Tuberculous meningitis results from the hematogenous spread of primary or postprimary pulmonary TB or from the rupture of a subependymal tubercle into the subarachnoid space. In more than half of cases, evidence of old pulmonary lesions or a miliary pattern is found on chest radiography. The disease often presents subtly as headache and slight mental changes after a prodrome of weeks of low-grade fever, malaise, anorexia, and irritability. If not recognized, tuberculous meningitis may evolve acutely with severe headache, confusion, lethargy, altered sensorium, and neck rigidity. Typically, the disease evolves over 1–2 weeks, a course longer than that of bacterial meningitis. Since meningeal involvement is pronounced at the base of the brain, paresis of cranial nerves (ocular nerves in particular) is a frequent finding, and the involvement of cerebral arteries may produce focal ischemia. The ultimate evolution is toward coma, with hydrocephalus and intracranial hypertension.

Lumbar puncture is the cornerstone of diagnosis. In general, examination of cerebrospinal fluid (CSF) reveals a high leukocyte count (up to 1000/μL), usually with a predominance of lymphocytes but sometimes with a predominance of neutrophils in the early stage; a protein content of 1–8 g/L (100–800 mg/dL); and a low glucose concentration. However, any of these three parameters can be within the normal range. AFB are seen on direct smear of CSF sediment in up to one-third of cases, but repeated lumbar punctures increase the yield. Culture of CSF is diagnostic in up to 80% of cases and remains the gold standard. Polymerase chain reaction (PCR) has a sensitivity of up to 80%, but rates of false-positivity reach 10%. Imaging studies (CT and MRI) may show hydrocephalus and abnormal enhancement of basal cisterns or ependyma. If unrecognized, tuberculous meningitis is uniformly fatal. This disease responds to chemotherapy; however, neurologic sequelae are documented in 25% of treated cases, in most of which the diagnosis has been delayed. Clinical trials have demonstrated that patients given adjunctive glucocorticoids may experience faster resolution of CSF abnormalities and elevated CSF pressure. In one study, adjunctive dexamethasone (0.4 mg/kg per day given IV and tapering by 0.1 mg/kg per week until the fourth week, when 0.1 mg/kg per day was administered; followed by 4 mg/d given by mouth and tapering by 1 mg per week until the fourth week, when 1 mg/d was administered) significantly enhanced the chances of survival among persons >14 years of age but did not reduce the frequency of neurologic sequelae.

Tuberculoma, an uncommon manifestation of central nervous system TB, presents as one or more space-occupying lesions and usually causes seizures and focal signs. CT or MRI reveals contrast-enhanced ring lesions, but biopsy is necessary to establish the diagnosis.

Gastrointestinal TB

Gastrointestinal TB is uncommon, making up 3.5% of extrapulmonary cases in the United States. Various

pathogenetic mechanisms are involved: swallowing of sputum with direct seeding, hematogenous spread, or (largely in developing areas) ingestion of milk from cows affected by bovine TB. Although any portion of the gastrointestinal tract may be affected, the terminal ileum and the cecum are the sites most commonly involved. Abdominal pain (at times similar to that associated with appendicitis) and swelling, obstruction, hematochezia, and a palpable mass in the abdomen are common findings at presentation. Fever, weight loss, anorexia, and night sweats are also common. With intestinal-wall involvement, ulcerations and fistulae may simulate Crohn's disease; the differential diagnosis with this entity is always difficult. Anal fistulae should prompt an evaluation for rectal TB. As surgery is required in most cases, the diagnosis can be established by histologic examination and culture of specimens obtained intraoperatively.

Tuberculous peritonitis follows either the direct spread of tubercle bacilli from ruptured lymph nodes and intraabdominal organs (e.g., genital TB in women) or hematogenous seeding. Nonspecific abdominal pain, fever, and ascites should raise the suspicion of tuberculous peritonitis. The coexistence of cirrhosis in patients with tuberculous peritonitis complicates the diagnosis. In tuberculous peritonitis, paracentesis reveals an exudative fluid with a high protein content and leukocytosis that is usually lymphocytic (although neutrophils occasionally predominate). The yield of direct smear and culture is relatively low; culture of a large volume of ascitic fluid can increase the yield, but peritoneal biopsy (with a specimen best obtained by laparoscopy) is often needed to establish the diagnosis.

Pericardial TB (tuberculous pericarditis)

Due either to direct extension from adjacent mediastinal or hilar lymph nodes or to hematogenous spread, pericardial TB has often been a disease of the elderly in countries with low TB prevalence. However, it also develops frequently in HIV-infected patients. Case-fatality rates are as high as 40% in some series. The onset may be subacute, although an acute presentation, with dyspnea, fever, dull retrosternal pain, and a pericardial friction rub, is possible. An effusion eventually develops in many cases; cardiovascular symptoms and signs of cardiac tamponade may ultimately appear (Chap. 21). In the presence of effusion, TB must be suspected if the patient belongs to a high-risk population (HIV-infected, originating in a high-prevalence country); if there is evidence of previous TB in other organs; or if echocardiography, CT, or MRI shows effusion and thickness across the pericardial space. A definitive diagnosis can be obtained by pericardiocentesis under echocardiographic guidance. The pericardial fluid must be submitted for biochemical, cytologic, and microbiologic study. The effusion is exudative in nature, with a high count of lymphocytes and monocytes. Hemorrhagic effusion is common. Direct smear examination is very rarely positive. Culture of pericardial fluid reveals *M. tuberculosis* in up to two-thirds of cases, while pericardial biopsy has a higher yield. High levels of ADA, lysozyme, and IFN-γ may suggest a tuberculous etiology. PCR may also be useful.

Without treatment, pericardial TB is usually fatal. Even with treatment, complications may develop, including chronic constrictive pericarditis with thickening of the pericardium, fibrosis, and sometimes calcification, which may be visible on a chest radiograph. Systematic reviews and meta-analyses show that adjunctive glucocorticoid treatment remains controversial with no conclusive evidence of benefits for all principal outcomes of pericarditis—i.e., no significant impact on resolution of effusion, no significant difference in functional status after treatment, and no significant reduction in the frequency of development of constriction or death. However, in HIV-infected patients, glucocorticoids do improve functional status after treatment.

Caused by direct extension from the pericardium or through retrograde lymphatic extension from affected mediastinal lymph nodes, tuberculous myocarditis is an extremely rare disease. Usually it is fatal and is diagnosed post-mortem.

Miliary or disseminated TB

Miliary TB is due to hematogenous spread of tubercle bacilli. Although in children it is often the consequence of primary infection, in adults it may be due to either recent infection or reactivation of old disseminated foci. The lesions are usually yellowish granulomas 1–2 mm in diameter that resemble millet seeds (thus the term *miliary*, coined by nineteenth-century pathologists). Clinical manifestations are nonspecific and protean, depending on the predominant site of involvement. Fever, night sweats, anorexia, weakness, and weight loss are presenting symptoms in the majority of cases. At times, patients have a cough and other respiratory symptoms due to pulmonary involvement as well as abdominal symptoms. Physical findings include hepatomegaly, splenomegaly, and lymphadenopathy. Eye examination may reveal choroidal tubercles, which are pathognomonic of miliary TB, in up to 30% of cases. Meningismus occurs in <10% of cases. A high index of suspicion is required for the diagnosis of miliary TB. Frequently, chest radiography (Fig. 70-4) reveals a miliary reticulonodular pattern (more easily seen on underpenetrated film), although no radiographic abnormality may be evident early in the course and among HIV-infected patients. Other radiologic findings include large infiltrates, interstitial infiltrates (especially in HIV-infected patients), and pleural effusion. Sputum smear microscopy is negative in 80% of cases. Various hematologic abnormalities may be seen, including anemia with leukopenia, lymphopenia, neutrophilic leukocytosis and leukemoid reactions, and polycythemia. Disseminated intravascular coagulation has been reported. Elevation of alkaline phosphatase levels and other abnormal values in liver function tests are detected in patients with severe hepatic involvement. The TST may be negative in up to half of cases, but reactivity

may be restored during chemotherapy. Bronchoalveolar lavage and transbronchial biopsy are more likely to provide bacteriologic confirmation, and granulomas are evident in liver or bone-marrow biopsy specimens from many patients. If it goes unrecognized, miliary TB is lethal; with proper early treatment, however, it is amenable to cure. Glucocorticoid therapy has not proved beneficial.

A rare presentation seen in the elderly is *cryptic miliary TB* that has a chronic course characterized by mild intermittent fever, anemia, and—ultimately—meningeal involvement preceding death. An acute septicemic form, *nonreactive miliary TB*, occurs very rarely and is due to massive hematogenous dissemination of tubercle bacilli. Pancytopenia is common in this form of disease, which is rapidly fatal. At postmortem examination, multiple necrotic but nongranulomatous ("nonreactive") lesions are detected.

Less common extrapulmonary forms

TB may cause chorioretinitis, uveitis, panophthalmitis, and painful hypersensitivity-related phlyctenular conjunctivitis. Tuberculous otitis is rare and presents as hearing loss, otorrhea, and tympanic membrane perforation. In the nasopharynx, TB may simulate granulomatosis with polyangiitis. Cutaneous manifestations of TB include primary infection due to direct inoculation, abscesses and chronic ulcers, scrofuloderma, lupus vulgaris (a smoldering disease with nodules, plaques, and fissures), miliary lesions, and erythema nodosum. Tuberculous mastitis results from retrograde lymphatic spread, often from the axillary lymph nodes. Adrenal TB is a manifestation of disseminated disease presenting rarely as adrenal insufficiency. Finally, congenital TB results from transplacental spread of tubercle bacilli to the fetus or from ingestion of contaminated amniotic fluid. This rare disease affects the liver, spleen, lymph nodes, and various other organs.

HIV-associated TB

(See also Chap. 93) TB is one of the most common diseases among HIV-infected persons worldwide and a major cause of death. In some African countries, the rate of HIV infection among TB patients reaches 70–80% in certain urban settings. A person with a positive TST who acquires HIV infection has a 3–13% annual risk of developing active TB. A new TB infection acquired by an HIV-infected individual may evolve to active disease in a matter of weeks rather than months or years. TB can appear at any stage of HIV infection, and its presentation varies with the stage. When CMI is only partially compromised, pulmonary TB presents in a typical manner (Figs. 70-4 and 70-5), with upper-lobe infiltrates and cavitation and without significant lymphadenopathy or pleural effusion. In late stages of HIV infection, a primary TB–like pattern, with diffuse interstitial or miliary infiltrates, little or no cavitation, and intrathoracic lymphadenopathy, is more common. However, these forms are becoming less common because of the expanded use of antiretroviral treatment (ART). Overall, sputum smears may be positive less frequently among TB patients with HIV infection than among those without; thus, the diagnosis of TB may be unusually difficult, especially in view of the variety of HIV-related pulmonary conditions mimicking TB. Extrapulmonary TB is common among HIV-infected patients. In various series, extrapulmonary TB—alone or in association with pulmonary disease—has been documented in 40–60% of all cases in HIV-co-infected individuals. The most common forms are lymphatic, disseminated, pleural, and pericardial. Mycobacteremia and meningitis are also frequent, particularly in advanced HIV disease. The diagnosis of TB in HIV-infected patients may be difficult not only because of the increased frequency of sputum-smear negativity (up to 40% in culture-proven pulmonary cases) but also because of atypical radiographic findings, a lack of classic granuloma formation in the late stages, and a negative TST. Delays in treatment may prove fatal.

Exacerbations in systemic or respiratory symptoms, signs, and laboratory or radiographic manifestations of TB—termed the *immune reconstitution inflammatory syndrome* (IRIS)—have been associated with the administration of ART. Usually occurring 1–3 months after initiation of ART, IRIS is more common among patients with advanced immunosuppression and extrapulmonary TB. "Unmasking IRIS" may also develop after the initiation of ART in patients with undiagnosed subclinical TB. The presumed pathogenesis of IRIS is an immune response that is elicited by antigens released as bacilli are killed during effective chemotherapy and that is temporally associated with improving immune function. The first priority in the management of a possible case of IRIS is to ensure that the clinical syndrome does not represent a failure of TB treatment or the development of another infection. Mild paradoxical reactions can be managed with symptom-based treatment. Glucocorticoids have been used for more severe reactions, although their use in this setting has not been formally evaluated in clinical trials.

Recommendations for the prevention and treatment of TB in HIV-infected individuals are provided next.

DIAGNOSIS

The key to the diagnosis of TB is a high index of suspicion. Diagnosis is not difficult with a high-risk patient—e.g., a homeless alcoholic who presents with typical symptoms and a classic chest radiograph showing upper-lobe infiltrates with cavities (Fig. 70-5). On the other hand, the diagnosis can easily be missed in an elderly nursing home resident or a teenager with a focal infiltrate. Often, the diagnosis is first entertained

when the chest radiograph of a patient being evaluated for respiratory symptoms is abnormal. If the patient has no complicating medical conditions that cause immunosuppression, the chest radiograph may show typical upper-lobe infiltrates with cavitation (Fig. 70-5). The longer the delay between the onset of symptoms and the diagnosis, the more likely is the finding of cavitary disease. In contrast, immunosuppressed patients, including those with HIV infection, may have "atypical" findings on chest radiography—e.g., lower-zone infiltrates without cavity formation.

AFB MICROSCOPY

A presumptive diagnosis is commonly based on the finding of AFB on microscopic examination of a diagnostic specimen, such as a smear of expectorated sputum or of tissue (e.g., a lymph node biopsy). Although inexpensive, AFB microscopy has relatively low sensitivity (40–60%) in culture-confirmed cases of pulmonary TB. The traditional method—light microscopy of specimens stained with Ziehl-Neelsen basic fuchsin dyes—is nevertheless satisfactory, although time-consuming. Most modern laboratories processing large numbers of diagnostic specimens use auramine-rhodamine staining and fluorescence microscopy. Less expensive light-emitting diode (LED) fluorescence microscopes are now available and should, over time, replace conventional light and fluorescence microscopes, especially facilitating the use of this technology in developing countries. For patients with suspected pulmonary TB, it has been recommended that two or three sputum specimens, preferably collected early in the morning, should be submitted to the laboratory for AFB smear and mycobacterial culture. Recent reviews have emphasized that two specimens collected on the same visit may be as effective as three. If tissue is obtained, it is critical that the portion of the specimen intended for culture not be put in formaldehyde. The use of AFB microscopy on urine or gastric lavage fluid is limited by the presence of commensal mycobacteria that can cause false-positive results.

MYCOBACTERIAL CULTURE

Definitive diagnosis depends on the isolation and identification of *M. tuberculosis* from a clinical specimen or the identification of specific sequences of DNA in a nucleic acid amplification test (see next). Specimens may be inoculated onto egg- or agar-based medium (e.g., Löwenstein-Jensen or Middlebrook 7H10) and incubated at 37°C (under 5% CO_2 for Middlebrook medium). Because most species of mycobacteria, including *M. tuberculosis*, grow slowly, 4–8 weeks may be required before growth is detected. Although *M. tuberculosis* may be identified presumptively on the basis of growth time and colony pigmentation and morphology, a variety of biochemical tests have traditionally been used to speciate mycobacterial isolates. In modern, well-equipped laboratories, the use of liquid culture for isolation and species identification by molecular methods or high-pressure liquid chromatography of mycolic acids has replaced isolation on solid media and identification by biochemical tests. A low-cost, rapid immunochromatographic lateral flow assay based on detection of MTP64 antigen may also be used for species identification of *M. tuberculosis* complex in culture isolates. These new methods, which should be introduced rapidly in developing countries, have decreased the time required for bacteriologic confirmation of TB to 2–3 weeks.

NUCLEIC ACID AMPLIFICATION

Several test systems based on amplification of mycobacterial nucleic acid are available. These systems permit the diagnosis of TB in as little as several hours, with high specificity and sensitivity approaching that of culture. These tests are most useful for the rapid confirmation of TB in persons with AFB-positive specimens but also have utility for the diagnosis of AFB-negative pulmonary and extrapulmonary TB. In settings where these tests are available, nucleic acid amplification testing should be performed on at least one respiratory specimen from patients being evaluated for suspected pulmonary TB.

DRUG SUSCEPTIBILITY TESTING

The initial isolate of *M. tuberculosis* should be tested for susceptibility to isoniazid and rifampin to detect MDR-TB, particularly if one or more risk factors for drug resistance are identified or the patient either fails to respond to initial therapy or has a relapse after the completion of treatment (see "Treatment Failure and Relapse," later). In addition, expanded susceptibility testing for second-line anti-TB drugs (especially the fluoroquinolones and the injectable drugs) is mandatory when MDR-TB is found. Susceptibility testing may be conducted directly (with the clinical specimen) or indirectly (with mycobacterial cultures) on solid or liquid medium. Results are obtained rapidly by direct susceptibility testing on liquid medium, with an average reporting time of 3 weeks. With indirect testing on solid medium, results may be unavailable for ≥8 weeks. Molecular methods for the rapid identification of genetic mutations known to be associated with resistance to rifampin and isoniazid (such as the line probe assays) have been developed and are being widely implemented for screening patients at increased risk of drug-resistant TB. Until the capacity for molecular testing is developed, a few noncommercial culture and drug-susceptibility testing methods (e.g., microscopically observed drug susceptibility, nitrate reductase assays, and colorimetric redox indicator assays) may be useful in resource-limited settings. Their use is limited to national reference laboratories with proven proficiency and adequate external quality control.

RADIOGRAPHIC PROCEDURES

As noted earlier, the initial suspicion of pulmonary TB is often based on abnormal chest radiographic findings in a patient with respiratory symptoms. Although the

"classic" picture is that of upper-lobe disease with infiltrates and cavities (Fig. 70-5), virtually any radiographic pattern—from a normal film or a solitary pulmonary nodule to diffuse alveolar infiltrates in a patient with adult respiratory distress syndrome—may be seen. In the era of AIDS, no radiographic pattern can be considered pathognomonic. CT (Fig. 70-6) may be useful in interpreting questionable findings on plain chest radiography and may be helpful in diagnosing some forms of extrapulmonary TB (e.g., Pott's disease; Fig. 70-8). MRI is useful in the diagnosis of intracranial TB.

ADDITIONAL DIAGNOSTIC PROCEDURES

Other diagnostic tests may be used when pulmonary TB is suspected. Sputum induction by ultrasonic nebulization of hypertonic saline may be useful for patients who cannot produce a sputum specimen spontaneously. Frequently, patients with radiographic abnormalities that are consistent with other diagnoses (e.g., bronchogenic carcinoma) undergo fiberoptic bronchoscopy with bronchial brushings and endobronchial or transbronchial biopsy of the lesion. Bronchoalveolar lavage of a lung segment containing an abnormality may also be performed. In all cases, it is essential that specimens be submitted for AFB smear and mycobacterial culture. For the diagnosis of primary pulmonary TB in children, who often do not expectorate sputum, induced sputum specimens and specimens from early-morning gastric lavage may yield positive cultures.

Invasive diagnostic procedures are indicated for patients with suspected extrapulmonary TB. In addition to testing of specimens from involved sites (e.g., CSF for tuberculous meningitis, pleural fluid and biopsy samples for pleural disease), biopsy and culture of bone marrow and liver tissue have a good diagnostic yield in disseminated (miliary) TB, particularly in HIV-infected patients, who also have a high frequency of positive blood cultures. In some cases, cultures are negative but a clinical diagnosis of TB is supported by consistent epidemiologic evidence (e.g., a history of close contact with an infectious patient), a positive TST or IFN-γ release assay (IGRA; see later), and a compatible clinical and radiographic response to treatment. In the United States and other industrialized countries with low rates of TB, some patients with limited abnormalities on chest radiographs and sputum positive for AFB are infected with nontuberculous mycobacteria, most commonly organisms of the *M. avium* complex or *M. kansasii* (Chap. 72). Factors favoring the diagnosis of nontuberculous mycobacterial disease over TB include an absence of risk factors for TB, a negative TST or IGRA, and underlying chronic pulmonary disease.

Patients with HIV-associated TB pose several diagnostic problems (see "HIV-associated TB," earlier). Moreover, HIV-infected patients with sputum culture–positive, AFB-positive TB may present with a normal chest radiograph. With the advent of ART, the occurrence of disseminated *M. avium* complex disease that can be confused with TB has become much less common.

SEROLOGIC AND OTHER DIAGNOSTIC TESTS FOR ACTIVE TB

A number of serologic tests based on detection of antibodies to a variety of mycobacterial antigens are marketed in developing countries but not in the United States. Careful independent assessments of these tests suggest that they are not useful as diagnostic aids, especially in persons with a low probability of TB. Various methods aimed at detection of mycobacterial antigens in diagnostic specimens are being investigated but are limited at present by low sensitivity. Determinations of ADA and IFN-γ levels in pleural fluid may be useful as adjunct tests in the diagnosis of pleural TB; the utility of these tests in the diagnosis of other forms of extrapulmonary TB (e.g., pericardial, peritoneal, and meningeal) is less clear.

DIAGNOSIS OF LATENT *M. TUBERCULOSIS* INFECTION

Tuberculin skin testing

In 1891, Robert Koch discovered that components of *M. tuberculosis* in a concentrated liquid culture medium, subsequently named "old tuberculin," were capable of eliciting a skin reaction when injected subcutaneously into patients with TB. In 1932, Seibert and Munday purified this product by ammonium sulfate precipitation to produce an active protein fraction known as *tuberculin purified protein derivative* (PPD). In 1941, PPD-S, developed by Seibert and Glenn, was chosen as the international standard. Later, the WHO and UNICEF sponsored large-scale production of a master batch of PPD (RT23) and made it available for general use. The greatest limitation of PPD is its lack of mycobacterial species specificity, a property due to the large number of proteins in this product that are highly conserved in the various species. In addition, subjectivity of the skin-reaction interpretation, deterioration of the product, and batch-to-batch variations limit the usefulness of PPD.

Skin testing with tuberculin-PPD (TST) is most widely used in screening for latent *M. tuberculosis* infection (LTBI). The test is of limited value in the diagnosis of active TB because of its relatively low sensitivity and specificity and its inability to discriminate between latent infection and active disease. False-negative reactions are common in immunosuppressed patients and in those with overwhelming TB. False-positive reactions may be caused by infections with nontuberculous mycobacteria (Chap. 72) and by BCG vaccination.

IFN-γ *release assays*

Two in vitro assays that measure T cell release of IFN-γ in response to stimulation with the highly TB-specific antigens ESAT-6 and CFP-10 are available. The T-SPOT.

TB® (Oxford Immunotec, Oxford, UK) is an enzyme-linked immunospot (ELISpot) assay, and the QuantiFERON-TB Gold® (Cellestis Ltd., Carnegie, Australia) is a whole-blood enzyme-linked immunosorbent assay (ELISA) for measurement of IFN-γ. The QuantiFERON-TB Gold In-Tube assay, which facilitates blood collection and initial incubation, also contains another specific antigen, TB7.7.

IGRAs are more specific than the TST as a result of less cross-reactivity due to BCG vaccination and sensitization by nontuberculous mycobacteria. Although diagnostic sensitivity for LTBI cannot be directly estimated because of the lack of a gold standard, these tests have shown better correlation than the TST with exposure to *M. tuberculosis* in contact investigations in low-incidence settings. However, their performance in high TB- and/or HIV-burden settings has been much more varied. Although limited, direct comparative studies of the two assays in routine practice suggest that the ELISpot has a lower rate of indeterminate results and probably has a higher degree of diagnostic sensitivity than whole-blood ELISA. Other potential advantages of IGRAs include logistical convenience, the need for fewer patient visits to complete testing, the avoidance of somewhat subjective measurements such as skin induration, and the ability to perform serial testing without inducing the boosting phenomenon (a spurious TST conversion due to boosting of reactivity on subsequent TSTs among BCG-vaccinated persons and those infected with other mycobacteria). IGRAs require that blood be drawn from patients and delivered to the laboratory in a timely fashion. Because of high specificity and other potential advantages, IGRAs may replace the TST for LTBI diagnosis in low-incidence, high-income settings where cross-reactivity due to BCG might adversely impact the interpretation and utility of the TST.

A number of national guidelines on the use of IGRAs for LTBI testing have been issued. In the United States, an IGRA is preferred over the TST for most persons over the age of 5 years who are being screened for LTBI. However, for those at high risk of progression to active TB (e.g., HIV-infected persons), either test may be used, or both may be used to optimize sensitivity. Because of the paucity of data on IGRA testing in children, the TST is preferred for LTBI testing of children under age 5. In Canada and some European countries, a two-step approach for those with positive TSTs—i.e., initial TST followed by an IGRA—is recommended. However, a TST may boost an IGRA response if the interval between the two tests exceeds 3 days.

TREATMENT Tuberculosis

The two aims of TB treatment are (1) to interrupt transmission by rendering patients noninfectious and (2) to prevent morbidity and death by curing patients with TB while preventing the emergence of drug resistance. Chemotherapy for TB became possible with the discovery of streptomycin in 1943. Randomized clinical trials clearly indicated that the administration of streptomycin to patients with chronic TB reduced mortality rates and led to cure in the majority of cases. However, monotherapy with streptomycin was frequently associated with the development of resistance to this drug and the attendant failure of treatment. With the introduction into clinical practice of para-aminosalicylic acid (PAS) and isoniazid, it became axiomatic in the early 1950s that cure of TB required the concomitant administration of at least two agents to which the organism was susceptible. Furthermore, early clinical trials demonstrated that a long period of treatment—i.e., 12–24 months—was required to prevent recurrence. The introduction of rifampin (rifampicin) in the early 1970s heralded the era of effective short-course chemotherapy, with a treatment duration of <12 months. The discovery that pyrazinamide, which was first used in the 1950s, augmented the potency of isoniazid/rifampin regimens led to the use of a 6-month course of this triple-drug regimen as standard therapy.

DRUGS Four major drugs are considered the first-line agents for the treatment of TB: isoniazid, rifampin, pyrazinamide, and ethambutol (Table 70-2). These drugs are well absorbed after oral administration, with peak serum levels at 2–4 h and nearly complete elimination within 24 h. These agents are recommended

TABLE 70-2

RECOMMENDED DOSAGE[a] FOR INITIAL TREATMENT OF TUBERCULOSIS IN ADULTS[b]

DRUG	DOSAGE	
	DAILY DOSE	THRICE-WEEKLY DOSE[c]
Isoniazid	5 mg/kg, max 300 mg	10 mg/kg, max 900 mg
Rifampin	10 mg/kg, max 600 mg	10 mg/kg, max 600 mg
Pyrazinamide	25 mg/kg, max 2 g	35 mg/kg, max 3 g
Ethambutol[d]	15 mg/kg	30 mg/kg

[a]The duration of treatment with individual drugs varies by regimen, as detailed in Table 70-3.
[b]Dosages for children are similar, except that some authorities recommend higher doses of isoniazid (10–15 mg/kg daily; 20–30 mg/kg intermittent) and rifampin (10–20 mg/kg).
[c]Dosages for twice-weekly administration are the same for isoniazid and rifampin but are higher for pyrazinamide (50 mg/kg, with a maximum of 4 g/d) and ethambutol (40–50 mg/d).
[d]In certain settings, streptomycin (15 mg/kg daily, with a maximum dose of 1 g; or 25–30 mg/kg thrice weekly, with a maximum dose of 1.5 g) can replace ethambutol in the initial phase of treatment. However, streptomycin is no longer considered a first-line drug by the ATS, the IDSA, or the CDC.
Source: Based on recommendations of the American Thoracic Society, the Infectious Diseases Society of America, and the Centers for Disease Control and Prevention and of the World Health Organization.

on the basis of their bactericidal activity (i.e., their ability to rapidly reduce the number of viable organisms and render patients noninfectious), their sterilizing activity (i.e., their ability to kill all bacilli and thus sterilize the affected tissues, measured in terms of the ability to prevent relapses), and their low rate of induction of drug resistance. Rifapentine and rifabutin, two drugs related to rifampin, are also available in the United States and are useful for selected patients. For a detailed discussion of the drugs used for the treatment of TB, see Chap. 73.

Because of a lower degree of efficacy and a higher degree of intolerability and toxicity, six classes of second-line drugs are generally used only for the treatment of patients with TB resistant to first-line drugs. Included in this group are the injectable aminoglycosides streptomycin (formerly a first-line agent), kanamycin, and amikacin; the injectable polypeptide capreomycin; the oral agents ethionamide, cycloserine, and PAS; and the fluoroquinolone antibiotics. Of the quinolones, third-generation agents are preferred: levofloxacin, gatifloxacin (no longer marketed in the United States because of its severe toxicity), and moxifloxacin. Today amithiozone (thiacetazone) is used very rarely (mainly for MDR-TB) since it is associated with severe and sometimes even fatal skin reactions among HIV-infected patients. Other drugs of unproven efficacy that have been used in the treatment of patients with resistance to most of the first- and second-line agents include clofazimine, amoxicillin/clavulanic acid, clarithromycin, imipenem, and linezolid. Two novel drugs currently under clinical development—OPC-67683, a nitroimidazole; and TMC207, a diarylquinoline—are active against MDR-TB and offer promise in shortening the course of treatment required for drug-susceptible TB as well. Moxifloxacin and gatifloxacin (see earlier) are in late-phase clinical development as 4-month treatment-shortening regimens for drug-susceptible TB.

REGIMENS Standard short-course regimens are divided into an initial, or bactericidal, phase and a continuation, or sterilizing, phase. During the initial phase, the majority of the tubercle bacilli are killed, symptoms resolve, and usually the patient becomes noninfectious. The continuation phase is required to eliminate persisting mycobacteria and prevent relapse. The treatment regimen of choice for virtually all forms of TB in adults consists of a 2-month initial phase of isoniazid, rifampin, pyrazinamide, and ethambutol followed by a 4-month continuation phase of isoniazid and rifampin (Table 70-3). In children, most forms can be safely treated without ethambutol in the intensive phase. Treatment may be given daily throughout the course or intermittently (either three times weekly throughout the course or twice weekly after an initial phase of daily therapy, although the twice-weekly option is not recommended by the WHO). However, HIV-infected patients should receive their initial-phase regimen daily. A continuation phase of once-weekly rifapentine and isoniazid is equally effective for HIV-seronegative patients with noncavitary pulmonary TB who have negative sputum cultures at 2 months. Intermittent treatment is especially useful for patients whose therapy can be directly observed (see later). Patients with cavitary pulmonary TB and delayed sputum-culture conversion (i.e., those who remain culture-positive at 2 months) should have the continuation phase extended by 3 months, for a total course of 9 months. For patients with sputum culture–negative pulmonary TB, the duration of treatment may be reduced to a total of 4 months. To prevent isoniazid-related neuropathy, pyridoxine (10–25 mg/d) should be added to the regimen given to persons at high risk of vitamin B6 deficiency (e.g., alcoholics; malnourished persons; pregnant and lactating women; and patients with conditions such as chronic renal failure, diabetes, and HIV infection, which are also associated with neuropathy). A full course of therapy (completion of treatment) is defined more accurately by the total number of doses taken than by the duration of treatment. Specific recommendations on the required numbers of doses for each of the various treatment regimens have been published jointly by the American Thoracic Society, the Infectious Diseases Society of America, and the CDC. In some developing countries where the ability to ensure compliance with treatment is limited, a continuation-phase regimen of daily isoniazid and ethambutol for 6 months has been used. However, this regimen is associated with a higher rate of relapse and failure, especially among HIV-infected patients, and is no longer recommended by the WHO.

Lack of adherence to treatment is recognized worldwide as the most important impediment to cure. Moreover, the tubercle bacilli infecting patients who do not adhere to the prescribed regimen are likely to become drug resistant. Both patient- and provider-related factors may affect compliance. Patient-related factors include a lack of belief that the illness is significant and/or that treatment will have a beneficial effect; the existence of concomitant medical conditions (notably substance abuse); lack of social support; and poverty, with attendant joblessness and homelessness. Provider-related factors that may promote compliance include the education and encouragement of patients, the offering of convenient clinic hours, and the provision of incentives and enablers such as meals and travel vouchers. In addition to specific measures addressing noncompliance, two other strategic approaches are used: direct observation of treatment and provision of fixed-drug-combination products. Because it is difficult to predict which patients will adhere to the recommended treatment, all patients should have their therapy directly supervised, especially during the initial phase. In the United States, personnel to supervise therapy are usually available through TB control programs of local public health departments. Supervision increases the proportion of patients completing treatment

TABLE 70-3

RECOMMENDED ANTITUBERCULOSIS TREATMENT REGIMENS

	INITIAL PHASE		CONTINUATION PHASE	
INDICATION	**DURATION, MONTHS**	**DRUGS**	**DURATION, MONTHS**	**DRUGS**
New smear- or culture-positive cases	2	HRZE[a,b]	4	HR[a,c,d]
New culture-negative cases	2	HRZE[a]	4	HR[a]
Pregnancy	2	HRE[e]	7	HR
Relapses and treatment default (pending susceptibility testing)	3	HRZES[f]	5	HRE
Failures[g]	—	—	—	—
Resistance (or intolerance) to H	Throughout (6)	RZE[h]		
Resistance (or intolerance) to R	Throughout (12–18)	HZEQ[i]		
Resistance to H + R	Throughout (at least 20 months)	ZEQ + S (or another injectable agent[j])		
Resistance to all first-line drugs	Throughout (at least 20 months)	1 injectable agent[j] + 3 of these 4: ethionamide, cycloserine, Q, PAS		
Intolerance to Z	2	HRE	7	HR

[a]All drugs can be given daily or intermittently (three times weekly throughout). A twice-weekly regimen after 2–8 weeks of daily therapy during the initial phase is sometimes used, although it is not recommended by the WHO.
[b]Streptomycin can be used in place of ethambutol but is no longer considered to be a first-line drug by the ATS/IDSA/CDC.
[c]The continuation phase should be extended to 7 months for patients with cavitary pulmonary tuberculosis who remain sputum culture–positive after the initial phase of treatment.
[d]HIV-negative patients with noncavitary pulmonary tuberculosis who have negative sputum AFB smears after the initial phase of treatment can be given once-weekly rifapentine/isoniazid in the continuation phase.
[e]The 6-month regimen with pyrazinamide can probably be used safely during pregnancy and is recommended by the WHO and the International Union Against Tuberculosis and Lung Disease. If pyrazinamide is not included in the initial treatment regimen, the minimum duration of therapy is 9 months.
[f]Streptomycin should be discontinued after 2 months. Drug susceptibility results will determine the best regimen option.
[g]The regimen is tailored according to the results of drug susceptibility tests. The availability of rapid molecular methods to identify drug resistance allows initiation of a proper regimen at the start of treatment.
[h]A fluoroquinolone may strengthen the regimen for patients with extensive disease.
[i]Streptomycin for the initial 2 months may strengthen the regimen for patients with extensive disease.
[j]Amikacin, kanamycin, or capreomycin. All these agents should be used for at least 6 months and for 4 months after culture conversion. If susceptibility is confirmed, streptomycin could be used as the injectable agent.
Abbreviations: E, ethambutol; H, isoniazid; PAS, para-aminosalicylic acid; Q, a quinolone antibiotic; R, rifampin; S, streptomycin; Z, pyrazinamide.

and greatly lessens the chances of relapse and acquired drug resistance. Fixed-drug-combination products (e.g., isoniazid/rifampin, isoniazid/rifampin/pyrazinamide, and isoniazid/rifampin/pyrazinamide/ethambutol) are available (except, in the United States, for the four-drug fixed drug combination) and are strongly recommended as a means of minimizing the likelihood of prescription error and of the development of drug resistance as the result of monotherapy. In some formulations of these combination products, the bioavailability of rifampin has been found to be substandard. In North America and Europe, regulatory authorities ensure that combination products are of good quality; however, this type of quality assurance cannot be assumed to be operative in less affluent countries. Alternative regimens for patients who exhibit drug intolerance or adverse reactions are listed in Table 70-3. However, severe side effects prompting discontinuation of any of the first-line drugs and use of these alternative regimens are uncommon.

MONITORING TREATMENT RESPONSE AND DRUG TOXICITY Bacteriologic evaluation is essential in monitoring the response to treatment for TB. Patients with pulmonary disease should have their sputum examined monthly until cultures become negative. With the recommended regimen, >80% of patients will have negative sputum cultures at the end of the second

month of treatment. By the end of the third month, virtually all patients should be culture-negative. In some patients, especially those with extensive cavitary disease and large numbers of organisms, AFB smear conversion may lag behind culture conversion. This phenomenon is presumably due to the expectoration and microscopic visualization of dead bacilli. As noted earlier, patients with cavitary disease in whom sputum culture conversion does not occur by 2 months require extended treatment. When a patient's sputum cultures remain positive at ≥3 months, treatment failure and drug resistance or poor adherence to the regimen should be suspected (see later). A sputum specimen should be collected by the end of treatment to document cure. If mycobacterial cultures are not practical, then monitoring by AFB smear examination should be undertaken at 2, 5, and 6 months. Patients whose smears remain positive at 2 months should undergo a repeat examination at 3 months. Smears that are positive after 3 months of treatment when the patient is known to be adherent are indicative of treatment failure and possible drug resistance. Therefore, drug susceptibility testing should be done. Bacteriologic monitoring of patients with extrapulmonary TB is more difficult and often is not feasible. In these cases, the response to treatment must be assessed clinically and radiographically.

Monitoring of the response during chemotherapy by serial chest radiographs is not recommended, as radiographic changes may lag behind bacteriologic response and are not highly sensitive. After the completion of treatment, neither sputum examination nor chest radiography is recommended for routine follow-up purposes. However, a chest radiograph obtained at the end of treatment may be useful for comparative purposes should the patient develop symptoms of recurrent TB months or years later. Patients should be instructed to report promptly for medical assessment should they develop any such symptoms.

During treatment, patients should be monitored for drug toxicity (Table 70-3). The most common adverse reaction of significance is hepatitis. Patients should be carefully educated about the signs and symptoms of drug-induced hepatitis (e.g., dark urine, loss of appetite) and should be instructed to discontinue treatment promptly and see their health care provider should these symptoms occur. Although biochemical monitoring is not routinely recommended, all adult patients should undergo baseline assessment of liver function (e.g., measurement of serum levels of hepatic aminotransferases and serum bilirubin). Older patients, those with concomitant diseases, those with a history of hepatic disease (especially hepatitis C), and those using alcohol daily should be monitored especially closely (i.e., monthly), with repeated measurements of aminotransferases, during the initial phase of treatment. Up to 20% of patients have small increases in aspartate aminotransferase (up to three times the upper limit of normal) that are not accompanied by symptoms and are of no consequence. For patients with symptomatic hepatitis and those with marked (five- to sixfold) elevations in serum levels of aspartate aminotransferase, treatment should be stopped and drugs reintroduced one at a time after liver function has returned to normal. Hypersensitivity reactions usually require the discontinuation of all drugs and rechallenge to determine which agent is the culprit. Because of the variety of regimens available, it is usually not necessary—although it is possible—to desensitize patients. Hyperuricemia and arthralgia caused by pyrazinamide can usually be managed by the administration of acetylsalicylic acid; however, pyrazinamide treatment should be stopped if the patient develops gouty arthritis. Individuals who develop autoimmune thrombocytopenia secondary to rifampin therapy should not receive the drug thereafter. Similarly, the occurrence of optic neuritis with ethambutol is an indication for permanent discontinuation of this drug. Other common manifestations of drug intolerance, such as pruritus and gastrointestinal upset, can generally be managed without the interruption of therapy.

TREATMENT FAILURE AND RELAPSE As stated earlier, treatment failure should be suspected when a patient's sputum smears and/or cultures remain positive after 3 months of treatment. In the management of such patients, it is imperative that the current isolate be tested for susceptibility to first- and second-line agents. Initial molecular testing for rifampin resistance should also be done if the technology is available. When the results of susceptibility testing are expected to become available within a few weeks, changes in the regimen can be postponed until that time. However, if the patient's clinical condition is deteriorating, an earlier change in regimen may be indicated. A cardinal rule in the latter situation is always to add more than one drug at a time to a failing regimen: at least two and preferably three drugs that have never been used and to which the bacilli are likely to be susceptible should be added. The patient may continue to take isoniazid and rifampin along with these new agents pending the results of susceptibility tests.

Patients who experience a recurrence after apparently successful treatment (relapses) are less likely to harbor drug-resistant strains (see next) than are patients in whom treatment has failed. However, if the regimen administered initially does not contain rifampin, the probability of isoniazid resistance is high. Acquired resistance is uncommon among strains from patients who relapse after completing a standard short-course regimen. However, it is prudent to begin the treatment of all patients who have relapsed with all four first-line drugs plus streptomycin, pending the results of susceptibility testing. In less affluent countries and other settings where facilities for culture and drug susceptibility testing are not yet routinely available, the WHO

recommends that a standard regimen with all four first-line drugs plus streptomycin be used in all instances of relapse and treatment default. Patients with treatment failure should receive an empirical regimen, including second-line agents, based on their history of anti-TB treatment and the drug resistance patterns in the population (Table 70-3). Once drug susceptibility testing results are available, the regimen should be adjusted accordingly.

DRUG-RESISTANT TB Strains of *M. tuberculosis* resistant to individual drugs arise by spontaneous point mutations in the mycobacterial genome that occur at low but predictable rates (10^{-7}–10^{-10} for the key drugs). Because there is no cross-resistance among the commonly used drugs, the probability that a strain will be resistant to two drugs is the product of the probabilities of resistance to each drug and thus is low. The development of drug-resistant TB is invariably the result of monotherapy—i.e., the failure of the health care provider to prescribe at least two drugs to which tubercle bacilli are susceptible or of the patient to take properly prescribed therapy. Drug-resistant TB may be either primary or acquired. Primary drug resistance is that which develops in a strain infecting a patient who has not previously been treated. Acquired resistance develops during treatment with an inappropriate regimen. In North America and western Europe, rates of primary resistance are generally low, and isoniazid resistance is most common. In the United States, while rates of primary isoniazid resistance have been stable at ~7–8%, the rate of primary MDR-TB has declined from 2.5% in 1993 to 1% since 2000. Resistance rates are higher among foreign-born and HIV-infected patients. As described earlier, worldwide, MDR-TB is an increasingly serious problem in some regions, especially in the states of the former Soviet Union and in other parts of Asia (Fig. 70-9). Even more serious is the recently described occurrence of virtually untreatable XDR-TB due to MDR strains that are resistant to all fluoroquinolones and to at least one of three second-line injectable agents (amikacin, kanamycin, and capreomycin). Drug-resistant TB can be prevented by adherence to the principles of sound therapy: the inclusion of at least two bactericidal drugs to which the organism is susceptible, the use of fixed-drug-combination products, and the verification that patients complete the prescribed course.

Although the 6-month regimen described in Table 70-3 is generally effective for patients with initial isoniazid-resistant disease, it is prudent to include at least ethambutol and possibly pyrazinamide for the full 6 months. In such cases, isoniazid probably does not contribute to a successful outcome and could be omitted. For patients with extensive disease, a fluoroquinolone may be added. Patients whose isolates exhibit monoresistance to rifampin should receive a regimen containing isoniazid, pyrazinamide, ethambutol, and a fluoroquinolone for 12–18 months. MDR-TB is more difficult to manage than is disease caused by drug-susceptible organisms, especially because resistance to other first-line drugs besides isoniazid and rifampin is common. For treatment of TB due to strains resistant to isoniazid and rifampin, combinations of a fluoroquinolone, ethambutol, pyrazinamide, and streptomycin or, for strains resistant to streptomycin as well, another injectable agent (amikacin, kanamycin, or capreomycin) should be used. For patients with bacilli resistant to all of the first-line agents, cure may be attained with a combination of four second-line drugs,

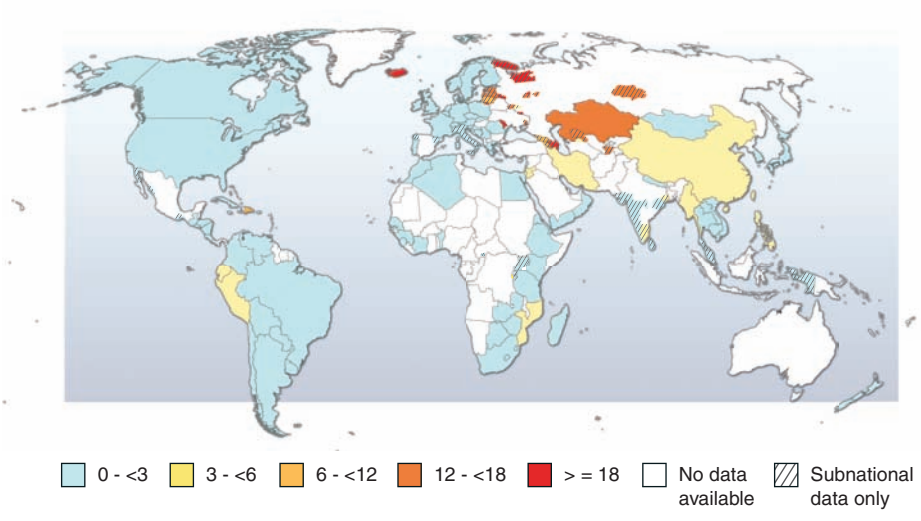


FIGURE 70-9
Percentage of new tuberculosis cases with multidrug resistance in all countries surveyed by the WHO/Union Global Drug Resistance Surveillance Project during 1994–2008. (*See disclaimer in Fig. 70-2. Courtesy of the Stop TB Department, WHO; with permission.*)

including one injectable agent (Table 70-3). Although the optimal duration of treatment is not known, a course of at least 20 months, is recommended. Patients with XDR-TB have fewer treatment options and a much poorer prognosis. However, observational studies have shown that aggressive management of cases comprising early drug-susceptibility testing, rational combination of at least five drugs, readjustment of the regimen, strict directly observed therapy, bacteriologic monitoring, and intensive patient support may result in cure rates of up to 60% and may avert deaths. Table 70-4 describes how to manage patients with XDR-TB. For patients with localized disease and sufficient pulmonary reserve, lobectomy or pneumonectomy may be considered. Because the management of patients with MDR- and XDR-TB is complicated by both social and medical factors, care of these patients is ideally provided in specialized centers or, in their absence, in the context of programs with adequate resources and capacity.

TABLE 70-4

MANAGEMENT GUIDELINES FOR PATIENTS WITH DOCUMENTED OR STRONGLY SUSPECTED XDR-TB

1. Use any first-line oral agents that may be effective.
2. Use an injectable agent to which the strain is susceptible, and consider an extended duration of use (12 months or possibly the whole treatment period). If the strain is resistant to all injectable agents, use of an agent that the patient has not previously received is recommended.[a]
3. Use a later-generation fluoroquinolone, such as moxifloxacin.
4. Use all second-line oral agents (para-aminosalicylic acid, cycloserine, ethionamide, or prothionamide) that have not been used extensively in a previous regimen or any that are likely to be effective.
5. Use two or more of the following drugs of unclear role: clofazimine, amoxicillin/clavulanic acid, clarithromycin, imipenem, linezolid, thiacetazone.
6. Consider treatment with high-dose isoniazid if low-level resistance to this drug is documented.
7. Consider adjuvant surgery if there is localized disease.
8. Enforce strong infection-control measures.
9. Implement strict directly observed therapy and full adherence support as well as comprehensive bacteriologic and clinical monitoring.

[a]This recommendation is made because, while the reproducibility and reliability of susceptibility testing with injectable agents are good, there are few data on the correlation of clinical efficacy with test results. Options with XDR-TB are very limited, and some strains may be affected in vivo by an injectable agent even though they test resistant in vitro.

Source: Adapted from the World Health Organization: Guidelines for the programmatic management of drug-resistant tuberculosis. Emergency update 2008. Geneva, WHO, 2008.

HIV-ASSOCIATED TB In general, the standard treatment regimens are equally efficacious in HIV-negative and HIV-positive patients. However, adverse drug effects may be more pronounced in HIV-infected patients. Three important considerations are relevant to TB treatment in HIV-infected patients: an increased frequency of paradoxical reactions, drug interactions between ART and rifamycins, and development of rifampin monoresistance with widely spaced intermittent treatment. IRIS—i.e., the exacerbation of symptoms and signs of TB—has been described earlier. All HIV-infected TB patients are candidates for ART, and the optimal timing for its initiation is as soon as possible and within the first 8 weeks of anti-TB therapy. Rifampin, a potent inducer of enzymes of the cytochrome P450 system, lowers serum levels of many HIV protease inhibitors and some nonnucleoside reverse transcriptase inhibitors—essential drugs used in ART. In such cases, rifabutin, which has much less enzyme-inducing activity, has been recommended in place of rifampin. However, dosage adjustment for rifabutin and/or the antiretroviral drugs may be necessary. Because recommendations are frequently updated, consultation of the CDC website is advised (*www.cdc.gov/tb*). Several clinical trials have found that patients with HIV-associated TB whose immunosuppression is advanced (CD4+ T cell counts of <100/μL) are prone to treatment failure and relapse with rifampin-resistant organisms when treated with "highly intermittent" (i.e., once- or twice-weekly) rifamycin-containing regimens. Consequently, it is recommended that these patients receive daily therapy for at least the initial phase.

SPECIAL CLINICAL SITUATIONS Although comparative clinical trials of treatment for extrapulmonary TB are limited, the available evidence indicates that most forms of disease can be treated with the 6-month regimen recommended for patients with pulmonary disease. The American Academy of Pediatrics recommends that children with bone and joint TB, tuberculous meningitis, or miliary TB receive 9–12 months of treatment. Treatment for TB may be complicated by underlying medical problems that require special consideration. As a rule, patients with chronic renal failure should not receive aminoglycosides and should receive ethambutol only if serum drug levels can be monitored. Isoniazid, rifampin, and pyrazinamide may be given in the usual doses in cases of mild to moderate renal failure, but the dosages of isoniazid and pyrazinamide should be reduced for all patients with severe renal failure except those undergoing hemodialysis. Patients with hepatic disease pose a special problem because of the hepatotoxicity of isoniazid, rifampin, and pyrazinamide. Patients with severe hepatic disease may be treated with ethambutol, streptomycin, and possibly another drug (e.g., a fluoroquinolone); if required, isoniazid and rifampin may be administered under close supervision. The use of pyrazinamide by patients with liver failure should be avoided. Silicotuberculosis necessitates the extension of therapy by at least 2 months.

The regimen of choice for pregnant women (Table 70-3) is 9 months of treatment with isoniazid and rifampin supplemented by ethambutol for the first 2 months. Although the WHO has recommended routine use of pyrazinamide for pregnant women, this drug has not been recommended in the United States because of insufficient data documenting its safety in pregnancy. Streptomycin is contraindicated because it is known to cause eighth-cranial-nerve damage in the fetus. Treatment for TB is not a contraindication to breast-feeding; most of the drugs administered will be present in small quantities in breast milk, albeit at concentrations far too low to provide any therapeutic or prophylactic benefit to the child.

Medical consultation on difficult-to-manage cases is provided by the CDC Regional Training and Medical Consultation Centers (*www.cdc.gov/tb/education/rtmc/*).

PREVENTION

The best way to prevent TB is to diagnose and isolate infectious cases rapidly and to administer appropriate treatment until patients are rendered noninfectious (usually 2–4 weeks after the start of proper treatment) and the disease is cured. Additional strategies include BCG vaccination and treatment of persons with latent tuberculosis infection who are at high risk of developing active disease.

BCG VACCINATION

BCG was derived from an attenuated strain of *M. bovis* and was first administered to humans in 1921. Many BCG vaccines are available worldwide; all are derived from the original strain, but the vaccines vary in efficacy, ranging from 80% to nil in randomized, placebo-controlled trials. A similar range of efficacy was found in recent observational studies (case-control, historic cohort, and cross-sectional) in areas where infants are vaccinated at birth. These studies also found higher rates of efficacy in the protection of infants and young children from relatively serious forms of TB, such as tuberculous meningitis and miliary TB. BCG vaccine is safe and rarely causes serious complications. The local tissue response begins 2–3 weeks after vaccination, with scar formation and healing within 3 months. Side effects—most commonly, ulceration at the vaccination site and regional lymphadenitis—occur in 1–10% of vaccinated persons. Some vaccine strains have caused osteomyelitis in ~1 case per million doses administered. Disseminated BCG infection ("BCGitis") and death have occurred in 1–10 cases per 10 million doses administered, although this problem is restricted almost exclusively to persons with impaired immunity, such as children with severe combined immunodeficiency syndrome or adults with HIV infection. BCG vaccination induces TST reactivity, which tends to wane with time. The presence or size of TST reactions after vaccination does not predict the degree of protection afforded.

BCG vaccine is recommended for routine use at birth in countries with high TB prevalence. However, because of the low risk of transmission of TB in the United States, the unreliable protection afforded by BCG, and its impact on the TST, the vaccine has never been recommended for general use in the United States. HIV-infected adults and children should not receive BCG vaccine. Moreover, infants whose HIV status is unknown but who have signs and symptoms consistent with HIV infection or who are born to HIV-infected mothers should not receive BCG.

TREATMENT Latent Tuberculosis Infection

Treatment of selected persons with LTBI aims at preventing active disease. This intervention (also called *preventive chemotherapy* or *chemoprophylaxis*) is based on the results of a large number of randomized, placebo-controlled clinical trials demonstrating that a 6- to 12-month course of isoniazid reduces the risk of active TB in infected people by up to 90%. Analysis of available data indicates that the optimal duration of treatment is 9–10 months. In the absence of reinfection, the protective effect is believed to be lifelong. Clinical trials have shown that isoniazid reduces rates of TB among TST-positive persons with HIV infection. Studies in HIV-infected patients have also demonstrated the effectiveness of shorter courses of rifampin-based treatment.

Candidates for treatment of LTBI (Table 70-5) are identified by TST or IGRA of persons in defined high-risk groups. For skin testing, 5 tuberculin units of polysorbate-stabilized PPD should be injected intradermally into the volar surface of the forearm (Mantoux method). Multipuncture tests are not recommended. Reactions are read at 48–72 h as the transverse diameter (in millimeters) of induration; the diameter of erythema is not considered. In some persons, TST reactivity wanes with time but can be recalled by a second skin test administered ≥1 week after the first (i.e., two-step testing). For persons periodically undergoing the TST, such as health care workers and individuals admitted to long-term-care institutions, initial two-step testing may preclude subsequent misclassification of persons with boosted reactions as TST converters. The cutoff for a positive TST (and thus for treatment) is related both to the probability that the reaction represents true infection and to the likelihood that the individual, if truly infected, will develop TB (Table 70-5). Thus, positive reactions for close contacts of infectious cases, persons with HIV infection, persons receiving drugs that suppress the immune system, and previously untreated persons whose chest radiograph is consistent with healed TB are defined as an area of induration ≥5 mm in diameter. A 10-mm cutoff is used to define positive reactions

TABLE 70-5

TUBERCULIN REACTION SIZE AND TREATMENT OF LATENT *MYCOBACTERIUM TUBERCULOSIS* INFECTION

RISK GROUP	TUBERCULIN REACTION SIZE, mm
HIV-infected persons or persons receiving immunosuppressive therapy	≥5
Close contacts of tuberculosis patients	≥5[a]
Persons with fibrotic lesions on chest radiography	≥5
Recently infected persons (≤2 years)	≥10
Persons with high-risk medical conditions[b]	≥10
Low-risk persons[c]	≥15

[a]Tuberculin-negative contacts, especially children, should receive prophylaxis for 2–3 months after contact ends and should then undergo repeat TST. Those whose results remain negative should discontinue prophylaxis. HIV-infected contacts should receive a full course of treatment regardless of TST results.
[b]Includes diabetes mellitus, some hematologic and reticuloendothelial diseases, injection drug use (with HIV seronegativity), end-stage renal disease, and clinical situations associated with rapid weight loss.
[c]Except for employment purposes where longitudinal TST screening is anticipated, TST is not indicated for these low-risk persons. A decision to treat should be based on individual risk/benefit considerations.

in most other at-risk persons. For persons with a very low risk of developing TB if infected, a cutoff of 15 mm is used. (Except for employment purposes where longitudinal screening is anticipated, the TST is not indicated for these low-risk persons.) Treatment should be considered for persons from TB-endemic countries who have a history of BCG vaccination. A positive IGRA is based on the manufacturers' recommendations. For the ELISpot assay, there is an uncertainty zone (5–7 spots) for which epidemiologic and clinical factors guide the decision to implement treatment for LTBI. This approach has also been suggested for interpretation of results in the whole-blood assay that are close to the recommended cutoff for a positive test (0.35 IU of IFN-γ). Some TST- and IGRA-negative individuals are also candidates for treatment. Infants and children who have come into contact with infectious cases should be treated and should have a repeat skin test 2 or 3 months after contact ends. Those whose test results remain negative should discontinue treatment. HIV-infected persons who have been exposed to an infectious TB patient should receive treatment regardless of the TST result. Any HIV-infected candidate for LTBI treatment must be screened carefully to exclude active TB, which would necessitate full treatment.

Isoniazid is administered at a daily dose of 5 mg/kg (up to 300 mg/d) for 9 months (Table 70-6). On the basis of cost-benefit analyses, a 6-month period of treatment has been recommended in the past and may be considered for HIV-negative adults with normal chest radiographs when financial considerations are important. When supervised treatment is desirable and feasible, isoniazid may be given at a dose of 15 mg/kg (up to 900 mg) twice weekly. An alternative regimen for adults is 4 months of daily rifampin. A 3-month regimen of isoniazid and rifampin is recommended in the United Kingdom for both adults and children. A previously recommended regimen of 2 months of rifampin and pyrazinamide has been associated with serious and fatal hepatotoxicity and now is generally not recommended. The rifampin regimen should be considered for persons who are likely to have been infected with an isoniazid-resistant strain. Pending the results of a large-scale study of LTBI treatment conducted by the CDC, it is possible that a regimen of isoniazid and rifapentine given once weekly for 12 weeks will also become an option. Furthermore, clinical trials are under way to assess the efficacy of long-term isoniazid administration (i.e., for at least 3 years). Isoniazid should not be given to persons with active liver disease. All persons at increased risk of hepatotoxicity (e.g., those abusing alcohol daily and those with a history of liver disease) should undergo baseline and then monthly assessment of liver function. All patients should be carefully educated about hepatitis and instructed to discontinue use of the drug immediately should any symptoms develop. Moreover, patients should be seen and questioned monthly during therapy about adverse reactions and should be given no more than 1 month's supply of drug at each visit.

It may be more difficult to ensure compliance when treating persons with latent infection than when treating those with active TB. If family members of active cases are being treated, compliance and monitoring may be easier. When feasible, twice-weekly supervised therapy may increase the likelihood of completion. As in active cases, the provision of incentives may also be helpful.

PRINCIPLES OF TB CONTROL

The highest priority in any TB control program is the prompt detection of cases and the provision of short-course chemotherapy to all TB patients under proper case-management conditions, including directly observed therapy. In addition, in low-prevalence countries with adequate resources (and increasingly in developing countries as well), screening of high-risk groups, such as immigrants from high-prevalence countries, migratory workers, prisoners, homeless individuals, substance abusers, and HIV-seropositive persons, is recommended. TST-positive high-risk persons should be treated for latent infection. Contact investigation is an important component of efficient TB control. In the

TABLE 70-6

REVISED DRUG REGIMENS FOR TREATMENT OF LATENT TUBERCULOSIS INFECTION (LTBI) IN ADULTS

			RATING[b] (EVIDENCE[c])	
DRUG	**INTERVAL AND DURATION**	**COMMENTS[a]**	**HIV-NEGATIVE**	**HIV-INFECTED**
Isoniazid	Daily for 9 months[d,e]	In HIV-infected persons, isoniazid may be administered concurrently with nucleoside reverse transcriptase inhibitors, protease inhibitors, or NNRTIs.	A (II)	A (II)
	Twice weekly for 9 months[d,e]	DOT must be used with twice-weekly dosing.	B (II)	B (II)
	Daily for 6 months[e]	Regimen is not indicated for HIV-infected persons, those with fibrotic lesions on chest radiographs, or children.	B (I)	C (I)
	Twice weekly for 6 months[e]	DOT must be used with twice-weekly dosing.	B (II)	C (I)
Rifampin[f]	Daily for 4 months	Regimen is used for contacts of patients with isoniazid-resistant, rifampin-susceptible tuberculosis. In HIV-infected persons, most protease inhibitors and delavirdine should not be administered concurrently with rifampin. Rifabutin, with appropriate dose adjustments, can be used with protease inhibitors (saquinavir should be augmented with ritonavir) and NNRTIs (except delavirdine). Clinicians should consult web-based updates for the latest specific recommendations.	B (II)	B (III)
Rifampin plus pyrazinamide	Daily for 2 months	Regimen generally should not be offered for treatment of LTBI in either HIV-infected or HIV-negative persons.	D (II)	D (II)
	Twice weekly for 2–3 months		D (III)	D (III)

[a]Interactions with HIV-related drugs are updated frequently and are available at *www.aidsinfo.nih.gov/guidelines*.
[b]Strength of the recommendation: A. Both strong evidence of efficacy and substantial clinical benefit support recommendation for use. Should always be offered. B. Moderate evidence for efficacy or strong evidence for efficacy but only limited clinical benefit supports recommendation for use. Should generally be offered. C. Evidence for efficacy is insufficient to support a recommendation for or against use, or evidence for efficacy might not outweigh adverse consequences (e.g., drug toxicity, drug interactions) or cost of the treatment or alternative approaches. Optional. D. Moderate evidence for lack of efficacy or for adverse outcome supports a recommendation against use. Should generally not be offered. E. Good evidence for lack of efficacy or for adverse outcome supports a recommendation against use. Should never be offered.
[c]Quality of evidence supporting the recommendation: I. Evidence from at least one properly randomized controlled trial. II. Evidence from at least one well-designed clinical trial without randomization, from cohort or case-controlled analytic studies (preferably from more than one center), from multiple time-series studies, or from dramatic results in uncontrolled experiments. III. Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees.
[d]Recommended regimen for persons aged <18 years.
[e]Recommended regimen for pregnant women.
[f]The substitution of rifapentine for rifampin is not recommended because rifapentine's safety and effectiveness have not been established for patients with LTBI.
Abbreviations: DOT, directly observed therapy; NNRTIs, nonnucleoside reverse transcriptase inhibitors.
Source: Adapted from CDC: Targeted tuberculin testing and treatment of latent tuberculosis infection. MMWR Recomm Rep 49:RR-6, 2000.

United States and other countries worldwide, a great deal of attention has been given to the transmission of TB (particularly in association with HIV infection) in institutional settings such as hospitals, homeless shelters, and prisons. Measures to limit such transmission include respiratory isolation of persons with suspected TB until they are proven to be noninfectious (i.e., at least by sputum AFB smear negativity), proper ventilation in rooms of patients with infectious TB, use of ultraviolet irradiation in areas of increased risk of TB transmission, and periodic screening of personnel who may come into contact with known or unsuspected cases of TB. In the past, radiographic surveys, especially those conducted with portable equipment and miniature films, were advocated for case finding. Today, however, the prevalence of TB in industrialized countries is sufficiently low that "mass miniature radiography" is not cost-effective.

In high-prevalence countries, most TB control programs have made remarkable progress in reducing morbidity and mortality during the past 15 years by adopting and implementing the DOTS strategy promoted by the WHO. Between 1995 and 2008, 36 million TB cases were cured and more than 6 million deaths averted compared with the pre-DOTS period. The DOTS approach consists of: (1) political commitment

with increased and sustained financing; (2) case detection through quality-assured bacteriology (starting with microscopic examination of sputum from patients with cough of >2–3 weeks' duration, culture, and possibly drug susceptibility testing); (3) administration of standardized short-course chemotherapy, with direct supervision and patient support; (4) an effective drug supply and management system; and (5) a monitoring and evaluation system, with impact measurement (including assessment of treatment outcomes—e.g., cure, completion of treatment without bacteriologic proof of cure, death, treatment failure, and default—in all cases registered and notified). In 2006, the WHO indicated that, while DOTS remains the essential component of any control strategy, additional steps must be undertaken to reach the 2015 TB control targets set within the United Nations Millennium Development Goals. Thus, a new "Stop TB Strategy" with six components has been promoted: (1) Pursue high-quality DOTS expansion and enhancement. (2) Address HIV-associated TB, MDR-TB, and the needs of poor and vulnerable populations. (3) Contribute to health system strengthening. (4) Engage all care providers. (5) Empower people with TB and [their] communities. (6) Enable and promote research. As part of the fourth component, evidence-based International Standards for Tuberculosis Care, focused on diagnosis, treatment, and public health responsibilities, have recently been introduced for wide adoption by medical and professional societies, academic institutions, and all practitioners worldwide. Care and control of HIV-associated TB is particularly challenging in developing countries, since existing interventions require collaboration between HIV/AIDS and TB programs as well as standard services. While TB programs must test every patient for HIV in order to provide access to trimethoprim-sulfamethoxazole prophylaxis against common infections and ART, HIV/AIDS programs must regularly screen persons living with HIV/AIDS for active TB and provide treatment for LTBI. Early and active case detection is considered an important intervention not only among persons living with HIV/AIDS but also among other vulnerable populations, as it reduces transmission in a community and provides early effective care. For TB control efforts to succeed, programs must optimize their performance and include additional interventions as described. However, bold public health policies must be enforced to support work on TB control and care. These policies include free access to diagnosis and treatment, at least for the poorest patients; sound regulations to ensure drug quality; rational use of drugs by all care providers; laboratory networks equipped with the latest technology for rapid diagnosis; and airborne infection control in all facilities and congregate settings attended by TB patients, especially where HIV prevalence is high. Finally, elimination of TB will require control and attenuation of the multitude of risk factors (e.g., HIV, smoking, and diabetes) and socioeconomic determinants (e.g., extreme poverty, inadequate living conditions and bad housing, alcoholism, malnutrition, and indoor air pollution) with clear policies within the health sector and other sectors linked to human development and welfare.

CHAPTER 71

LEPROSY

Robert H. Gelber

Leprosy, first described in ancient Indian texts from the sixth century b.c., is a nonfatal, chronic infectious disease caused by *Mycobacterium leprae,* the clinical manifestations of which are largely confined to the skin, peripheral nervous system, upper respiratory tract, eyes, and testes. The unique tropism of *M. leprae* for peripheral nerves (from large nerve trunks to microscopic dermal nerves) and certain immunologically mediated reactional states are the major causes of morbidity in leprosy. The propensity of the disease, when untreated, to result in characteristic deformities and the recognition in most cultures that the disease is communicable from person to person have resulted historically in a profound social stigma. Today, with early diagnosis and the institution of appropriate and effective antimicrobial therapy, patients can lead productive lives in the community, and deformities and other visible manifestations can largely be prevented.

ETIOLOGY

M. leprae is an obligate intracellular bacillus (0.3–1 μm wide and 1–8 μm long) that is confined to humans, armadillos in certain locales, and sphagnum moss. The organism is acid-fast, indistinguishable microscopically from other mycobacteria, and ideally detected in tissue sections by a modified Fite stain. Strain variability has been documented in this organism. *M. leprae* produces no known toxins and is well adapted to penetrate and reside within macrophages, yet it may survive outside the body for months. In untreated patients, only ~1% of *M. leprae* organisms are viable. The morphologic index (MI), a measure of the number of acid-fast bacilli (AFB) in skin scrapings that stain uniformly bright, correlates with viability. The bacteriologic index (BI), a logarithmic-scaled measure of the density of *M. leprae* in the dermis, may be as high as 4–6+ in untreated patients and falls by 1 unit per year during effective antimicrobial therapy; the rate of decrease is independent of the relative potency of therapy. A rising MI or BI suggests relapse and perhaps—if the patient is being treated—drug resistance. Drug resistance can be confirmed or excluded in the mouse model of leprosy, and resistance to dapsone and rifampin can be documented by the recognition of mutant genes. However, the availability of these technologies is extremely limited.

As a result of reductive evolution, almost half of the *M. leprae* genome contains nonfunctional genes; only 1605 genes encode for proteins, and 1439 genes are shared with *Mycobacterium tuberculosis*. In contrast, *M. tuberculosis* uses 91% of its genome to encode for 4000 proteins. Among the lost genes in *M. leprae* are those for catabolic and respiratory pathways; transport systems; purine, methionine, and glutamine synthesis; and nitrogen regulation. The genome of *M. leprae* provides a metabolic rationale for its obligate intracellular existence and reliance on host biochemical support, a template for targets of drug development, and ultimately a pathway to cultivation. The finding of strain variability among *M. leprae* isolates has provided a powerful tool with which to address anew the organism's epidemiology and pathobiology and to determine whether relapse represents reactivation or reinfection. The bacterium's complex cell wall contains large amounts of an *M. leprae*–specific phenolic glycolipid (PGL-1), which is detected in serologic tests. The unique trisaccharide of *M. leprae* binds to the basal lamina of Schwann cells; this interaction is probably relevant to the fact that *M. leprae* is the only bacterium to invade peripheral nerves.

Although it was the first bacterium to be etiologically associated with human disease, *M. leprae* remains one of the few bacterial species that still has not been cultivated on artificial medium or tissue culture. The multiplication of *M. leprae* in mouse footpads (albeit limited, with a doubling time of ~2 weeks) has provided a means to evaluate antimicrobial agents, monitor clinical trials, and screen vaccines. *M. leprae* grows best in cooler tissues (the skin, peripheral nerves, anterior chamber of the eye, upper respiratory tract, and testes), sparing warmer areas of the skin (the axilla, groin, scalp, and midline of the back).

EPIDEMIOLOGY

Demographics

Leprosy is almost exclusively a disease of the developing world, affecting areas of Asia, Africa, Latin America, and the Pacific **(Fig. 71-1)**. While Africa has the highest disease prevalence, Asia has the most cases. More than 80% of the world's cases occur in a few countries: India, China, Myanmar, Indonesia, Brazil, Nigeria, Madagascar, and Nepal. Within endemic locales, the distribution of leprosy is quite uneven, with areas of high prevalence bordering on

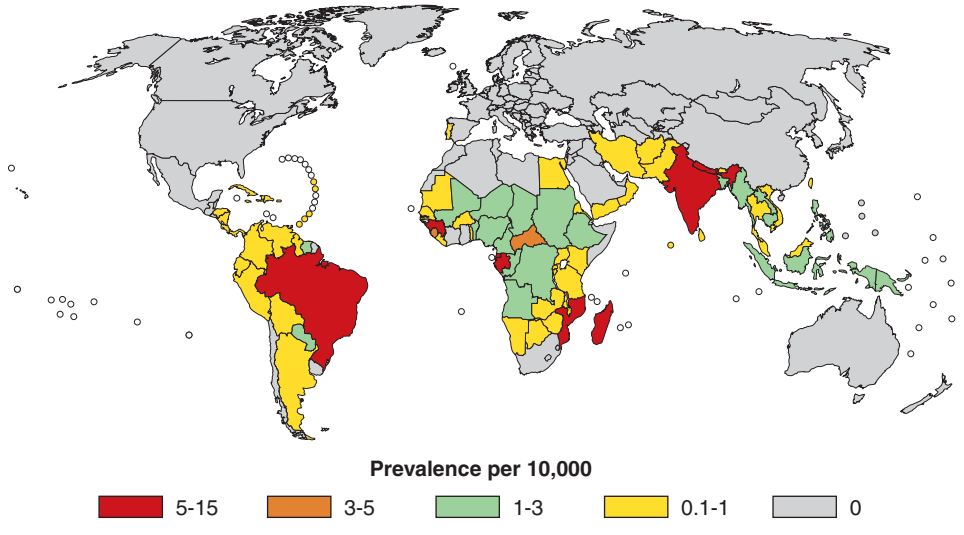


FIGURE 71-1
Estimated prevalence of leprosy at the turn of the millennium. Because data on leprosy prevalence in many endemic countries are unreliable, global prevalence is difficult to assess with any great degree of accuracy; however, it is not falling (see text). (*Courtesy of Patrick J. Brennan, PhD, with permission.*)

areas with little or no disease. In Brazil the majority of cases occur in the Amazon basin and two western states, while in Mexico leprosy is mostly confined to the Pacific coast. Except as imported cases, leprosy is largely absent from the United States, Canada, and northwestern Europe. In the United States, ~4000 persons have leprosy and 100–200 new cases are reported annually, most of them in California, Texas, New York, and Hawaii among immigrants from Mexico, Southeast Asia, the Philippines, and the Caribbean. The comparative genomics of single-nucleotide polymorphisms support the likelihood that four distinct strains exist, having originated in East Africa or Central Asia. A mutation spread to Europe and subsequently underwent two separate mutations that were then followed by spread to West Africa and the Americas.

The global prevalence of leprosy is difficult to assess, given that many of the locales with high prevalence lack a significant medical or public health infrastructure. Estimates range from 0.6 to 8 million affected individuals. The lower estimate includes only persons who have not completed chemotherapy, excluding those who may be physically or psychologically damaged from leprosy and who may yet relapse or develop immune-mediated reactions. The higher figure includes patients whose infections probably are already cured and many who have no leprosy-related deformity or disability. Although the figures on the worldwide prevalence of leprosy are debatable, it is not falling; there are an estimated 600,000 new cases annually, 60% of them in India.

Leprosy is associated with poverty and rural residence. It appears not to be associated with AIDS, perhaps because of leprosy's long incubation period. Most individuals appear to be naturally immune to leprosy and do not develop disease manifestations after exposure. The time of peak onset is in the second and third decades of life. The most severe lepromatous form of leprosy is twice as common among men as among women and is rarely encountered in children. The frequency of the polar forms of leprosy in different countries varies widely and may in part be genetically determined; certain human leukocyte antigen (HLA) associations are known for both polar forms of leprosy (see later). Furthermore, variations in immunoregulatory genes are associated with an increased susceptibility to leprosy, particularly the multibacillary form. In India and Africa, 90% of cases are tuberculoid; in Southeast Asia, 50% are tuberculoid and 50% lepromatous; and in Mexico, 90% are lepromatous. (For definitions of disease types, see **Table 71-1** and "Clinical, Histologic, and Immunologic Spectrum," later in the chapter.)

Transmission

The route of transmission of leprosy remains uncertain, and transmission routes may in fact be multiple. Nasal droplet infection, contact with infected soil, and even insect vectors have been considered the prime candidates. Aerosolized *M. leprae* can cause infection in immunosuppressed mice, and a sneeze from an untreated lepromatous patient may contain $>10^{10}$ AFB. Furthermore, both IgA antibody to *M. leprae* and genes of *M. leprae*—demonstrable by polymerase chain reaction (PCR)—have been found in the nose of individuals without signs of leprosy from endemic areas and in 19% of occupational contacts of lepromatous patients. Several lines of evidence implicate soil transmission. (1) In endemic countries such as India, leprosy is primarily a rural and not an urban disease. (2) *M. leprae* products reside in soil in endemic locales. (3) Direct dermal inoculation (e.g., during tattooing) may transmit *M. leprae*, and common sites of leprosy in children are the buttocks and thighs, suggesting that microinoculation of infected soil may transmit the disease. Evidence for insect vectors of leprosy includes the demonstration that bedbugs and mosquitoes in the vicinity of leprosaria regularly harbor *M. leprae* and that experimentally infected mosquitoes can transmit infection to mice. Skin-to-skin contact is generally not considered an important route of transmission.

In endemic countries, ~50% of leprosy patients have a history of intimate contact with an infected person (often a household member), while, for unknown reasons, leprosy patients in nonendemic locales can identify such contact only 10% of the time. Moreover, household contact with an infected lepromatous case carries an eventual risk of disease acquisition of ~10% in endemic areas as opposed to only 1% in nonendemic locales. Contact with a tuberculoid case carries a very low risk. Physicians and nurses caring for leprosy patients and the co-workers of these patients are not at risk for leprosy.

Although multilocus variable-number short-nucleotide tandem-repeat (VNTR) analyses have generally demonstrated considerable variability among isolates, highly similar and even identical VNTR results have been obtained with isolates from a limited number of families with multiple cases. Moreover, VNTR results have been similar for isolates within certain geographic locales and divergent for isolates within others. These findings suggest that genomic analyses may prove useful in the future for defining *M. leprae* transmission patterns.

M. leprae causes disease primarily in humans. However, in Texas and Louisiana, 15% of nine-banded armadillos are infected, and armadillo contact occasionally results in human disease. Armadillos develop disseminated infection after IV inoculation of live *M. leprae*.

CLINICAL, HISTOLOGIC, AND IMMUNOLOGIC SPECTRUM

The incubation period prior to manifestation of clinical disease can vary between 2 and 40 years, although it is generally 5–7 years in duration. This long incubation period is probably, at least in part, a consequence of the extremely long doubling time for *M. leprae* (14 days in mice versus in vitro doubling times of 1 day and 20 min for *M. tuberculosis* and *Escherichia coli*, respectively). Leprosy presents as a spectrum of clinical manifestations that have bacteriologic, pathologic, and immunologic counterparts. The spectrum from polar tuberculoid (TT)

TABLE 71-1

CLINICAL, BACTERIOLOGIC, PATHOLOGIC, AND IMMUNOLOGIC SPECTRUM OF LEPROSY

FEATURE	TUBERCULOID (TT, BT) LEPROSY	BORDERLINE (BB, BL) LEPROSY	LEPROMATOUS (LL) LEPROSY
Skin lesions	One or a few sharply defined annular asymmetric macules or plaques with a tendency toward central clearing, elevated borders	Intermediate between BT- and LL-type lesions; ill-defined plaques with an occasional sharp margin; few or many in number	Symmetric, poorly marginated, multiple infiltrated nodules and plaques or diffuse infiltration; xanthoma-like or dermatofibroma papules; leonine facies and eyebrow alopecia
Nerve lesions	Skin lesions anesthetic early; nerve near lesions sometimes enlarged; nerve abscesses most common in BT	Hypesthetic or anesthetic skin lesions; nerve trunk palsies, at times symmetric	Hypesthesia a late sign; nerve palsies variable; acral, distal, symmetric anesthesia common
Acid-fast bacilli (BI[a])	0–1+	3–5+	4–6+
Lymphocytes	2+	1+	0–1+
Macrophage differentiation	Epithelioid	Epithelioid in BB; usually undifferentiated, but may have foamy changes in BL	Foamy change the rule; may be undifferentiated in early lesions
Langhans giant cells	1–3+	—	—
Lepromin skin test	+++	—	—
Lymphocyte transformation test	Generally positive	1–10%	1–2%
CD4+/CD8+ T cell ratio in lesions	1.2	BB (NT); BL: 0.48	0.50
M. leprae PGL-1 antibodies	60%	85%	95%

[a]See text.

Abbreviations: BB, mid-borderline; BL, borderline lepromatous; BT, borderline tuberculoid; TT, polar tuberculoid; LL, polar lepromatous; BI, bacteriologic index; NT, not tested; PGL-1, phenolic glycolipid 1.

to borderline tuberculoid (BT) to mid-borderline (BB, which is rarely encountered) to borderline lepromatous (BL) to polar lepromatous (LL) disease is associated with an evolution from asymmetric localized macules and plaques to nodular and indurated symmetric generalized skin manifestations, an increasing bacterial load, and loss of *M. leprae*–specific cellular immunity (Table 71-1). Distinguishing dermatopathologic characteristics include the number of lymphocytes, giant cells, and AFB as well as the nature of epithelioid cell differentiation. Where a patient presents on the clinical spectrum largely determines prognosis, complications, reactional states, and the intensity of antimicrobial therapy required.

Tuberculoid leprosy

At the less severe end of the spectrum is tuberculoid leprosy, which encompasses TT and BT disease. In general, these forms of leprosy result in symptoms confined to the skin and peripheral nerves. The skin lesions of tuberculoid leprosy consist of one or a few hypopigmented macules or plaques **(Fig. 71-2)** that are sharply demarcated and hypesthetic, often have erythematous or raised borders, and are devoid of the normal skin organs (sweat glands and hair follicles) and thus are dry, scaly, and anhidrotic. AFB are generally absent or few in number. Tuberculoid leprosy patients may

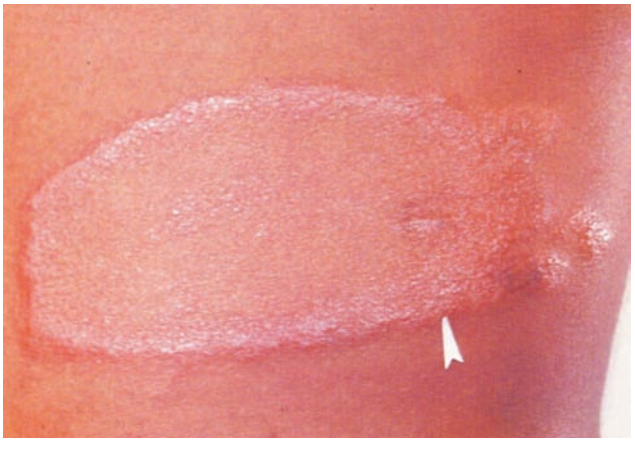


FIGURE 71-2

Tuberculoid (TT) leprosy: a well-defined, hypopigmented, anesthetic macule with anhidrosis and a raised granular margin *(arrowhead).*

have asymmetric enlargement of one or a few peripheral nerves. Indeed, leprosy and certain rare hereditary neuropathies are the only human diseases associated with peripheral-nerve enlargement. Although any peripheral nerve may be enlarged (including small digital and supraclavicular nerves), those most commonly affected are the ulnar, posterior auricular, peroneal, and posterior tibial nerves, with associated hypesthesia and myopathy. TT leprosy is the most common form of the disease encountered in India and Africa but is virtually absent in Southeast Asia, where BT leprosy is frequent.

In tuberculoid leprosy, T cells breach the perineurium, and destruction of Schwann cells and axons may be evident, resulting in fibrosis of the epineurium, replacement of the endoneurium with epithelial granulomas, and occasionally caseous necrosis. Such invasion and destruction of nerves in the dermis by T cells are pathognomonic for leprosy.

Circulating lymphocytes from patients with tuberculoid leprosy readily recognize *M. leprae* and its constituent proteins, patients have positive lepromin skin tests (see "Diagnosis," later in the chapter), and—owing to a type 1 cytokine pattern in tuberculoid tissues—strong T cell and macrophage activation results in a localized infection. In tuberculoid leprosy tissue, there is a 2:1 predominance of helper CD4+ over CD8+ T lymphocytes. Tuberculoid tissues are rich in the mRNAs of the proinflammatory T_H1 family of cytokines: interleukin (IL) 2, interferon γ (IFN-γ), and IL-12; in contrast, IL-4, IL-5, and IL-10 mRNAs are scarce.

Lepromatous leprosy

Lepromatous leprosy patients present with symmetrically distributed skin nodules **(Fig. 71-3)**, raised plaques, or diffuse dermal infiltration, which, when on the face, results in leonine facies. Late manifestations include loss of eyebrows (initially the lateral margins only) and eyelashes, pendulous earlobes, and dry scaling skin, particularly on the feet. In LL leprosy, bacilli are numerous in the skin (as many as 10^9/g), where they are often found in large clumps (*globi*), and in peripheral nerves, where they initially invade Schwann cells, resulting in foamy degenerative myelination and axonal degeneration and later in Wallerian degeneration. In addition, bacilli are plentiful in circulating blood and in all organ systems except the lungs and the central nervous system. Nevertheless, patients are afebrile, and there is no evidence of major organ system dysfunction. Found almost exclusively in western Mexico and the Caribbean is a form of lepromatous leprosy without visible skin lesions but with diffuse dermal infiltration and a demonstrably thickened dermis, termed *diffuse lepromatosis*. In lepromatous leprosy, nerve enlargement and damage tend to be symmetric, result from actual bacillary invasion, and are more insidious but ultimately more extensive than in tuberculoid leprosy. Patients with LL leprosy have acral, distal, symmetric peripheral neuropathy and a tendency toward symmetric nerve-trunk enlargement. They may also have signs and symptoms related to involvement of the upper respiratory tract, the anterior chamber of the eye, and the testes.

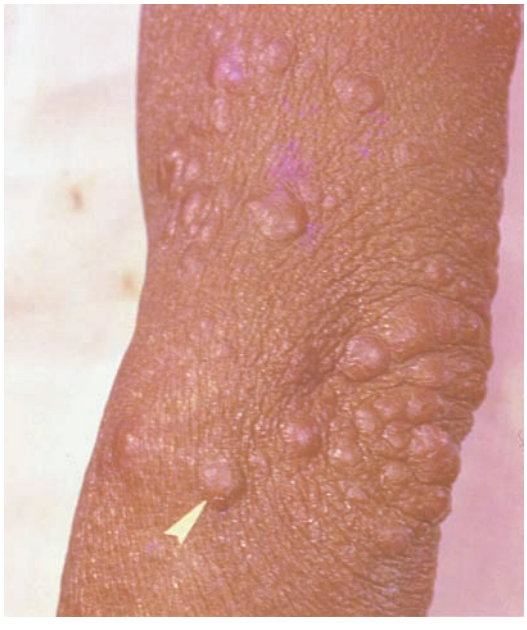


FIGURE 71-3
Lepromatous (LL) leprosy: advanced nodular lesions.

In untreated LL patients, lymphocytes regularly fail to recognize either *M. leprae* or its protein constituents, and lepromin skin tests are negative (see "Diagnosis," later in the chapter). This loss of protective cellular immunity appears to be antigen-specific, as patients are not unusually susceptible to opportunistic infections, cancer, or AIDS and maintain delayed-type hypersensitivity to *Candida*, *Trichophyton*, mumps, tetanus toxoid, and even purified protein derivative of tuberculin. At times, *M. leprae*–specific anergy is reversible with effective chemotherapy. In LL tissues, there is a 2:1 ratio of CD8+ to CD4+ T lymphocytes. LL patients have a predominant T_H2 response and hyperglobulinemia, and LL tissues demonstrate a T_H2 cytokine profile, being rich in mRNAs for IL-4, IL-5, and IL-10 and poor in those for IL-2, IFN-γ, and IL-12. It appears that cytokines mediate a protective tissue response in leprosy, as injection of IFN-γ or IL-2 into lepromatous lesions causes a loss of AFB and histopathologic conversion toward a tuberculoid pattern. Macrophages of lepromatous leprosy patients appear to be functionally intact; circulating monocytes exhibit normal microbicidal function and responsiveness to IFN-γ.

Reactional states

Lepra reactions comprise several common immunologically mediated inflammatory states that cause considerable morbidity. Some of these reactions precede diagnosis and the institution of effective antimicrobial therapy; indeed, these reactions may precipitate presentation for medical attention and diagnosis. Other reactions occur after the initiation of appropriate chemotherapy and may cause patients to perceive that their leprosy is worsening and to lose confidence in conventional therapy. Only by

warning patients of the potential for these reactions and describing their manifestations can physicians treating leprosy patients ensure continued credibility.

Type 1 lepra reactions (downgrading and reversal reactions)

Type 1 lepra reactions occur in almost half of patients with borderline forms of leprosy but not in patients with pure lepromatous disease. Manifestations include classic signs of inflammation within previously involved macules, papules, and plaques and, on occasion, the appearance of new skin lesions, neuritis, and (less commonly) fever—generally low-grade. The nerve trunk most commonly involved in this process is the ulnar nerve at the elbow, which may be painful and exquisitely tender. If patients with affected nerves are not treated promptly with glucocorticoids (see later), irreversible nerve damage may result in as little as 24 h. The most dramatic manifestation is footdrop, which occurs when the peroneal nerve is involved.

When type 1 lepra reactions precede the initiation of appropriate antimicrobial therapy, they are termed *downgrading reactions*, and the case becomes histologically more lepromatous; when they occur after the initiation of therapy, they are termed *reversal reactions*, and the case becomes more tuberculoid. Reversal reactions often occur in the first months or years after the initiation of therapy but may also develop several years thereafter.

Edema is the most characteristic microscopic feature of type 1 lepra lesions, whose diagnosis is primarily clinical. Reversal reactions are typified by a T_H1 cytokine profile, with an influx of CD4+ T helper cells and increased levels of IFN-γ and IL-2. In addition, type 1 reactions are associated with large numbers of T cells bearing γ/δ receptors—a unique feature of leprosy.

Type 2 lepra reactions: erythema nodosum leprosum

Erythema nodosum leprosum (ENL) **(Fig. 71-4)** occurs exclusively in patients near the lepromatous end of the leprosy spectrum (BL-LL), affecting nearly 50% of this group. Although ENL may precede leprosy diagnosis and initiation of therapy (sometimes, in fact, prompting the diagnosis), in 90% of cases it follows the institution of chemotherapy, generally within 2 years. The most common features of ENL are crops of painful erythematous papules that resolve spontaneously in a few days to a week but may recur; malaise; and fever that can be profound. However, patients may also experience symptoms of neuritis, lymphadenitis, uveitis, orchitis, and glomerulonephritis and may develop anemia, leukocytosis, and abnormal liver function tests (particularly increased aminotransferase levels). Individual patients may have either a single bout of ENL or chronic recurrent manifestations. Bouts may be either mild or severe and generalized; in rare instances, ENL results in death. Skin biopsy of ENL papules reveals vasculitis or panniculitis, sometimes with many lymphocytes but characteristically with polymorphonuclear leukocytes as well.

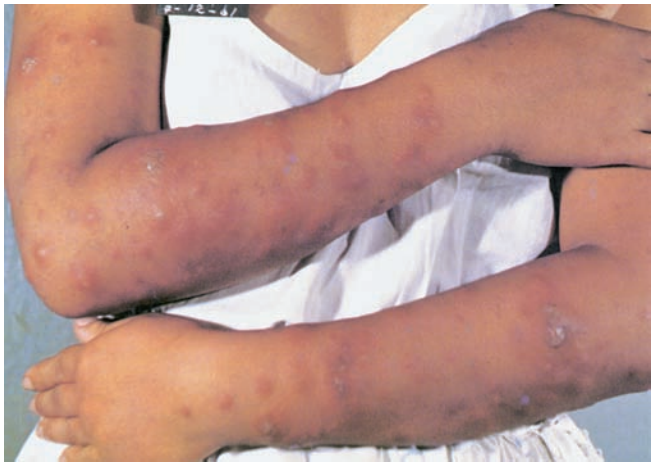


FIGURE 71-4
Moderately severe skin lesions of erythema nodosum leprosum (ENL), some with pustulation and ulceration.

Elevated levels of circulating tumor necrosis factor (TNF) have been demonstrated in ENL; thus, TNF may play a central role in the pathobiology of this syndrome. ENL is thought to be a consequence of immune complex deposition, given its T_H2 cytokine profile and its high levels of IL-6 and IL-8. However, in ENL tissue, the presence of HLA-DR framework antigen of epidermal cells—considered a marker for a delayed-type hypersensitivity response—and evidence of higher levels of IL-2 and IFN-γ than are usually seen in polar lepromatous disease suggest an alternative mechanism.

Lucio's phenomenon

Lucio's phenomenon is an unusual reaction seen exclusively in patients from the Caribbean and Mexico who have the diffuse lepromatosis form of lepromatous leprosy, most often those who are untreated. Patients with this reaction develop recurrent crops of large, sharply marginated, ulcerative lesions—particularly on the lower extremities—that may be generalized and, when so, are frequently fatal as a result of secondary infection and consequent septic bacteremia. Histologically, the lesions are characterized by ischemic necrosis of the epidermis and superficial dermis, heavy parasitism of endothelial cells with AFB, and endothelial proliferation and thrombus formation in the larger vessels of the deeper dermis. Like ENL, the Lucio phenomenon is probably mediated by immune complexes.

Complications

The extremities

Complications of the extremities in leprosy patients are primarily a consequence of neuropathy leading to insensitivity and myopathy. Insensitivity affects fine touch, pain, and heat receptors but generally spares position and vibration appreciation. The most commonly affected nerve trunk is the ulnar nerve at the elbow, whose involvement results in clawing of the fourth and fifth fingers, loss of dorsal interosseous musculature in the affected hand, and loss of sensation in these distributions. Median nerve involvement in leprosy impairs thumb

opposition and grasp; radial nerve dysfunction, although rare in leprosy, leads to wristdrop. Tendon transfers can restore hand function but should not be performed until 6 months after the initiation of antimicrobial therapy and the conclusion of episodes of acute neuritis.

Plantar ulceration, particularly at the metatarsal heads, is probably the most frequent complication of leprous neuropathy. Therapy requires careful debridement; administration of appropriate antibiotics; avoidance of weight-bearing until ulcerations are healed, with slowly progressive ambulation thereafter; and wearing of special shoes to prevent recurrence.

Footdrop as a result of peroneal nerve palsy should be treated with a simple nonmetallic brace within the shoe or with surgical correction attained by tendon transfers. Although uncommon, Charcot's joints, particularly of the foot and ankle, may result from leprosy.

The loss of distal digits in leprosy is a consequence of insensitivity, trauma, secondary infection, and—in lepromatous patients—a poorly understood and sometimes profound osteolytic process. Conscientious protection of the extremities during cooking and work and the early institution of therapy have substantially reduced the frequency and severity of distal digit loss in recent times.

The nose

In lepromatous leprosy, bacillary invasion of the nasal mucosa can result in chronic nasal congestion and epistaxis. Saline nose drops may relieve these symptoms. Long-untreated LL leprosy may further result in destruction of the nasal cartilage, with consequent saddle-nose deformity or anosmia (more common in the preantibiotic era than at present). Nasal reconstructive procedures can ameliorate significant cosmetic defects.

The eye

Owing to cranial nerve palsies, lagophthalmos and corneal insensitivity may complicate leprosy, resulting in trauma, secondary infection, and (without treatment) corneal ulcerations and opacities. For patients with these conditions, eyedrops during the day and ointments at night provide some protection from such consequences. Furthermore, in LL leprosy, the anterior chamber of the eye is invaded by bacilli, and ENL may result in uveitis, with consequent cataracts and glaucoma. Thus leprosy is a major cause of blindness in the developing world. Slit-lamp evaluation of LL patients often reveals "corneal beading," representing globi of *M. leprae*.

The testes

M. leprae invades the testes, while ENL may cause orchitis. Thus males with lepromatous leprosy often manifest mild to severe testicular dysfunction, with an elevation of luteinizing and follicle-stimulating hormones, decreased testosterone, and aspermia or hypospermia in 85% of LL patients but in only 25% of BL patients. LL patients may become impotent and infertile. Impotence is sometimes responsive to testosterone replacement.

Amyloidosis

Secondary amyloidosis is a complication of LL leprosy and ENL that is encountered infrequently in the antibiotic era. This complication may result in abnormalities of hepatic and particularly renal function.

Nerve abscesses

Patients with various forms of leprosy, but particularly those with the BT form, may develop abscesses of nerves (most commonly the ulnar) with an adjacent cellulitic appearance of the skin. In such conditions, the affected nerve is swollen and exquisitely tender. Although glucocorticoids may reduce signs of inflammation, rapid surgical decompression is necessary to prevent irreversible sequelae.

DIAGNOSIS

Leprosy most commonly presents with both characteristic skin lesions and skin histopathology. Thus, the disease should be suspected when a patient from an endemic area has suggestive skin lesions or peripheral neuropathy. The diagnosis should be confirmed by histopathology. In tuberculoid leprosy, lesional areas—preferably the advancing edge—must be biopsied because normal-appearing skin does not have pathologic features. In lepromatous leprosy, nodules, plaques, and indurated areas are optimal biopsy sites, but biopsies of normal-appearing skin are also generally diagnostic. Lepromatous leprosy is associated with diffuse hyperglobulinemia, which may result in false-positive serologic tests (e.g., Venereal Disease Research Laboratory, rheumatoid arthritis, and antinuclear antibody tests) and therefore may cause diagnostic confusion. On occasion, tuberculoid lesions may not (1) appear typical, (2) be hypesthetic, and (3) contain granulomas but only nonspecific lymphocytic infiltrates. In such instances, two of these three characteristics are considered sufficient for a diagnosis. It is preferable to overdiagnose leprosy rather than to allow a patient to remain untreated.

IgM antibodies to PGL-1 are found in 95% of patients with untreated lepromatous leprosy; the titer decreases with effective therapy. However, in tuberculoid leprosy—the form of disease most often associated with diagnostic uncertainty owing to the absence or paucity of AFB—patients have significant antibodies to PGL-1 only 60% of the time; moreover, in endemic locales, exposed individuals without clinical leprosy may harbor antibodies to PGL-1. Thus, PGL-1 serology is of little diagnostic utility in tuberculoid leprosy. Heat-killed *M. leprae* (lepromin) has been used as a skin test reagent. It generally elicits a reaction in tuberculoid leprosy patients, may do so in individuals without leprosy, and gives negative results in lepromatous leprosy patients; consequently, it is likewise of little diagnostic value. Unfortunately, PCR of the skin for *M. leprae*, although positive in LL and BL leprosy, yields negative results in 50% of tuberculoid leprosy cases, again offering little diagnostic assistance.

Included in the differential diagnosis of lesions that resemble leprosy are sarcoidosis, leishmaniasis, lupus vulgaris, dermatofibroma, histiocytoma, lymphoma, syphilis, yaws, granuloma annulare, and various other

disorders causing hypopigmentation (notably pityriasis alba, tinea, and vitiligo). Sarcoidosis may result in perineural inflammation, but actual granuloma formation within dermal nerves is pathognomonic for leprosy. In lepromatous leprosy, sputum specimens may be loaded with AFB—a finding that can be inappropriately interpreted as representing pulmonary tuberculosis.

TREATMENT Leprosy

ANTIMICROBIAL THERAPY

Active Agents Established agents used to treat leprosy include dapsone (50–100 mg/d), clofazimine (50–100 mg/d, 100 mg three times weekly, or 300 mg monthly), and rifampin (600 mg daily or monthly; see "Choice of Regimens," next). Of these drugs, only rifampin is bactericidal. The sulfones (folate antagonists), the foremost of which is dapsone, were the first antimicrobial agents found to be effective for the treatment of leprosy and are still the mainstay of therapy. With sulfone treatment, skin lesions resolve and numbers of viable bacilli in the skin are reduced. Although primarily bacteriostatic, dapsone monotherapy results in only a 2.5% resistance-related relapse rate; after ≥18 years of therapy and subsequent discontinuation, only another 10% of patients relapse, developing new, usually asymptomatic, shiny, "histoid" nodules. Dapsone is generally safe and inexpensive. Individuals with glucose-6-phosphate dehydrogenase deficiency who are treated with dapsone may develop severe hemolysis; those without this deficiency also have reduced red cell survival and a hemoglobin decrease averaging 1 g/dL. Dapsone's usefulness is limited occasionally by allergic dermatitis and rarely by the sulfone syndrome (including high fever, anemia, exfoliative dermatitis, and a mononucleosis-type blood picture). It must be remembered that rifampin induces microsomal enzymes, necessitating increased doses of medications such as glucocorticoids and oral birth control regimens. Clofazimine is often cosmetically unacceptable to light-skinned leprosy patients because it causes a red-black skin discoloration that accumulates, particularly in lesional areas, and makes the patient's diagnosis obvious to members of the community.

Other antimicrobial agents active against *M. leprae* in animal models and at the usual daily doses used in clinical trials include ethionamide/prothionamide; the aminoglycosides streptomycin, kanamycin, and amikacin (but not gentamicin or tobramycin); minocycline; clarithromycin; and several fluoroquinolones, particularly ofloxacin. Next to rifampin, minocycline, clarithromycin, and ofloxacin appear to be most bactericidal for *M. leprae*, but these drugs have not been used extensively in leprosy control programs. Most recently, rifapentine and moxifloxacin have been found to be especially potent against *M. leprae* in mice. In a clinical trial in lepromatous leprosy, moxifloxacin was profoundly bactericidal, matched in potency only by rifampin.

Choice of Regimens Antimicrobial therapy for leprosy must be individualized, depending on the clinical/pathologic form of the disease encountered. Tuberculoid leprosy, which is associated with a low bacterial burden and a protective cellular immune response, is the easiest form to treat and can be cured reliably with a finite course of chemotherapy. In contrast, lepromatous leprosy may have a higher bacillary load than any other human bacterial disease, and the absence of a salutary T cell repertoire requires prolonged or even lifelong chemotherapy. Hence, careful classification of disease prior to therapy is important.

In developed countries, clinical experience with leprosy classification is limited; fortunately, however, the resources needed for skin biopsy are highly accessible and pathologic interpretation is readily available. In developing countries, clinical expertise is greater but is now waning substantially as the care of leprosy patients is integrated into general health services. In addition, access to dermatopathology services is often limited. In such instances, skin smears may prove useful, but in many locales access to the resources needed for their preparation and interpretation may also be unavailable. Use of skin smears is no longer encouraged by the World Health Organization (WHO) and is often replaced by mere counting of lesions, which, together with the lack of histopathology, may negatively affect decisions about chemotherapy, increase the potential for reactions, and worsen the ultimate prognosis. A reasoned approach to the treatment of leprosy is confounded by these and several other issues:

1. Even without therapy, TT leprosy may heal spontaneously, and prolonged dapsone monotherapy (even for LL leprosy) is generally curative in 80% of cases.
2. In tuberculoid disease, it is common for no bacilli to be found in the skin prior to therapy, and thus there is no objective measure of therapeutic success. Furthermore, despite adequate treatment, TT and particularly BT lesions often resolve little or incompletely, while relapse and late type 1 lepra reactions can be difficult to distinguish.
3. LL leprosy patients commonly harbor viable persistent *M. leprae* organisms after prolonged intensive therapy; the propensity of these organisms to initiate clinical relapse is unclear. Because relapse in LL patients after discontinuation of rifampin-containing regimens usually begins only after 7–10 years, follow-up over the very long term is necessary to assess ultimate clinical outcomes.
4. Even though primary dapsone resistance is exceedingly rare and multidrug therapy is generally recommended (at least for lepromatous leprosy), there is a paucity of information from experimental animals and clinical trials on the optimal combination of antimicrobial agents, dosing schedule, or duration of therapy.

In 1982, the WHO made recommendations for "the chemotherapy of leprosy for control programs." These recommendations came on the heels of the demonstration of the relative success of long-term dapsone

monotherapy and in the context of concerns about dapsone resistance. Other complicating considerations included the limited resources available for leprosy care in the very areas where it is most prevalent and the frustration and discouragement of patients and program managers with the previous requirement for lifelong therapy for many leprosy patients. Thus, for the first time, the WHO delineated a finite duration of therapy for all forms of leprosy and—given the prohibitive cost of daily rifampin treatment in developing countries—encouraged the monthly administration of this agent as part of a multidrug regimen. Over the ensuing years, the WHO recommendations have been broadly implemented, and the duration of therapy required, particularly for lepromatous leprosy, has been progressively shortened. For treatment purposes, the WHO classifies patients as *paucibacillary* or *multibacillary*. Previously, patients without demonstrable AFB in the dermis were classified as paucibacillary and those with AFB as multibacillary. Currently, in light of the perceived unreliability of skin smears in the field, patients are classified as multibacillary if they have six or more skin lesions and as paucibacillary if they have fewer. (Unfortunately, this classification method has been found wanting, as some patients near the lepromatous pole have only one or a few skin lesions.) The WHO recommends that paucibacillary adults be treated with 100 mg of dapsone daily and 600 mg of rifampin monthly (supervised) for 6 months (Table 71-2). For patients with single-lesion paucibacillary leprosy, the WHO recommends as an alternative a single dose of rifampin (600 mg), ofloxacin (400 mg), and minocycline (100 mg). Multibacillary adults should be treated with 100 mg of dapsone plus 50 mg of clofazimine daily (unsupervised) and with 600 mg of rifampin plus 300 mg of clofazimine monthly (supervised). Originally, the WHO recommended that lepromatous patients be treated for 2 years or until smears became negative (generally in ~5 years); subsequently, the acceptable course was reduced to 1 year—a change that remains especially controversial in the absence of supporting clinical trials.

Several factors have caused many authorities to question the WHO recommendations and to favor a more intensive approach. Among these factors are—for multibacillary patients—a high (double-digit) relapse rate in three locales (reaching 20–40% in one locale, with the rate directly related to the initial bacterial burden) and—for paucibacillary patients—demonstrable lesional activity for years in fully half of patients after the completion of therapy. The more intensive approach (Table 71-2) calls for tuberculoid leprosy to be treated with dapsone (100 mg/d) for 5 years and for lepromatous leprosy to be treated with rifampin (600 mg/d) for 3 years and with dapsone (100 mg/d) throughout life.

With effective antimicrobial therapy, new skin lesions and signs and symptoms of peripheral neuropathy cease appearing. Nodules and plaques of lepromatous leprosy noticeably flatten in 1–2 months and resolve in 1 year or a few years, while tuberculoid skin lesions may disappear, improve, or remain relatively unchanged. Although the peripheral neuropathy of leprosy may improve somewhat in the first few months of therapy, rarely is it significantly alleviated by treatment.

Given the recent findings that moxifloxacin, like rifampin, is profoundly bactericidal in leprosy patients and that short-course chemotherapy for tuberculosis is possible only when two or more bactericidal agents are used, a moxifloxacin/rifampin-based regimen including either minocycline or clarithromycin appears promising; such a regimen may prove to be more reliably curative than WHO-recommended multidrug therapy for lepromatous leprosy and may allow a considerably shorter course of treatment.

THERAPY FOR REACTIONS

Type 1 Type 1 lepra reactions are best treated with glucocorticoids (e.g., prednisone, initially at doses of 40–60 mg/d). As the inflammation subsides, the glucocorticoid dose can be tapered, but steroid therapy must be continued for at least 3–6 months lest recurrence supervene. Because of the myriad toxicities of prolonged glucocorticoid therapy, the indications for its initiation are strictly limited to lesions whose intense inflammation poses a threat of ulceration; lesions at cosmetically important sites, such as the face; and cases in which neuritis is present. Mild to moderate lepra reactions that do not meet these criteria should be tolerated and glucocorticoid treatment withheld. Thalidomide is

TABLE 71-2

ANTIMICROBIAL REGIMENS RECOMMENDED FOR THE TREATMENT OF LEPROSY IN ADULTS

FORM OF LEPROSY	MORE INTENSIVE REGIMEN	WHO RECOMMENDED REGIMEN (1982)
Tuberculoid (paucibacillary)	Dapsone (100 mg/d) for 5 years	Dapsone (100 mg/d, unsupervised) *plus* rifampin (600 mg/month, supervised) for 6 months
Lepromatous (multibacillary)	Rifampin (600 mg/d) for 3 years *plus* dapsone (100 mg/d) indefinitely	Dapsone (100 mg/d) *plus* clofazimine (50 mg/d), unsupervised; *and* rifampin (600 mg) *plus* clofazimine (300 mg) monthly (supervised) for 1–2 years

Note: See text for discussion and comparison of WHO recommendations and more intensive approach as well as alternative WHO regimen for single-lesion paucibacillary leprosy.

ineffective against type 1 lepra reactions. Clofazimine (200–300 mg/d) is of questionable benefit but in any event is far less efficacious than glucocorticoids.

Type 2 Treatment of ENL must be individualized. If ENL is mild (i.e., without fever or other organ involvement, with occasional crops of only a few skin papules), it may be treated with antipyretics alone. However, in cases with many skin lesions, fever, malaise, and other tissue involvement, brief courses (1–2 weeks) of glucocorticoids (initially 40–60 mg/d) are often effective. With or without therapy, individual inflamed papules last for >1 week. Successful therapy is defined by the cessation of skin lesion development and the disappearance of other systemic signs and symptoms. If, despite two courses of glucocorticoid therapy, ENL appears to be recurring and persisting, treatment with thalidomide (100–300 mg nightly) should be initiated, with the dose depending on the initial severity of the reaction. Because even a single dose of thalidomide administered early in pregnancy may result in severe birth defects, including phocomelia, the use of this drug in the United States for the treatment of fertile female patients is tightly regulated and requires informed consent, prior pregnancy testing, and maintenance of birth control measures. Although the mechanism of thalidomide's dramatic action against ENL is not entirely clear, the drug's efficacy is probably attributable to its reduction of TNF levels and IgM synthesis and its slowing of polymorphonuclear leukocyte migration. After the reaction is controlled, lower doses of thalidomide (50–200 mg nightly) are effective in preventing relapses of ENL. Clofazimine in high doses (300 mg nightly) has some efficacy against ENL, but its use permits only a modest reduction of the glucocorticoid dose necessary for ENL control.

Lucio's Phenomenon Neither glucocorticoids nor thalidomide is effective against this syndrome. Optimal wound care and therapy for bacteremia are indicated. Ulcers tend to be chronic and heal poorly. In severe cases, exchange transfusion may prove useful.

PREVENTION AND CONTROL

Vaccination at birth with bacille Calmette-Guérin (BCG) has proved variably effective in preventing leprosy: the results have ranged from total inefficacy to 80% efficacy. The addition of heat-killed *M. leprae* to BCG does not increase the effectiveness of vaccine. Because whole mycobacteria contain large amounts of lipids and carbohydrates that have proved in vitro to be immunosuppressive for lymphocytes and macrophages, *M. leprae* proteins may prove to be superior vaccines. Data from a mouse model support this possibility.

Chemoprophylaxis with dapsone may reduce the number of cases of tuberculoid leprosy but not of lepromatous leprosy and hence is not recommended, even for household contacts. Because leprosy transmission appears to require close prolonged household contact, hospitalized patients need not be isolated.

In 1992, the WHO—on the basis of that organization's treatment recommendations—launched a landmark campaign to eliminate leprosy as a public health problem by the year 2000 (goal, <1 case per 10,000 population). The campaign mobilized and energized nongovernmental organizations and national health services to treat leprosy with multiple drugs and to clean up outdated registries. In these respects, the effort has proven hugely successful, with >6 million patients completing therapy. However, the target of leprosy elimination has not yet been reached. In fact, the success of the WHO campaign in reducing the number of cases worldwide has been largely attributable to the redefinition of what constitutes a case of leprosy. Formerly calculated by disease prevalence, the case count is now limited to those not yet treated with multiple drugs. In each of the 23 countries with the largest number of leprosy cases, the annual incidence of leprosy is stable or actually rising. Furthermore, after the completion of therapy, when a patient is no longer considered to represent a "case," half of all patients continue to manifest disease activity for years; relapse rates (at least for multibacillary patients) are unacceptably high; disabilities and deformities go unchecked; and the social stigma of the disease persists.

During most of the twentieth century, nongovernmental organizations, particularly Christian missionaries, provided a medical infrastructure devoted to the care and treatment of leprosy patients—the envy of those with other medical priorities in the developing world. With the public perception that leprosy is near eradication, resources for patient care are rapidly being diverted, and the burden of patient care is being transferred to nonexistent or overloaded national health services and to health workers who lack the tools and skills needed for disease diagnosis, classification, and nuanced therapy (particularly in cases of reactional neuritis). Thus, the prerequisites for a salutary outcome increasingly go unmet.

CHAPTER 72

NONTUBERCULOUS MYCOBACTERIAL INFECTIONS

Steven M. Holland

Several terms—nontuberculous mycobacteria (NTM), atypical mycobacteria, mycobacteria other than tuberculosis, and environmental mycobacteria—all refer to mycobacteria other than *Mycobacterium tuberculosis*, its close relatives (*M. bovis, M. caprae, M. africanum, M. pinnipedii, M. canetti*), and *M. leprae*. The number of identified species of NTM is growing and will continue to do so because of the use of DNA sequence typing for speciation. The number of known species currently exceeds 150. NTM are highly adaptable and can inhabit hostile environments, including industrial solvents.

EPIDEMIOLOGY

NTM are ubiquitous in soil and water. Specific organisms have recurring niches, such as *M. simiae* in certain aquifers, *M. fortuitum* in pedicure baths, and *M. immunogenum* in metalworking fluids. Most NTM cause disease in humans only rarely unless some aspect of host defense is impaired, as in bronchiectasis, or breached, as by inoculation (e.g., liposuction, trauma). There are no known instances of human-to-human transmission of NTM. Because infections due to NTM are rarely reported to health agencies and because their identification is sometimes problematic, reliable data on incidence and prevalence are lacking. Disseminated disease denotes significant immune dysfunction (e.g., advanced HIV infection), whereas pulmonary disease, which is much more common, is highly associated with pulmonary epithelial defects but not with systemic immunodeficiency.

In the United States, the incidence and prevalence of pulmonary infection with NTM, mostly in association with bronchiectasis (Chap. 19), have for many years been several-fold higher than the corresponding figures for tuberculosis, and rates of the former are increasing among the elderly. Among patients with cystic fibrosis, who often have bronchiectasis, rates of clinical infection with NTM range from 3% to 15%, with even higher rates among older patients. Although NTM may be recovered from the sputa of many individuals, it is critical to differentiate active disease from commensal harboring of the organisms. A scheme to help with the proper diagnosis of pulmonary infection caused by NTM has been developed by the American Thoracic Society and is widely used. The bulk of nontuberculous mycobacterial disease in North America is due to *M. kansasii*, organisms of the *M. avium* complex (MAC), and *M. abscessus*.

In Europe, Asia, and Australia, the distribution of NTM in clinical specimens is roughly similar to that in North America, with MAC species and rapidly growing organisms such as *M. abscessus* encountered frequently. *M. xenopi* and *M. malmoense* are especially prominent in northern Europe. *M. ulcerans* causes the distinct clinical entity Buruli ulcer, which occurs throughout tropical zones, especially in western Africa. *M. marinum* is a common cause of cutaneous and tendon infections in coastal regions and among individuals exposed to fish tanks or swimming pools.

The true international epidemiology of infections due to NTM is hard to determine since the isolation of these organisms often is not reported and speciation often is not performed. The increasing ease of identification and speciation of these organisms should have a major impact on the description of their international epidemiology in the next few years.

PATHOBIOLOGY

Because exposure to NTM is essentially universal and disease is rare, it can be assumed that normal host defenses against these organisms must be strong and that otherwise healthy individuals in whom significant disease develops are highly likely to have specific susceptibility factors that permit NTM to become established, multiply, and cause disease. At the advent of HIV infection, CD4+ T lymphocytes were recognized as key effector cells against NTM; the development of disseminated MAC disease was highly correlated with a decline in CD4+ T lymphocyte numbers. Such a

decrease has also been implicated in disseminated MAC infection in patients with idiopathic CD4+ T lymphocytopenia. Potent inhibitors of tumor necrosis factor α (TNF-α), such as infliximab, adalimumab, certolizumab, and etanercept, can neutralize this critical cytokine. The occasional result is severe mycobacterial or fungal infection; these associations indicate that TNF-α is a crucial element in mycobacterial control. However, in cases without the above risk factors, much of the genetic basis of susceptibility to disseminated infection with NTM is accounted for by specific mutations in the interferon γ (IFN-γ)/interleukin 12 (IL-12) synthesis and response pathways.

Mycobacteria are typically phagocytosed by macrophages, which respond with the production of IL-12, a heterodimer composed of IL-12p35 and IL-12p40 moieties that together make up IL-12p70. IL-12 activates T lymphocytes and natural killer cells through binding to its receptor (composed of IL-12Rβ1 and IL-12Rβ2/IL-23R), with consequent phosphorylation of STAT4. IL-12 stimulation of STAT4 leads to secretion of IFN-γ, which activates neutrophils and macrophages to produce reactive oxidants, increase expression of the major histocompatibility complex and Fc receptors, and concentrate certain antibiotics intracellularly. Signaling by IFN-γ through its receptor (composed of IFN-γR1 and IFN-γR2) leads to phosphorylation of STAT1, which in turn regulates IFN-γ-responsive genes, such as those coding for IL-12 and TNF-α. TNF-α signals through its own receptor via a downstream complex containing the nuclear factor κB (NFκB) essential modulator (NEMO). Therefore, the positive feedback loop between IFN-γ and IL-12/IL-23 drives the immune response to mycobacteria and other intracellular infections. These genes are known to be the critical ones in the pathway of mycobacterial control: specific Mendelian mutations have been identified in IFN-γR1, IFN-γR2, STAT1, IL-12A, IL-12Rβ1, and NEMO **(Fig. 72-1)**. Despite the identification of genes associated with disseminated disease, only ~50% of cases of disseminated nontuberculous mycobacterial infections that are not associated with HIV infection have a genetic diagnosis; the implication is that more mycobacterial susceptibility genes and pathways remain to be identified.

In contrast to the recognized genes and mechanisms associated with disseminated nontuberculous mycobacterial infection, the best-recognized underlying condition for pulmonary infection with NTM is bronchiectasis (Chap. 19). Most of the well-characterized forms of bronchiectasis, including cystic fibrosis, primary ciliary dyskinesia, STAT3-deficient hyper-IgE syndrome, and idiopathic bronchiectasis, have high rates of association with nontuberculous mycobacterial infection. The precise mechanism by which bronchiectasis predisposes to locally destructive but not systemic involvement is unknown.

Unlike disseminated or pulmonary infection, "hot-tub lung" represents pulmonary hypersensitivity to NTM—most commonly MAC organisms—growing in underchlorinated, often indoor hot tubs.

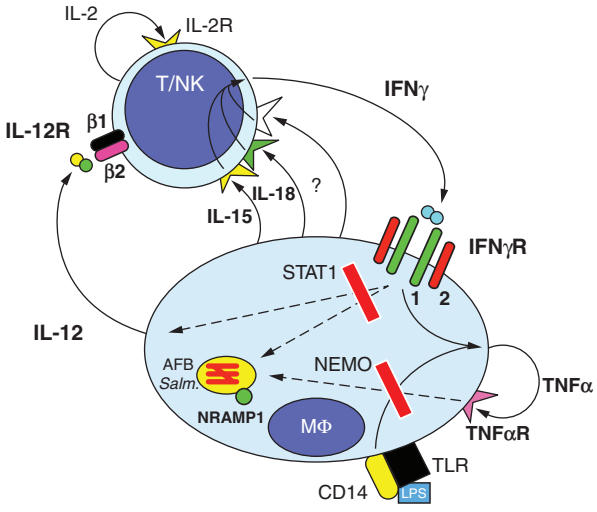


FIGURE 72-1
Cytokine interactions of infected macrophages (Mϕ) with T and natural killer (NK) lymphocytes. Infection of macrophages by mycobacteria (AFB) leads to the release of heterodimeric interleukin 12 (IL-12). IL-12 acts on its receptor complex, with consequent STAT4 activation and production of homodimeric interferon γ (IFNγ). IFNγ acts through its receptor to activate STAT1, to stimulate the production of tumor necrosis factor α (TNFα), and to kill intracellular organisms such as mycobacteria, salmonellae, and some fungi. Homotrimeric TNFα acts through its receptor and requires nuclear factor κB essential modulator (NEMO) to activate nuclear factor κB, which also contributes to the killing of intracellular bacteria. Both IFNγ and TNFα lead to upregulation of IL-12. TNFα-blocking antibodies work either by blocking the ligand (infliximab, adalimumab, certolizumab) or by providing soluble receptor (etanercept). Mutations in IFNγR1, IFNγR2, IL-12p40, IL-12Rβ1, STAT1, and NEMO have been associated with a predisposition to mycobacterial infections. Other cytokines, such as IL-15 and IL-18, also contribute to IFNγ production. Signaling through the Toll-like receptor (TLR) complex and CD14 also upregulates TNFα production. LPS, lipopolysaccharide; NRAMP1, natural resistance-associated macrophage protein 1.

CLINICAL MANIFESTATIONS

Disseminated disease

Disseminated MAC or *M. kansasii* infections in patients with advanced HIV infection are now uncommon in North America because of effective antimycobacterial prophylaxis and improved treatment of HIV infection. When such mycobacterial disease was common, the portal of entry was the bowel, with spread to bone marrow and the bloodstream. Surprisingly, disseminated infections with rapidly growing NTM (e.g., *M. abscessus*, *M. fortuitum*) are very rare in HIV-infected patients, even those with very advanced HIV infection. Because these organisms are of low intrinsic virulence and disseminate only in conjunction with impaired immunity, disseminated disease can be indolent and progressive over weeks to months. Typical manifestations of malaise, fever, and

weight loss are often accompanied by organomegaly, lymphadenopathy, and anemia. Since special cultures or stains are required to identify the organisms, the most critical step in diagnosis is to suspect infection with NTM. Blood cultures may be negative, but involved organs typically have significant organism burdens, sometimes with a grossly impaired granulomatous response. In a child, disseminated involvement (i.e., involvement of two or more organs) without an underlying iatrogenic cause should prompt an investigation of the IFN-γ/IL-12 pathway. Recessive mutations in IFN-γR1 and IFN-γR2 typically lead to severe infection with NTM. In contrast, dominant negative mutations in IFN-γR1, which lead to overaccumulation of a defective interfering mutant receptor on the cell surface, inhibit normal IFN-γ signaling and thus lead to nontuberculous mycobacterial osteomyelitis. Dominant negative mutations in STAT1 and recessive mutations in IL-12Rβ1 can have variable phenotypes consistent with their residual capacities for IFN-γ synthesis and response. Male patients who have disseminated nontuberculous mycobacterial infections along with conical, peg, or missing teeth and an abnormal hair pattern should be evaluated for defects in the pathway that activates NFκB through NEMO. These patients may have associated immune globulin defects as well. A recently recognized group of patients that often develops disseminated infections with rapidly growing NTM (predominantly *M. abscessus*) as well as other opportunistic infections has high-titer neutralizing autoantibodies to IFN-γ. Thus far, this syndrome has been reported most frequently in East Asian female patients.

IV catheters can become infected with NTM, usually as a consequence of contaminated water. *M. abscessus* and *M. fortuitum* sometimes infect deep indwelling lines as well as fluids used in eye surgery, subcutaneous injections, and local anesthetics. Infected catheters should be removed.

Pulmonary disease

Lung disease is by far the most common form of nontuberculous mycobacterial infection in North America and the rest of the industrialized world. The clinical presentation typically consists of months or years of throat clearing, nagging cough, and slowly progressive fatigue. Patients will often have seen physicians multiple times and received symptom-based or transient therapy before the diagnosis is entertained and samples are sent for mycobacterial stains and cultures. Because not all patients can produce sputum, bronchoscopy may be required for diagnosis. The typical lag between onset of symptoms and diagnosis is ~5 years in older women. Predisposing factors include underlying lung diseases such as bronchiectasis (Chap. 19), pneumoconiosis, chronic obstructive pulmonary disease, primary ciliary dyskinesia (Chap. 19), alpha-1 antitrypsin deficiency, and cystic fibrosis. Bronchiectasis and nontuberculous mycobacterial infection often coexist and progress in tandem. This situation makes causality difficult to determine in a given index case, but bronchiectasis is certainly among the most critical predisposing factors that are exacerbated by infection.

MAC organisms are the most common causes of pulmonary nontuberculous mycobacterial infection in North America, but rates vary somewhat by region. MAC infection most commonly develops during the sixth or seventh decade of life in women who have had months or years of nagging intermittent cough and fatigue, with or without sputum production or chest pain. The constellation of pulmonary disease due to NTM in a tall and thin woman who may have chest wall abnormalities is often referred to as Lady Windermere's syndrome, after an Oscar Wilde character of the same name. In fact, pulmonary MAC infection does afflict older nonsmoking white women more than men, with onset at ~60 years. Patients tend to be taller and thinner than the general population, with high rates of scoliosis, mitral valve prolapse, and pectus anomalies. Whereas male smokers with upper-lobe cavitary disease tend to carry the same single strain of MAC indefinitely, nonsmoking females with nodular bronchiectasis tend to carry several strains of MAC simultaneously, with changes over the course of their disease.

M. kansasii can cause a clinical syndrome that strongly resembles tuberculosis, consisting of hemoptysis, chest pain, and cavitary lung disease. The rapidly growing NTM, such as *M. abscessus*, have been associated with esophageal motility disorders such as achalasia. Patients with pulmonary alveolar proteinosis are prone to pulmonary nontuberculous mycobacterial and *Nocardia* infections; the underlying mechanism may be inhibition of alveolar macrophage function due to the autoantibodies to granulocyte-macrophage colony-stimulating factor found in these patients.

Cervical lymph node disease

The most common form of nontuberculous mycobacterial infection among young children in North America is isolated cervical lymphadenopathy, most frequently caused by MAC organisms but also by other NTM. The cervical swelling is typically firm and relatively painless, with a paucity of systemic signs. Since the differential diagnosis of painless adenopathy includes malignancy, many children have infection with NTM diagnosed inadvertently at biopsy; cultures and special stains may not have been requested because mycobacterial disease was not ranked high in the differential. Local fistulae usually resolve completely with resection and/or antibiotic therapy. Likewise, the entity of isolated pediatric intrathoracic nontuberculous mycobacterial infection, which is probably related to cervical lymph node infection, is usually mistaken for cancer. In neither isolated cervical nor isolated intrathoracic infections with NTM have children with underlying immune defects been identified, nor do the affected children go on to develop other opportunistic infections.

Skin and soft tissue disease

Cutaneous involvement with NTM usually requires a break in the skin for introduction of the bacteria. Pedicure bath–associated infection with *M. fortuitum* is more

likely if skin abrasion (e.g., during leg shaving) has occurred just before the pedicure. Outbreaks of skin infection are often caused by rapidly growing NTM (especially *M. abscessus*, *M. fortuitum*, and *M. chelonae*) acquired via skin contamination from surgical instruments (especially in cosmetic surgery), injections, and other procedures. These infections are typically accompanied by painful, erythematous, draining subcutaneous nodules, usually without associated fever or systemic symptoms.

M. marinum lives in many water sources and can be acquired from fish tanks, swimming pools, barnacles, and fish scales. This organism typically causes papules or ulcers ("fish-tank granuloma"), but the infection can progress to tendonitis with significant impairment of manual dexterity. Lesions appear days to weeks after inoculation of organisms by a typically minor trauma (e.g., incurred during the cleaning of boats or the handling of fish). Tender nodules due to *M. marinum* can advance up the arm in a pattern also seen with *Sporothrix schenckii* (*sporotrichoid spread*). The typical carpal tendon involvement may be the first presenting manifestation and may lead to surgical exploration or steroid injection. The index of suspicion must be high for *M. marinum* infections to ensure that proper specimens obtained during procedures are sent for culture.

M. ulcerans, another waterborne skin pathogen, is found mainly in the tropics, especially in tropical areas of Africa. Infection follows skin trauma or insect bites that allow admission to contaminated water. The skin lesions are typically painless, clean ulcers that slough and can cause osteomyelitis. The toxin mycolactone accounts for the modest host inflammatory response and the painless ulcerations.

DIAGNOSIS

NTM can be detected on acid-fast or fluorochrome smears of sputum or other body fluids. When the organism burden is high, the organisms may appear as gram-positive beaded rods, but this finding is unreliable. (In contrast, nocardiae may appear as gram-positive and beaded but filamentous bacteria.) Again, the requisite and most sensitive step in the diagnosis of any mycobacterial disease is to think of including it in the differential. In almost all laboratories, mycobacterial sample processing, staining, and culture are conducted separately from routine bacteriologic tests; thus, many infections go undiagnosed because of the physician's failure to request the appropriate test. In addition, mycobacteria usually require separate blood culture media. NTM are broadly differentiated into rapidly growing (<7 days) and slowly growing (≥7 days) forms. Because *M. tuberculosis* typically takes ≥2 weeks to grow, many laboratories refuse to consider culture results final until 6 weeks have elapsed. Newer techniques using liquid culture media permit more rapid isolation of mycobacteria from specimens than is possible with traditional media. Species more readily detected with incubation at 30°C include *M. marinum*, *M. haemophilum*, and *M. ulcerans*. *M. haemophilum* prefers iron supplementation or blood, while *M. genavense* requires supplemented medium with the additive mycobactin J. Bacterial formation of pigment in light conditions (photochromogenicity) or dark conditions (scotochromogenicity) or a lack of bacterial pigment formation (nonchromogenicity) has been used to help categorize NTM. In contrast to NTM, *M. tuberculosis* is beige, rough, dry, and flat. Current identification schemes can reliably use biochemical, nucleic acid, or cell wall composition, as assessed by high-performance liquid chromatography or mass spectrometry, for speciation. With the remarkable decline in U.S. cases of tuberculosis over recent decades, NTM have become the mycobacteria most commonly isolated from humans in North America. However, not all isolations of NTM, especially from the lung, reflect pathology and require treatment. Whereas identification of an organism in a blood or organ biopsy specimen in a compatible clinical setting is diagnostic, the American Thoracic Society recommends that pulmonary infection due to NTM be diagnosed only when disease is clearly demonstrable—i.e., in an appropriate clinical and radiographic setting (nodules, bronchiectasis, cavities) and with repeated isolation of NTM from expectorated sputum or recovery of NTM from bronchoscopy or biopsy specimens. Given the large number of species of NTM and the importance of accurate diagnosis for the implementation of proper therapy, identification of these organisms is ideally taken to the species level.

The purified protein derivative (PPD) of tuberculin is delivered intradermally to evoke a memory T cell response to mycobacterial antigens. This test is variously referred to as the PPD test, the tuberculin skin test, and the Mantoux test, among other designations. Unfortunately, the cutaneous immune response to these tuberculosis-derived filtrate proteins does not differentiate well between infection with NTM and that with *M. tuberculosis*. Since intermediate reactions (~10 mm) to PPD in latent tuberculosis and nontuberculous mycobacterial infections can overlap significantly, the progressive decline in active tuberculosis in the United States means that NTM probably account for increasing proportions of PPD reactivity. In addition, bacille Calmette-Guérin (BCG) can cause some degree of cross-reactivity, posing problems of interpretation for patients who have received BCG vaccine. Assays to measure the elaboration of IFN-γ in response to the relatively tuberculosis-specific proteins ESAT6 and CFP10 form the basis for IFN-γ-release assays (IGRAs). These assays can be performed with whole blood or on membranes. It is important to note that *M. marinum*, *M. kansasii*, and *M. szulgai* also have ESAT6 and CFP10 and may cause false-positive reactions in IGRAs. Despite cross-reactivity with NTM, large PPD reactions (>15 mm) most commonly signify tuberculosis.

Isolation of NTM from blood specimens is clear evidence of disease. Whereas rapidly growing mycobacteria may proliferate in routine blood culture media, slow-growing NTM typically do not; thus it is imperative to suspect the diagnosis and to use the correct bottles for cultures. Isolation of NTM from a biopsy specimen constitutes strong evidence for infection, but cases of laboratory contamination do occur.

Identification of organisms on stained sections of biopsy material confirms the authenticity of the culture. Certain NTM require lower incubation temperatures (*M. genavense*) or special additives (*M. haemophilum*) for growth. Some NTM (e.g., *M. tilburgii*) remain noncultivable but can be identified molecularly in clinical samples.

The radiographic appearance of nontuberculous mycobacterial disease in the lung depends on the underlying disease, the severity of the infection, and the imaging modality used. The advent and increase in the use of CT has allowed the identification of characteristic changes that are highly consistent with nontuberculous mycobacterial infection, such as the "tree-in-bud" pattern of bronchiolar inflammation **(Fig. 72-2)**. Involvement of the lingual and right-middle lobes is commonly seen on chest CT but is difficult to appreciate on plain film. Severe bronchiectasis and cavity formation are common in more advanced disease. Isolation of NTM from respiratory samples can be confusing. *M. gordonae* is often recovered from respiratory samples but is not usually seen on smear and is almost never a pathogen. Patients with bronchiectasis occasionally have NTM recovered from sputum culture with a negative smear. The American Thoracic Society has developed guidelines for the diagnosis of infection with MAC, *M. abscessus*, and *M. kansasii*. A positive diagnosis requires the growth of NTM from two of three sputum samples, regardless of smear findings; a positive bronchoscopic alveolar sample, regardless of smear findings; or a pulmonary parenchyma biopsy sample with granulomatous inflammation or mycobacteria found on section and NTM on culture. These guidelines probably apply to other NTM as well.

While many laboratories use DNA probes to identify *M. tuberculosis*, MAC, *M. gordonae*, and *M. kansasii*, speciation of NTM helps determine the antimycobacterial therapy to be used. Only testing of MAC organisms for susceptibility to clarithromycin and of *M. kansasii* for susceptibility to rifampin is indicated; few data support other in vitro susceptibility tests, attractive though they appear. MAC isolates that have not been exposed to macrolides are almost always susceptible. NTM that have persisted beyond a course of antimicrobial therapy are often tested for antibiotic susceptibility, but the value and meaning of these tests are undetermined.

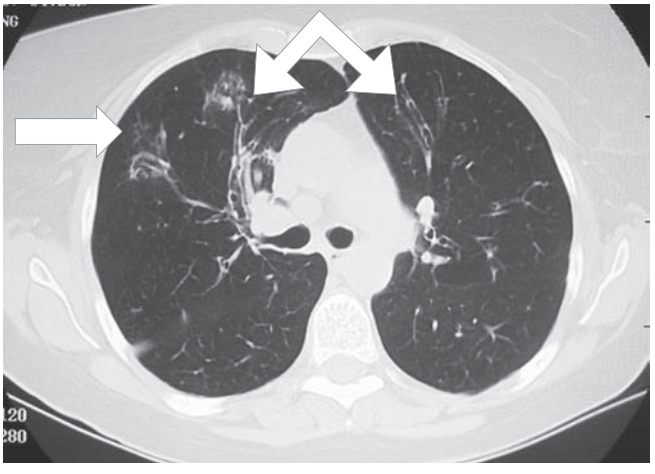


FIGURE 72-2
Chest CT of a patient with pulmonary MAC infection. Arrows indicate the "tree-in-bud" pattern of bronchiolar inflammation (peripheral right lung) and bronchiectasis (central right and left lungs).

PREVENTION

Prophylaxis of MAC disease in patients infected with HIV is started when the CD4+ T lymphocyte count falls to <50/μL. Azithromycin (1200 mg weekly), clarithromycin (1000 mg daily), or rifabutin (300 mg daily) is effective. Macrolide prophylaxis in immunodeficient patients who are susceptible to NTM (e.g., those with defects in the IFN-γ/IL-12 axis) has not been prospectively validated but seems prudent.

TREATMENT Nontuberculous Mycobacteria

NTM cause chronic infections that evolve relatively slowly over a period of weeks to years. Therefore, it is rarely necessary to initiate treatment on an emergent basis before the diagnosis is clear and the infecting species is known. Treatment of NTM is complex, often poorly tolerated, and potentially toxic. Just as in tuberculosis, inadequate single-drug therapy is almost always associated with the emergence of antimicrobial resistance and relapse.

MAC infection often requires multidrug therapy, the foundation of which is a macrolide (clarithromycin or azithromycin), ethambutol, and a rifamycin (rifampin or rifabutin). For disseminated nontuberculous mycobacterial disease in HIV-infected patients, the use of rifamycins poses special problems—i.e., rifamycin interactions with protease inhibitors. For pulmonary MAC disease, thrice-weekly administration of a macrolide, a rifamycin, and ethambutol has been successful. Therapy is prolonged, generally continuing for 12 months after culture conversion; typically, a course lasts for at least 18 months. Other drugs with activity against MAC organisms include IV and aerosolized aminoglycosides, fluoroquinolones, and clofazimine. In elderly patients, rifabutin can exert significant toxicity. However, with only modest efforts, most antimycobacterial regimens are well tolerated by most patients. Resection of cavitary lesions or severely bronchiectatic segments has been advocated for some patients, especially those with macrolide-resistant infections. The success of therapy for pulmonary MAC infections depends on whether disease is nodular or cavitary and on whether it is early or advanced, ranging from 20% to 80%.

M. kansasii lung disease is similar to tuberculosis in many ways and is also effectively treated with isoniazid (300 mg/d), rifampin (600 mg/d), and ethambutol (15 mg/kg per day). Other drugs with very high-level

activity against *M. kansasii* include clarithromycin, fluoroquinolones, and aminoglycosides. Treatment should continue until cultures have been negative for at least 1 year. In most instances, *M. kansasii* infection is easily cured.

Rapidly growing mycobacteria pose special therapeutic problems. Extrapulmonary disease in an immunocompetent host is usually due to inoculation (e.g., via surgery, injections, or trauma) or to line infection and is often treated successfully with a macrolide and another drug (with the choice based on in vitro susceptibility), along with removal of the offending focus. In contrast, pulmonary disease, especially that caused by *M. abscessus*, is extremely difficult to cure. Repeated courses of treatment are usually effective in reducing the infectious burden and symptoms. Therapy generally includes a macrolide along with an IV-administered agent such as amikacin, a carbapenem, cefoxitin, or tigecycline. Other oral agents (used according to in vitro susceptibility testing and tolerance) include fluoroquinolones, doxycycline, and linezolid. Because nontuberculous mycobacterial infections are chronic, care must be taken in the long-term use of drugs with neurotoxicities, such as linezolid and ethambutol. Prophylactic pyridoxine has been suggested in these cases. Durations of therapy for *M. abscessus* lung disease are difficult to predict since so many cases are chronic and require intermittent therapy. Expert consultation and management are strongly recommended.

Once recognized, *M. marinum* infection is highly responsive to antimicrobial therapy and is cured relatively easily with any combination of a macrolide, ethambutol, and a rifamycin. Therapy should be continued for 1–2 months after clinical resolution of isolated soft tissue disease; tendon and bone involvement may require longer courses in light of clinical evolution. Other drugs with activity against *M. marinum* include sulfonamides, trimethoprim-sulfamethoxazole, doxycycline, and minocycline.

Treatment of the other NTM is less well defined, but macrolides and aminoglycosides are usually effective, with other agents added as indicated. Expert consultation is strongly encouraged for difficult or unusual infections due to NTM.

PROGNOSIS

The outcomes of nontuberculous mycobacterial infections are closely tied to the underlying condition (e.g., IFN-γ/IL-12 pathway defect, cystic fibrosis) and can range from recovery to death. With no or inadequate treatment, symptoms and signs can be debilitating, including persistent cough, fever, anorexia, and severe lung destruction. With treatment, patients typically regain strength and energy. The optimal duration of therapy when NTM persist in sputum is unknown, but treatment in this situation can be prolonged.

CHAPTER 73

ANTIMYCOBACTERIAL AGENTS

Max R. O'Donnell ■ Jussi J. Saukkonen

Agents used for the treatment of mycobacterial infections, including tuberculosis (TB), leprosy (Hansen's disease), and infections due to nontuberculous mycobacteria (NTM), are administered in multiple-drug regimens for prolonged courses. Currently, more than 150 species of mycobacteria have been identified, the majority of which do not cause disease in humans. While the incidence of disease caused by *M. tuberculosis* has been declining in the United States, TB remains a leading cause of morbidity and mortality in developing countries—particularly in sub-Saharan Africa, where the HIV epidemic rages. Not only effective drug regimens are needed; without a well-organized infrastructure for diagnosis and treatment of TB, therapeutic and control efforts are severely hampered. Infections with NTM have gained in clinical prominence in the United States and other developed countries. These largely environmental organisms often establish infection in immunocompromised patients or in persons with structural lung disease.

TUBERCULOSIS

GENERAL PRINCIPLES

The earliest recorded human case of TB dates back 9000 years. Early treatment modalities, such as bloodletting, were replaced by sanatorium regimens in the late 19th century. The discovery of streptomycin in 1943 launched the era of antibiotic treatment for TB. Over subsequent decades, the discovery of additional agents and the use of multiple-drug regimens allowed progressive shortening of the treatment course from years to as little as 6 months with the regimen for drug-susceptible TB. Latent TB infection (LTBI) and active TB disease are diagnosed by history, physical examination, tuberculin skin test, interferon γ release assay, radiographic imaging, and/or mycobacterial cultures. LTBI is treated with either isoniazid (9 months) or rifampin (4 months) **(Table 73-1)**.

For active or suspected TB disease, clinical factors, including HIV co-infection, symptom duration, radiographic appearance, and public health concerns about TB transmission, drive diagnostic testing and treatment initiation. Multiple-drug regimens are used for the treatment of TB disease **(Table 73-2)**. Initially, an intensive phase consisting of four drugs—isoniazid, rifampin, pyrazinamide, and ethambutol given for 2 months—is followed by a continuation phase of isoniazid and rifampin for 4 months, for a total treatment duration of 6 months. The continuation phase is extended to 7 months (for a total treatment duration of 9 months) if the 2-month course of pyrazinamide is not completed or, for patients with cavitary pulmonary TB, if sputum cultures remain positive beyond 2 months of treatment (delayed culture conversion).

Treatment of TB in individuals co-infected with HIV poses significant challenges, but some progress is being made. Recent data show improved survival when antiretroviral therapy (ART) is initiated early in TB therapy. Interactions of rifampin with protease inhibitors or nonnucleotide reverse transcriptase inhibitors are significant and require close monitoring and dose adjustments. The TB immune reconstitution inflammatory syndrome (IRIS) may appear as early as 1 week after initiation of ART and manifests as paradoxical worsening or unmasking of existing TB infection. Conservative management consists of continued administration of ART and TB medications; however, severe or debilitating IRIS has been anecdotally treated with varying doses of glucocorticoids. Intermittent therapy in patients co-infected with HIV and *M. tuberculosis* has been associated with low plasma levels of several key TB drugs and with higher rates of treatment failure or relapse; therefore, intermittent twice-weekly therapy for TB in HIV-co-infected individuals is not recommended.

Adherence to medications is critical in achieving a cure with antimycobacterial therapy. Consequently, directly observed therapy (DOT) by trained staff, either in the clinic or at home, is recommended to ensure adherence. In addition, monthly dispensing of TB medicines is recommended, since monthly clinical monitoring for hepatotoxicity due to these medications is essential for all patients. Discontinuation of suspected offending agents at the onset of hepatitis symptoms reduces the risk of progression to fatal hepatitis. Clinical monitoring includes at least monthly assessment for symptoms (nausea, vomiting, abdominal discomfort, and unexplained fatigue) and signs (jaundice, dark urine, light stools, diffuse pruritus) of hepatotoxicity, although the latter represent comparatively late manifestations **(Table 73-3)**. The presence of such symptoms and signs mandates provisional discontinuation of potentially hepatotoxic agents. Biochemical testing of at least serum alanine aminotransferase and total bilirubin levels and exclusion of other causes of these abnormalities are also indicated. For patients with active TB, monthly mycobacterial cultures of sputum are recommended until it is certain that the organisms have been cleared and the patient has responded to therapy or until no sputum is available for culture.

If significant clinical improvement does not occur or the patient's condition deteriorates over the course of therapy, possibilities include treatment failure due to nonadherence to therapy, poor medication absorption, or the development of resistance. For patients co-infected with HIV and *M. tuberculosis*, immune reconstitution inflammatory syndrome (IRIS) is a possibility and is a diagnosis of exclusion. or mycobacterial resistance should be suspected. Drug susceptibility testing should be repeated at this point. If resistance is documented or strongly suspected, at least two efficacious drugs to which the isolate is susceptible or which the patient has not already taken should be added to the therapeutic regimen.

TABLE 73-1

REGIMENS FOR THE TREATMENT OF LATENT TUBERCULOSIS INFECTION (LTBI) IN ADULTS

REGIMEN	SCHEDULE	DURATION	COMMENTS
Isoniazid	300 mg daily (5 mg/kg) Alternative: 900 mg twice weekly (15 mg/kg)	9 months	Supplement with pyridoxine (25–50 mg daily). Twice-weekly regimens require directly observed therapy.
Rifampin	600 mg daily (10 mg/kg)	4 months	Broader efficacy studies are needed.
Isoniazid plus rifapentine[a]	900 mg weekly + 900 mg weekly (15 mg/kg)	4 months	Weekly regimens require directly observed therapy. Supplement with pyridoxine (25–50 mg daily).

[a]Under investigation.

TABLE 73-2

SIMPLIFIED APPROACH TO TREATMENT OF ACTIVE TUBERCULOSIS IN ADULTS

CULTURE RESULTS	INTENSIVE PHASE	CONTINUATION PHASE	EXTENSION OF TOTAL TREATMENT
Culture positive	HRZE for 2 months, daily or intermittent (with dose adjustment)	HR for 4 months, daily or 5 d/wk *or* HR for 4 months, intermittent (with dose adjustment)	To 9 months, if 2 months of Z is not completed or culture conversion is prolonged[a] and/or cavitation is documented
Culture negative	HRZE for 2 months	2 months	To 6 months, if patient is infected with HIV
Resistant to H	RZE or S (Q[b]) for 6 months	. . .	Prolonged culture conversion, cavitation
Resistant to R	HZEQ[b] (IA[c]) for 2 months	HEQ(S) for 10–16 months	Prolonged culture conversion, delayed response
Resistant to HR[d]	ZEQ[b] (IA[c]) ± alternative agents[e] for 18–24 months	. . .	Prolonged culture conversion

[a]Beyond 2 months.
[b]Moxifloxacin and levofloxacin are the preferred fluoroquinolones; ciprofloxacin should be avoided.
[c]Injectable agents: streptomycin, amikacin, kanamycin, and capreomycin.
[d]Management of multidrug-resistant TB should be performed by or in close consultation with an expert TB clinician. Surgical management should be considered.
[e]Alternative agents: cycloserine, ethionamide, para-aminosalicylic acid, clarithromycin, linezolid, and amoxicillin-clavulanate.
Abbreviations: E, ethambutol; H, isoniazid; IA, injectable agent; Q, fluoroquinolone; R, rifampin; S, streptomycin; Z, pyrazinamide.

Multidrug-resistant tuberculosis (MDR-TB) is defined as disease caused by a strain of *M. tuberculosis* that is resistant to both isoniazid and rifampin—the most efficacious of the first-line TB drugs. The risk of MDR-TB is elevated in patients presenting from geographic areas in which ≥5% of incident TB is MDR-TB and in patients previously treated for TB. Treatment regimens for MDR-TB generally include a late-generation fluoroquinolone and an injectable second-line agent (such as capreomycin, amikacin, or kanamycin). Regimens of at least five drugs are recommended for the treatment of MDR-TB. Both standardized and optimized/customized regimens are in use around the world. Extensively drug-resistant tuberculosis (XDR-TB) is defined as MDR-TB with additional resistance to any fluoroquinolone and at least one of the second-line injectable agents. Treatment of XDR-TB is individualized on the basis of extended antimicrobial susceptibility testing. Therapeutic regimens for either MDR-TB or XDR-TB should be constructed with input from clinicians experienced in the management of TB.

FIRST-LINE ANTITUBERCULOSIS DRUGS

Isoniazid

Isoniazid is a critical drug for treatment of both TB disease and LTBI. Isoniazid has excellent bactericidal activity against both intracellular and extracellular, actively dividing *M. tuberculosis*. This drug is bacteriostatic against slowly dividing organisms. In treatment of LTBI, isoniazid is considered the first-line agent because it is generally well tolerated, has well-established efficacy, and is inexpensive. In this setting, the drug is taken daily or intermittently (i.e., twice weekly) as DOT for 9 months. The 9-month course is more efficacious than the 6-month course (75–90% vs. ≥65%), but extension of treatment to 12 months is not likely to provide further protection. A 6-month course of daily or intermittent isoniazid is considered second-line, but acceptable, therapy.

For treatment of TB, isoniazid is used in combination with other agents to ensure killing of both actively dividing *M. tuberculosis* and slowly growing "persister" organisms. Unless the organism is resistant, the standard regimen includes isoniazid, rifampin, ethambutol, and pyrazinamide (Table 73-2). Isoniazid is often given together with 25–50 mg of pyridoxine daily to prevent drug-related peripheral neuropathy.

Mechanism of action

Isoniazid is a prodrug activated by the mycobacterial KatG catalase/peroxidase; isoniazid is coupled with reduced nicotinamide adenine dinucleotide (NADH). The resulting isonicotinic acyl-NADH complex blocks the mycobacterial ketoenoylreductase known as InhA, binding to its substrate and inhibiting fatty acid synthase and ultimately mycolic acid synthesis. Mycolic acids are essential requirements for the mycobacterial cell wall. KatG activation of isoniazid also results in the release of free radicals that have antimycobacterial activity, including nitric oxide.

The minimal inhibitory concentrations (MICs) of isoniazid for wild-type (untreated) susceptible strains are <0.1 μg/mL for *M. tuberculosis* and 0.5–2 μg/mL for *M. kansasii*.

Pharmacology

Isoniazid is the hydrazide of isonicotinic acid, a small, water-soluble molecule. The usual adult oral daily dose of

TABLE 73-3

MONITORING AND CLINICAL MANAGEMENT OF TUBERCULOSIS TREATMENT IN ADULTS[a]

DRUG	ASSESSMENT	MANAGEMENT
LTBI Treatment		
With hepatic risk factors[b], check ALT and bilirubin at baseline. If ALT is ≥3 × ULN or total bilirubin is >2, defer treatment and reevaluate.		
Isoniazid	Determine whether hepatic risk factors are present. If so, obtain baseline and periodic ALT and bilirubin values.	If ALT is 5 × ULN (or 3 × ULN with symptoms)[c] or if bilirubin reaches jaundice levels (usually >2 × ULN), interrupt treatment. With normalization, consider an alternative agent.
Rifampin	Same	Same
TB Treatment		
Check ALT, bilirubin, platelets, creatinine, and hepatitis panel on all patients at baseline. If hepatic risk factors are present, check ALT and bilirubin monthly.		
Isoniazid	If ALT is >5 × ULN (or >3 × ULN with hepatitis symptoms)[c]	Obtain history of alcohol consumption and concomitant drugs. In most instances, discontinue H, Z, R, and other hepatotoxic drugs. Consider alternative agents. Obtain viral hepatitis serologies. Rechallenge: With normalization of liver enzymes, sequentially reintroduce R and then H. With no recurrence of hepatotoxicity, do not resume Z. Alternative rechallenge protocols have been proposed.
Rifampin	If primary elevation is in bilirubin and alkaline phosphatase, more likely rifampin	Discontinue R if bilirubin reaches jaundice levels (usually >2 × ULN). May try to reintroduce. If not tolerated, may substitute Q.
Ethambutol	Decrease in visual acuity or color vision or appearance on monthly screening	Discontinue ethambutol and repeat ocular exam. Peripheral neuropathy may be a precursor of ocular toxicity; if it occurs, consider repeat ocular exam.
Pyrazinamide	If ALT is >5 × ULN (or >3 × ULN with symptoms)[c]	Same as for H
Fluoroquinolone	If QT_c prolongation is discovered incidentally on ECG	Check audiometry and at least BUN and creatinine monthly.
Aminoglycoside	Abnormal results on audiometry testing, BUN, creatinine, electrolytes at baseline or on monthly check	Discontinue aminoglycoside if not MDR-TB. As appropriate, assess renal function, correct electrolytes, or seek ENT consultation.

[a] All regimens require monthly clinical monitoring.
[b] Hepatic risk factors: chronic alcohol use, viral hepatitis, preexisting liver disease, pregnancy or 3 months postpartum, hepatotoxic medications.
[c] Relevant manifestations include nausea, vomiting, abdominal pain, jaundice, or unexplained fatigue.
Abbreviations: ALT, alanine aminotransferase; BUN, blood urea nitrogen; H, isoniazid; Q, fluoroquinolone; R, rifampin; Z, pyrazinamide; ULN, upper limit of normal; MDR-TB, multidrug-resistant tuberculosis; ENT, ear, nose, and throat.

300 mg results in peak serum levels of 3–5 μg/mL within 30 min to 2 h after ingestion—well in excess of the MICs for most susceptible strains of *M. tuberculosis*. Both oral and IM preparations of isoniazid achieve good levels in the body, although antacids and high-carbohydrate meals may interfere with oral absorption. Isoniazid diffuses well throughout the body, reaching therapeutic concentrations in body cavities and fluids, with concentrations in cerebrospinal fluid (CSF) comparable to those in serum.

Isoniazid is metabolized in the liver via acetylation by *N*-acetyltransferase 2 (NAT2) and hydrolysis. Both fast- and slow-acetylation phenotypes occur; patients who are "fast acetylators" may have lower serum levels of isoniazid, whereas slow acetylators may have higher levels and experience more toxicity. Satisfactory isoniazid levels are attained in the majority of homozygous fast NAT2 acetylators given a dose of 6 mg/kg and in the majority of homozygous slow acetylators given only 3 mg/kg. Genotyping is increasingly being used to characterize isoniazid-related pharmacogenomic responses.

Isoniazid's interactions with other drugs are due primarily to its inhibition of the cytochrome P450 system. Among the drugs with significant isoniazid interactions are warfarin, carbamazepine, benzodiazepines, acetaminophen, clopidogrel, maraviroc, dronedarone, salmeterol, tamoxifen, eplerenone, and phenytoin.

Dosing

The recommended daily dose for the treatment of TB in the United States is 5 mg/kg for adults and

10–20 mg/kg for children, with a maximal daily dose of 300 mg for both. For intermittent therapy in adults (usually twice per week), the dose is 15 mg/kg with a maximal daily dose of 900 mg. Isoniazid does not require dosage adjustment in patients with renal disease.

Resistance

Although isoniazid is, along with rifampin, the mainstay of TB treatment regimens, ~7% of clinical *M. tuberculosis* isolates in the United States are resistant. Rates of primary isoniazid resistance among untreated patients are significantly higher in many populations born outside the United States. Four separate pathways for isoniazid resistance have been elucidated. Most strains have amino acid changes in either the catalase-peroxidase gene (*katG*) or the mycobacterial ketoenoylreductase gene (*inhA*). Less frequently, alterations in *kasA*, the gene for an enzyme involved in mycolic acid elongation, and loss of NADH dehydrogenase 2 activity confer isoniazid resistance.

Adverse effects

Although isoniazid is generally well tolerated, drug-induced liver injury and peripheral neuropathy are significant adverse effects associated with this agent. Isoniazid may cause asymptomatic transient elevation of aminotransferase levels (often termed *hepatic adaptation*) in up to 20% of recipients. Other adverse reactions include rash (2%), fever (1.2%), anemia, acne, arthritic symptoms, a systemic lupus erythematosus–like syndrome, optic atrophy, seizures, and psychiatric symptoms. Symptomatic hepatitis occurs in fewer than 0.1% of persons treated with isoniazid alone for LTBI, and fulminant hepatitis with hepatic failure occurs in fewer than 0.01%. Isoniazid-associated hepatitis is idiosyncratic, but its incidence increases with age, with daily alcohol consumption, and in women who are within 3 months postpartum.

In patients who have liver disorders or HIV infection, who are pregnant or in the 3-month postpartum period, who have a history of liver disease (e.g., hepatitis B or C, alcoholic hepatitis, or cirrhosis), who use alcohol regularly, who have multiple medical problems, or who have other risk factors for chronic liver disease, the risks and benefits of treatment for LTBI should be weighed. If treatment is undertaken, these patients should have serum concentrations of alanine aminotransferase (ALT) determined at baseline. Routine baseline hepatic ALT testing based solely on an age of >35 years is optional and depends on individual concerns. Monthly biochemical monitoring during isoniazid treatment is indicated for patients whose baseline liver function tests yield abnormal results and for persons at risk for hepatic disease, including the groups just mentioned. Guidelines recommend that isoniazid be discontinued in the presence of hepatitis symptoms or jaundice and an ALT level three times the upper limit of normal or in the absence of symptoms with an ALT level five times the upper limit of normal (Table 73-3).

Peripheral neuropathy associated with isoniazid occurs in up to 2% of patients given 5 mg/kg. Isoniazid appears to interfere with pyridoxine (vitamin B_6) metabolism. The risk of isoniazid-related neurotoxicity is greatest for patients with preexisting disorders that also pose a risk of neuropathy, such as HIV infection; for those with diabetes mellitus, alcohol abuse, or malnutrition; and for those simultaneously receiving other potentially neuropathic medications, such as stavudine. These patients should be given prophylactic pyridoxine (25–50 mg/d).

Rifampin

Rifampin is a semisynthetic derivative of *Amycolatopsis rifamycinica* (formerly known as *Streptomyces mediterranei*). The most active antimycobacterial agent available, rifampin is the keystone of first-line treatment for TB. Introduced in 1968, this drug eventually permitted dramatic shortening of TB treatment. Rifampin has bactericidal activity against both dividing and nondividing *M. tuberculosis*, with sterilizing activity. The drug is also active against an array of other organisms, including some gram-positive and gram-negative bacteria, *Legionella*, *M. kansasii*, and *M. marinum*.

Rifampin, administered for 4 months, is also an alternative agent to isoniazid for the treatment of LTBI, although efficacy data are scant at this time. A 3-month course of rifampin alone has been found to be similar in efficacy to a 6-month course of isoniazid. Although the 4-month regimen of rifampin has not yet been compared with 9 months of isoniazid, randomized safety and tolerability studies indicate that rates of discontinuation, hepatotoxicity, and adverse reaction are lower with the former than with the latter. The rates of treatment completion are also higher for the 4-month rifampin regimen.

Mechanism of action

Rifampin exerts both intracellular and extracellular bactericidal activity. Like other rifamycins, rifampin specifically binds to and inhibits mycobacterial DNA-dependent RNA polymerase, blocking RNA synthesis. Susceptible strains of *M. tuberculosis* as well as *M. kansasii* and *M. marinum* are inhibited by rifampin concentrations of 1 μg/mL.

Pharmacology

Rifampin is a fat-soluble, complex macrocyclic molecule readily absorbed after oral administration. Serum levels of 10–20 μg/mL are achieved 2.5 h after the usual adult oral dose of 10 mg/kg (given without food). Rifampin has a half-life of 1.5–5 h. The drug distributes well throughout most body tissues, including CSF. Rifampin turns body fluids such as urine, saliva, sputum, and tears a reddish-orange color—an effect that offers a simple means of assessing patients' adherence to this medication. Rifampin is excreted primarily through the bile and enters the enterohepatic circulation; <30% of a dose is renally excreted.

As a potent inducer of the hepatic cytochrome P450 system, rifampin can decrease the half-life of some drugs, such as digoxin, warfarin, phenytoin, prednisone, cyclosporine, methadone, oral contraceptives, clarithromycin, azole antifungal agents, quinidine, and antiretroviral protease inhibitors and nonnucleoside reverse

transcriptase inhibitors. The Centers for Disease Control and Prevention has issued guidelines for the management of drug interactions during treatment of HIV and *M. tuberculosis* co-infection (*www.cdc.gov/tb/*).

Dosing

The daily dosage of rifampin is 10 mg/kg for adults and 10–20 mg/kg for children, with a maximum of 600 mg/d for both. The drug is given once daily, twice weekly, or three times weekly. No adjustments of dose or frequency are necessary in patients with renal insufficiency.

Resistance

Resistance to rifampin in *M. tuberculosis*, *M. leprae*, and other organisms is the consequence of spontaneous, mostly missense point mutations in a core region of the bacterial gene coding for the β subunit of RNA polymerase (*rpoB*). RNA polymerase altered in this manner is no longer subject to inhibition by rifampin. Most rapidly and slowly growing NTM harbor intrinsic resistance to rifampin, for which the mechanism has yet to be determined.

Adverse effects

Adverse events associated with rifampin are infrequent and generally mild. Hepatotoxicity due to rifampin alone is uncommon in the absence of preexisting liver disease and often consists of isolated hyperbilirubinemia rather than aminotransferase elevation. Other adverse reactions include rash, pruritus, gastrointestinal symptoms, and pancytopenia. Rarely, a hypersensitivity reaction may occur with intermittent therapy, manifesting as fever, chills, malaise, rash, and—in some instances—renal and hepatic failure.

Ethambutol

Ethambutol is a bacteriostatic antimycobacterial agent first synthesized in 1961. A component of the standard first-line regimen, ethambutol provides synergy with the other drugs in the regimen and is generally well tolerated. Susceptible species include *M. tuberculosis*, *M. marinum*, *M. kansasii*, and organisms of the *M. avium* complex (MAC); however, among first-line drugs, ethambutol is the least potent against *M. tuberculosis*. This agent is also used in combination with other agents in the continuation phase of treatment in patients who cannot tolerate isoniazid or rifampin or who are infected with organisms resistant to either of the latter drugs.

Mechanism of action

Ethambutol is bacteriostatic against *M. tuberculosis*. Its primary mechanism of action is the inhibition of the arabinosyltransferases involved in cell wall synthesis, which probably inhibits the formation of arabinogalactan and lipoarabinomannan.

Pharmacology and dosing

From a single dose of ethambutol, 75–80% is absorbed within 2–4 h of administration. Serum levels peak at 2–4 μg/mL after the standard adult daily dose of 15 mg/kg. Ethambutol is well distributed throughout the body except in the CSF; a dosage of 25 mg/kg is necessary for attainment of a CSF level half of that in serum. For intermittent therapy, the dosage is 50 mg/kg twice weekly. To prevent toxicity, the dosage must be lowered and the frequency of administration reduced for patients with renal insufficiency.

Adverse effects

Ethambutol is usually well tolerated and has no significant interactions with other drugs. Optic neuritis, the most serious adverse effect reported, typically presents as reduced visual acuity, central scotoma, and loss of the ability to see green (or, less commonly, red). The cause of this neuritis is unknown, but it may be due to an effect of ethambutol on the amacrine and bipolar cells of the retina. Symptoms typically develop several months after initiation of therapy, but ocular toxicity soon after initiation of ethambutol has been described. The risk of ocular toxicity is dose dependent, with occurrence in 1–5% of patients, and can be increased by renal insufficiency. The routine use of ethambutol in younger children is not recommended, as monitoring for visual complications can be difficult. If drug-resistant TB is suspected, ethambutol can be used in children.

All patients starting therapy with ethambutol should have a baseline test for visual acuity, visual fields, and color vision and should undergo an examination of the optic fundus. Visual acuity and color vision should be monitored monthly or less often as needed. Cessation of ethambutol in response to early symptoms of ocular toxicity usually results in reversal of the deficit within several months. Recovery of all visual function may take up to 1 year. In the elderly and in patients in whom symptoms are not recognized early, deficits may be permanent. Some experts think that supplementation with hydroxycobalamin (vitamin B_{12}) is beneficial for patients with ethambutol-related ocular toxicity.

Other adverse effects of ethambutol are rare. Peripheral sensory neuropathy occurs in rare instances.

Resistance

Ethambutol resistance in *M. tuberculosis* and NTM is associated primarily with missense mutations in the *embB* gene that encodes for arabinosyltransferase. Mutations have been found in resistant strains at codon 306 in 50–70% of cases. Mutations at *embB*306 can cause significantly increased MICs of ethambutol, resulting in clinical resistance.

Pyrazinamide

A nicotinamide analog, pyrazinamide is an important bactericidal drug used in the initial phase of TB treatment. Its administration for the first 2 months of therapy with rifampin and isoniazid allows treatment duration to be shortened from 9 months to 6 months and decreases rates of relapse.

Mechanism of action

Pyrazinamide's antimycobacterial activity is essentially limited to *M. tuberculosis*. The drug is more

active against slowly replicating organisms than against actively replicating organisms. Pyrazinamide is a prodrug that is converted by the mycobacterial pyrimidase to the active form, pyrazinoic acid (POA). This agent is active only in acidic environments (pH <6.0), as are found within phagocytes or granulomas. The exact mechanism of action of POA is unclear, but fatty acid synthetase I may be the primary target in *M. tuberculosis*.

Pharmacology and dosing

Pyrazinamide is well absorbed after oral administration, with peak serum concentrations of 20–60 μg/mL at 1–2 h after ingestion of the recommended adult daily dose of 15–30 mg/kg (maximum, 2 g/d). It distributes well to various body compartments, including CSF, and is an important component of treatment for tuberculous meningitis. The serum half-life of the drug is 9–11 h with normal renal and hepatic function. Pyrazinamide is metabolized in the liver to POA, 5-hydroxypyrazinamide, and 5-hydroxy-POA. A high proportion of pyrazinamide and its metabolites (~70%) is excreted in the urine. The dosage must be adjusted according to the level of renal function in patients with reduced creatinine clearance.

Adverse effects

At the higher dosages used previously, hepatotoxicity was seen in as many as 15% of patients treated with pyrazinamide. However, at the currently recommended dosages, hepatotoxicity now occurs less commonly when this drug is administered with isoniazid and rifampin during the treatment of TB. Older age, active liver disease, HIV infection, and low albumin levels may increase the risk of hepatotoxicity. The use of pyrazinamide with rifampin for the treatment of LTBI is no longer recommended because of unacceptable rates of hepatotoxicity and death in this setting. Hyperuricemia is a common adverse effect of pyrazinamide therapy that usually can be managed conservatively. Clinical gout is rare.

Although pyrazinamide is recommended by international tuberculosis organizations for routine use in pregnancy, it is not recommended in the United States because of inadequate teratogenicity data.

Resistance

The basis of pyrazinamide resistance in *M. tuberculosis* is a mutation in the *pncA* gene coding for pyrazinamidase, the enzyme that converts the prodrug to active POA. Resistance to pyrazinamide is associated with loss of pyrazinamidase activity, which prevents conversion of pyrazinamide to POA. Of pyrazinamide-resistant *M. tuberculosis* isolates, 72–98% have mutations in *pncA*. Conventional methods of testing for susceptibility to pyrazinamide may produce both false-negative and false-positive results because the high-acidity environment required for the drug's activation also inhibits the growth of *M. tuberculosis*. There is some controversy as to the clinical significance of in vitro pyrazinamide resistance.

FIRST-LINE SUPPLEMENTAL DRUGS

Rifabutin

Rifabutin, a semisynthetic derivative of rifamycin S, inhibits mycobacterial DNA-dependent RNA polymerase. Although rifabutin is active in vitro against some strains of rifampin-resistant *M. tuberculosis*, its clinical utility in this situation is not clear. Rifabutin is more active than rifampin against MAC organisms and other NTM in vitro.

Rifabutin is recommended in place of rifampin for the treatment of HIV-co-infected individuals who are taking protease inhibitors or nonnucleoside reverse transcriptase inhibitors, particularly nevirapine. Rifabutin's effect on hepatic enzyme induction is less pronounced than that of rifampin. Protease inhibitors may cause significant increases in rifabutin levels through inhibition of hepatic metabolism.

Pharmacology

Like rifampin, rifabutin is lipophilic and is absorbed rapidly after oral administration, reaching peak serum levels 2–4 h after ingestion. Rifabutin distributes best to tissues, reaching levels 5–10 times higher than those in plasma. Unlike rifampin, rifabutin and its metabolites are partially cleared by the hepatic microsomal system. Rifabutin's slow clearance results in a mean serum half-life of 45 h—much longer than the 3- to 5-h half-life of rifampin. Clarithromycin (but not azithromycin) and fluconazole appear to increase rifabutin levels by inhibiting hepatic metabolism.

Adverse effects

Rifabutin is generally well tolerated, with adverse effects occurring at higher doses. The most common adverse events are gastrointestinal; other reactions include rash, headache, asthenia, chest pain, myalgia, and insomnia. Less common adverse reactions include fever, chills, a flulike syndrome, anterior uveitis, hepatitis, *Clostridium difficile*–associated diarrhea, a diffuse polymyalgia syndrome, and yellow skin discoloration ("pseudo-jaundice"). Laboratory abnormalities include neutropenia, leukopenia, thrombocytopenia, and increased levels of liver enzymes.

Resistance

Resistance to rifabutin is mediated by some mutations in *rpoB*.

Rifapentine

Rifapentine is a semisynthetic cyclopentyl rifamycin, sharing a mechanism of action with rifampin. Rifapentine is lipophilic and has a prolonged half-life that permits weekly or twice-weekly dosing (although dosing and frequency of administration are still being actively studied). Because of higher rates of relapse, rifapentine is not approved for administration to patients with HIV disease. It is being studied for treatment of LTBI in a weekly combination regimen with isoniazid given for 3 months (versus the standard 9-month regimen).

Pharmacology

Rifapentine's good absorption is improved when the drug is taken with food. After oral administration, rifapentine reaches peak serum concentrations in 5–6 h and achieves a steady state in 10 days. The half-life of rifapentine and its active metabolite, 25-desacetyl rifapentine, is ~13 h. The administered dose is excreted via the liver (70%).

Adverse effects

The adverse-effects profile of rifapentine is similar to that of other rifamycins. Rifapentine is teratogenic in animal models and is relatively contraindicated in pregnancy.

Resistance

Rifapentine resistance is mediated by mutations in *rpoB*. Mutations that cause resistance to rifampin also cause resistance to rifapentine.

Streptomycin

Streptomycin was the first antimycobacterial agent used for the treatment of TB. Derived from *Streptomyces griseus*, streptomycin is bactericidal against dividing *M. tuberculosis* organisms but has only low-level early bactericidal activity. This drug is administered only by the IM and IV routes. In developed nations, streptomycin is used infrequently because of its toxicity, the inconvenience of injections, and drug resistance. In developing countries, however, streptomycin is used because of its low cost.

Mechanism of action

Streptomycin inhibits protein synthesis by binding at a site on the 30S mycobacterial ribosome.

Pharmacology and dosing

Serum levels of streptomycin peak at 25–45 μg/mL after a 1-g dose. This agent penetrates poorly into the CSF, reaching levels that are only 20% of serum levels. The usual daily dose of streptomycin (given IM either daily or 5 days per week) is 15 mg/kg for adults and 20–40 mg/kg for children, with a maximum of 1 g/d for both. For patients ≥60 years of age, 10 mg/kg is the recommended daily dose, with a maximum of 750 mg/d. Because streptomycin is eliminated almost exclusively by the kidneys, its use in patients with renal impairment should be avoided or implemented with caution, with lower doses and less frequent administration.

Adverse effects

Adverse reactions occur frequently with streptomycin (10–20% of patients). Ototoxicity (primarily vestibulotoxicity), neuropathy, and renal toxicity are the most common and the most serious. Renal toxicity, usually manifested as nonoliguric renal failure, is less common with streptomycin than with other frequently used aminoglycosides, such as gentamicin. Manifestations of vestibular toxicity include loss of balance, vertigo, and tinnitus. Patients receiving streptomycin must be monitored carefully for these adverse effects, undergoing audiometry at baseline and monthly thereafter.

Resistance

Spontaneous mutations conferring resistance to streptomycin are relatively common, occurring in 1 in 10^6 organisms. In the two-thirds of streptomycin-resistant *M. tuberculosis* strains exhibiting high-level resistance, mutations have been identified in one of two genes: a 16S rRNA gene (*rrs*) or the gene encoding ribosomal protein S12 (*rpsL*). Both targets are believed to be involved in streptomycin ribosomal binding. However, low-level resistance, which is seen in about one-third of resistant isolates, has no associated resistance mutation. A gene (*gidB*) that confers low-level resistance to streptomycin has recently been identified. Strains of *M. tuberculosis* resistant to streptomycin generally are not cross-resistant to capreomycin or amikacin.

SECOND-LINE ANTITUBERCULOSIS DRUGS

Second-line antituberculosis agents are indicated for treatment of drug-resistant TB, for patients who are intolerant or allergic to first-line agents, and when first-line supplemental agents are unavailable.

Fluoroquinolones

Fluoroquinolones inhibit mycobacterial DNA gyrase and topoisomerase IV, preventing cell replication and protein synthesis, and are bactericidal. The later-generation fluoroquinolones moxifloxacin and levofloxacin are the most active against *M. tuberculosis* and are being investigated for their potential to shorten the course of treatment for TB. Gatifloxacin, although also being assessed for shortening of treatment duration, causes significant dysglycemia. Ciprofloxacin is no longer recommended for the treatment of TB because of poor efficacy.

The fluoroquinolones are well absorbed orally, achieve high serum levels, and distribute well into body tissues and fluids. Their absorption is decreased by coingestion with products containing multivalent cations, such as antacids. Adverse effects are relatively infrequent (0.5–10% of patients) and include gastrointestinal intolerance, rashes, dizziness, and headache. Most studies of fluoroquinolone side effects have been based on relatively short-term administration for bacterial infections, but trials have now shown the relative safety and tolerability of fluoroquinolones administered for months during TB treatment in adults. The potential to prolong the QT_c interval leading to cardiac arrhythmias has been a source of concern with fluoroquinolones. QT_c prolongation requiring cessation of treatment is rare. There is increasing interest in the use of fluoroquinolones in children, which has traditionally been avoided because of the risks of tendon rupture and cartilage damage, as the benefits in treatment of drug-resistant TB may outweigh the risks.

Mycobacterial resistance can develop rapidly when a fluoroquinolone is inadvertently administered alone. Empirical fluoroquinolone therapy for presumed community-acquired pneumonia is associated with increased resistance in *M. tuberculosis*. Mutations in the genes encoding for DNA gyrase (*gyrA* and *gyrB*) are implicated in many but not all cases of clinical resistance to fluoroquinolones.

Capreomycin

Capreomycin, a cyclic peptide antibiotic derived from *Streptomyces capreolus*, is an important second-line agent used for treatment of MDR-TB, particularly when additional resistance to aminoglycosides is documented. Capreomycin is administered by the IM route; an inhaled preparation is under study. A dose of 15 mg/kg per day is given five to seven times per week (maximal daily dose, 1 g) and results in peak blood levels of 20–40 μg/mL. The dosage may be reduced to 1 g two or three times per week 2–4 months after mycobacterial cultures become negative. For individuals ≥60 years of age, the dose should be reduced to 10 mg/kg per day (maximal daily dose, 750 mg). For patients with renal insufficiency, the drug should be given intermittently and at lower dosage (12–15 mg/kg two or three times per week). A minimal duration of 3 months is recommended for MDR-TB treatment. Penetration of capreomycin into the CSF is believed to be poor.

The mechanism of capreomycin's action is not well understood but involves interference with the mycobacterial ribosome and inhibition of protein synthesis. Resistance to capreomycin is associated with mutations that inactivate a ribosomal methylase (TlyA) or that encode genes for the 16S ribosomal subunit (*rrs*). Cross-resistance to kanamycin and amikacin is common. However, some strains that are resistant to streptomycin, kanamycin, and amikacin generally remain susceptible to capreomycin.

Adverse effects of capreomycin are relatively common. Significant hypokalemia and hypomagnesemia as well as oto- and renal toxicity have been reported.

Amikacin and kanamycin

Amikacin and kanamycin are aminoglycosides that exert mycobactericidal activity by binding to the 16S ribosomal subunit. The spectrum of antibiotic activity for amikacin and kanamycin includes *M. tuberculosis*, several NTM species, and aerobic gram-negative and gram-positive bacteria. Although amikacin is highly active against *M. tuberculosis*, it is used only infrequently because of its significant side effects. The usual daily adult dosage of both amikacin and kanamycin is 15–30 mg/kg given IM or IV (maximal daily dose, 1 g), with a reduction to 10 mg/kg for patients ≥60 years old. For patients with renal insufficiency, the dose and frequency should be reduced (12–15 mg/kg two or three times per week). Mycobacterial resistance is due to mutations in the genes encoding the16S ribosomal RNA gene. Cross-resistance among kanamycin, amikacin, and capreomycin is common. Isolates resistant to streptomycin are frequently susceptible to amikacin or kanamycin. Adverse effects of amikacin include ototoxicity (in up to 10% of recipients, with auditory dysfunction occurring more commonly than vestibulotoxicity), nephrotoxicity, and neurotoxicity. Kanamycin has a similar side-effects profile, but adverse reactions are thought to be less frequent and less severe.

Ethionamide

Ethionamide is a derivative of isonicotinic acid. Its mechanism of action is through inhibition of the *inhA* gene product enoyl–acyl carrier protein (acp) reductase, which is involved in mycolic acid synthesis. Ethionamide is bacteriostatic against metabolically active *M. tuberculosis* and some NTM. It is used in the treatment of drug-resistant TB, but its use is limited by severe gastrointestinal reactions (including abdominal pain, nausea, and vomiting) as well as significant central and peripheral neurologic side effects, reversible hepatitis (in ~5% of recipients), hypersensitivity reactions, and hypothyroidism. Ethionamide should be taken with food to reduce gastrointestinal effects and with pyridoxine (50–100 mg/d) to limit neuropathic side effects.

Para-aminosalicylic acid

Para-aminosalicylic acid (PAS, 4-aminosalicylic acid) is an oral agent used in the treatment of MDR- and XDR-TB. Its bacteriostatic activity is due to inhibition of folate synthesis and of iron uptake. PAS has relatively little activity as an anti-tuberculous agent, with a high level of nausea, vomiting, and diarrhea. PAS may cause hemolysis in patients with glucose-6-phosphate dehydrogenase deficiency. The drug should be taken with acidic foods to improve absorption. Enteric-coated PAS granules (4 g orally every 8 h) appear to be better tolerated than other formulations and produce higher therapeutic blood levels. PAS has a short half-life (1 h), and 80% of the dose is excreted in the urine.

Cycloserine

Cycloserine is an analog of the amino acid D-alanine and prevents cell wall synthesis. It inhibits the action of enzymes, including alanine racemase, that are involved in the production of peptidoglycans. Cycloserine is active against a range of bacteria, including *M. tuberculosis*. Mechanisms of mycobacterial resistance are not well understood, but overexpression of alanine racemase can confer resistance in *M. smegmatis*. Cycloserine is well absorbed after oral administration and is widely distributed throughout body fluids, including CSF. The usual adult dosage is 250 mg two or three times per day. Serious potential side effects include seizures and psychosis (with suicide in some cases), peripheral neuropathy, headache, somnolence, and allergic reactions. Drug levels are monitored to achieve optimal dosing and to reduce the risk of adverse effects, especially in patients with renal failure. Cycloserine should be administered as DOT only with caution and with support from experienced TB physicians to patients with epilepsy, active alcohol abuse, severe renal insufficiency, or a history of depression or psychosis.

NEWER ANTITUBERCULOSIS DRUGS IN CLINICAL TRIALS

Linezolid

Linezolid is an oxazolidinone used primarily for the treatment of drug-resistant gram-positive infections.

However, this drug is active in vitro against *M. tuberculosis* and NTM. Several case series have suggested that linezolid may help clear organisms relatively rapidly when included in a regimen for the treatment of complex MDR- and XDR-TB. Linezolid's mechanism of action is disruption of protein synthesis by binding to the 50S bacterial ribosome. Linezolid has nearly 100% oral bioavailability, with good penetration into tissues and fluids, including CSF. Clinical drug resistance to linezolid has been reported, but the mechanism is unclear. Adverse effects may include optic and peripheral neuropathy, pancytopenia, and lactic acidosis. Linezolid is a weak MAO inhibitor and can be associated with the serotonin syndrome when given concomitantly with serotonergic drugs (primarily antidepressants such as selective serotonin reuptake inhibitors). Prolonged administration for TB and other mycobacterial infections may be associated with an increased rate of side effects.

TMC207

TMC207 is a new diarylquinoline with a novel mechanism of action: inhibition of the mycobacterial ATP synthetase proton pump. TMC207 is bactericidal for drug-susceptible and MDR strains of *M. tuberculosis*. Resistance has been reported and is due to point mutations in the gene coding for the ATP synthetase proton pump. A phase 2 randomized controlled clinical trial demonstrated substantial improvement in rates of 2-month culture conversion, with improved clearance of mycobacterial cultures, for MDR-TB patients. This drug is metabolized by the hepatic cytochrome CYP3A4. Rifampin lowers TMC207 levels by 50%, and protease inhibitors also interact significantly with this drug. The oral bioavailability of TMC207 appears to be excellent. The dosage is 400 mg/d for the first 2 weeks and then 200 mg thrice weekly. The elimination half-life is long (>14 days). Adverse effects are reported to be minimal, with nausea and slight prolongation of the QT_c interval.

OPC-67683 and PA 824

The prodrugs OPC-67683 and PA 824 are novel nitro-dihydro-imidazooxazole derivatives whose antimycobacterial activity is attributable to inhibition of mycolic acid biosynthesis. Early clinical trials of these compounds are ongoing.

NONTUBERCULOUS MYCOBACTERIA

More than 150 species of NTM have been identified. Only a minority of these environmental organisms, which are found in soil and water, are important human pathogens. NTM cause extensive disease primarily in persons with preexisting pulmonary disease or immunocompromise but can cause nodular/bronchiectatic disease in otherwise seemingly normal hosts. They are also important causes of infections in surgical settings. Two major classes of NTM are the slow-growing and rapidly growing species. Subcultures of the latter grow within 1 week. The growth characteristics of NTM have diagnostic, thapeutic, and prognostic implications. The rate of growth can provide useful preliminary information within a specific clinical context, in that growth within 2–3 weeks is much more likely to indicate an NTM than *M. tuberculosis*. When NTM do grow from cultures, colonization should be distinguished from active disease in order to optimize the risk and benefit of prolonged treatment with multiple medications. Significant clinical manifestations and/or sputum radiographic evidence of progressive disease consistent with NTM as well as either reproducible sputum culture results or a single positive culture are required to diagnose NTM pulmonary disease, according to the recommendations of the American Thoracic Society and the Infectious Diseases Society of America. Isolation of NTM from blood or from an infected-appearing extrapulmonary site, such as soft tissue or bone, is usually indicative of disseminated or local NTM infection (see Chap. 72). Treatment of NTM disease is prolonged and requires multiple medications. Side effects of the regimens employed are common, and intermittent therapy is often used to mitigate these adverse events. Treatment regimens depend on the NTM species, the extent or type of disease, and—to some degree—drug susceptibility test results. The nodular bronchiectatic form of MAC infection is generally treated three times per week, whereas fibrocavitary or disseminated MAC infection is treated daily.

THERAPEUTIC CONSIDERATIONS FOR SPECIFIC NTM

M. avium complex

Among the NTM, MAC organisms most commonly cause human disease. In immunocompetent hosts, MAC species are most often found in conjunction with underlying significant lung disease, such as chronic obstructive pulmonary disease or bronchiectasis. For patients with nodular or bronchiectatic MAC lung disease, an initial regimen consisting of clarithromycin or azithromycin, rifampin or rifabutin, and ethambutol is given three times per week. Routine initial testing for macrolide resistance is recommended, as is testing at 6 months in a failing regimen (i.e., with cultures persistently positive for NTM).

In immunocompromised individuals, disseminated MAC infection is generally treated with clarithromycin, ethambutol, and rifabutin. Azithromycin may be substituted in patients unable to tolerate clarithromycin. Amikacin and fluoroquinolones are often used in salvage regimens. Treatment for disseminated MAC infection in AIDS patients may be lifelong in the absence of immune reconstitution. At least 12 months of MAC therapy and 6 months of effective immune reconstitution may be adequate.

Mycobacterium kansasii

M. kansasii is the second most common NTM causing human disease. It is also the second most common cause of NTM pulmonary disease in the United States, where most commonly reported in southeast region. *M. kansasii* infection can be treated with isoniazid, rifampin, and ethambutol; therapy continues for 12 months after culture conversion. Rifampin-resistant *M. kansasii* has been treated with clarithromycin, trimethoprim-sulfamethoxazole, and streptomycin.

Rapidly growing mycobacteria

Rapidly growing mycobacteria causing human disease include *M. abscessus*, *M. fortuitum*, and *M. chelonae*. Treatment of these mycobacteria is complex and should be undertaken with input from experienced clinicians. Testing for macrolide resistance is recommended. However, in rapidly growing mycobacteria, an inducible *erm* gene may confer in vivo macrolide resistance to isolates that are susceptible in vitro.

Mycobacterium marinum

M. marinum is an NTM found in salt water and freshwater, including swimming pools and fish tanks. It is a cause of localized soft tissue infections, which may require surgical management. Combination regimens include clarithromycin and either ethambutol or rifampin. Other agents with activity against *M. marinum* include doxycycline, minocycline, and trimethoprim-sulfamethoxazole.

DRUGS FOR THE TREATMENT OF NTM

Clarithromycin

Clarithromycin is a macrolide antibiotic with broad activity against many gram-positive and gram-negative bacteria as well as NTM. This drug is active against MAC organisms and many other NTM species, inhibiting protein synthesis by binding to the 50S mycobacterial ribosomal subunit. NTM resistance to macrolides is probably caused by overexpression of the gene *ermB*, with consequent methylation of the binding site. Clarithromycin is well absorbed orally and distributes well to tissues. It is cleared both hepatically and renally; the dosage should be reduced in renal insufficiency. Clarithromycin is a substrate for and inhibits cytochrome 3A4 and should not be administered with cisapride, pimozide, or terfenadine, as cardiac arrhythmias may occur. Numerous drugs interact with clarithromycin through the CYP3A4 metabolic pathway. Rifampin lowers clarithromycin levels; conversely, rifampin levels are increased by clarithromycin. However, the clinical relevance of this interaction does not appear to be prominent.

For patients with nodular/bronchiectatic MAC infection, the dosage of clarithromycin is 500 mg, given morning and evening, three times a week. For the treatment of fibrocavitary or severe nodular/bronchiectatic MAC infection, a dose of 500–1000 mg is given daily. Disseminated MAC infection is treated with 1000 mg daily. Clarithromycin is used in combination regimens that typically include ethambutol and a rifamycin in order to avoid the development of macrolide resistance. Adverse effects include frequent gastrointestinal intolerance, hepatotoxicity, headache, rash, and rare instances of hypoglycemia. Clarithromycin is contraindicated during pregnancy because of its teratogenicity in animal models.

Azithromycin

Azithromycin is a derivative of erythromycin. Although technically an azalide and not a macrolide, it works similarly to macrolides, inhibiting protein synthesis through binding to the 50S ribosomal subunit. Resistance to azithromycin is almost always associated with complete cross-resistance to clarithromycin. Azithromycin is well absorbed orally, with good tissue penetration and a prolonged half-life (~48 h). The usual dosage for treatment of MAC infection is 250 mg daily or 500 mg three times per week. Azithromycin is used in combination with other agents to avoid development of resistance. For prophylaxis against disseminated MAC infection in immunocompromised individuals, a dose of 1200 mg once per week is given. Because azithromycin is not metabolized by cytochrome P450, it interacts with few drugs. Adjustment of the dosage on the basis of renal function is not necessary.

Cefoxitin

Cefoxitin is a second-generation parenteral cephalosporin with activity against rapidly growing NTM, particularly *M. abscessus, M. marinum*, and *M. chelonae*. Its mechanism of action against NTM is unknown but may involve inactivation of cell wall synthesis enzymes. High doses are used for treatment of NTM: 200 mg/kg IV three or four times per day, with a maximal daily dose of 12 g. The half-life of cefoxitin is ~1 h, with primarily renal clearance that requires adjustment in renal insufficiency. Adverse effects are uncommon but include gastrointestinal manifestations, rash, eosinophilia, fever, and neutropenia.

CONCLUSION

Treatment of mycobacterial infections requires multiple-drug regimens that often exert significant side effects with the potential to limit tolerability. The prolonged duration of treatment has vastly improved results over those obtained in decades past, but drugs and regimens that will shorten treatment duration and limit adverse drug effects and interactions are needed.

CHAPTER 74

SYPHILIS

Sheila A. Lukehart

DEFINITION

Syphilis, a chronic systemic infection caused by *Treponema pallidum* subspecies *pallidum*, is usually sexually transmitted and is characterized by episodes of active disease interrupted by periods of latency. After an incubation period averaging 2–6 weeks, a primary lesion appears, often associated with regional lymphadenopathy. The secondary stage, associated with generalized mucocutaneous lesions and generalized lymphadenopathy, is followed by a latent period of subclinical infection lasting years or decades. Central nervous system (CNS) involvement may occur early in infection and may be symptomatic or asymptomatic. In about one-third of untreated cases, the tertiary stage appears, characterized by progressive destructive mucocutaneous, musculoskeletal, or parenchymal lesions; aortitis; or late CNS manifestations.

ETIOLOGY

The Spirochaetales include four genera that are pathogenic for humans and for a variety of other animals: *Leptospira* species, which cause leptospirosis (Chap. 76); *Borrelia* species, which cause relapsing fever and Lyme disease (Chaps. 77 and 78); *Brachyspira* species, which cause intestinal infections; and *Treponema* species, which cause the diseases known collectively as treponematoses (see also Chap. 75). The *Treponema* species include *T. pallidum* subspecies *pallidum*, which causes venereal syphilis; *T. pallidum* subspecies *pertenue*, which causes yaws; *T. pallidum* subspecies *endemicum*, which causes endemic syphilis or bejel; and *T. carateum*, which causes pinta. Until recently, the subspecies were distinguished primarily by the clinical syndromes they produce. Researchers have now identified molecular signatures that can differentiate the three subspecies of *T. pallidum* by culture-independent methods based on polymerase chain reaction (PCR). Other *Treponema* species found in the human mouth, genital mucosa, and gastrointestinal tract have been associated with disease (e.g., periodontitis), but their role as primary etiologic agents is unclear.

T. pallidum subspecies *pallidum* (referred to hereafter as *T. pallidum*), a thin spiral organism, has a cell body surrounded by a trilaminar cytoplasmic membrane, a delicate peptidoglycan layer providing some structural rigidity, and a lipid-rich outer membrane containing relatively few integral membrane proteins. Endoflagella wind around the cell body in the periplasmic space and are responsible for motility.

T. pallidum cannot be cultured in vitro, and little was known about its metabolism until the genome was sequenced in 1998. This spirochete possesses severely limited metabolic capabilities, lacking the genes required for de novo synthesis of most amino acids, nucleotides, and lipids. In addition, *T. pallidum* lacks genes encoding the enzymes of the Krebs cycle and oxidative phosphorylation. To compensate, the organism contains numerous genes predicted to encode transporters of amino acids, carbohydrates, and cations. In addition, genome analyses and other studies have revealed the existence of a 12-member gene family (*tpr*) that bears similarities to variable outer-membrane antigens of other spirochetes. One member, TprK, has discrete variable (V) regions that undergo antigenic variation during infection, probably as a mechanism for immune evasion.

The only known natural host for *T. pallidum* is the human. *T. pallidum* can infect many mammals, but only humans, higher apes, and a few laboratory animals regularly develop syphilitic lesions. Virulent strains of *T. pallidum* are grown in rabbits.

TRANSMISSION AND EPIDEMIOLOGY

Nearly all cases of syphilis are acquired by sexual contact with infectious lesions (i.e., the chancre, mucous patch, skin rash, or condylomata lata [see Fig. 11-20]). Less common modes of transmission include nonsexual personal contact, infection in utero, blood transfusion, and organ transplantation.

SYPHILIS IN THE UNITED STATES

With the advent of penicillin therapy, the total number of cases of syphilis reported annually in the United States declined significantly to a low of 31,575 in 2000—a 95% decrease from 1943—with <6000 reported cases of primary and secondary syphilis. Since 2000, the number of cases of infectious primary and secondary syphilis (a better indicator of disease activity) has more than doubled, with 13,500 cases reported in 2008. These cases have particularly affected men who have sex with men (MSM), many of whom are co-infected with HIV. This outbreak among MSM is occurring throughout North America. Increases in the number of cases among women in the United States in recent years indicate that heterosexual transmission is becoming more common. Surveillance of the number of new cases of primary and secondary syphilis has revealed multiple cycles of 7–10 years, which have been attributed to herd immunity in at-risk populations. A recent re-analysis of the data, however, fails to support this conclusion and proposes alternative explanations for the periodic rise and fall of infectious syphilis cases, including changing sexual behaviors and control efforts.

The populations at highest risk for acquiring syphilis have changed over time, with outbreaks among MSM in the late 1970s and early 1980s as well as at present. The epidemic that peaked in 1990 predominantly involved African-American heterosexual men and women and occurred largely in urban areas, where infectious syphilis was correlated significantly with the exchange of sex for crack cocaine. Although the rate of primary and secandary syphilis among African Americans declined from 1996 through 2003, the rate has nearly doubled since then and remains higher than rates for other racial/ethnic groups.

The incidence of congenital syphilis roughly parallels that of infectious syphilis in females. In 2008, 431 cases in infants <1 year of age were reported. The case definition for congenital syphilis was broadened in 1989 and now includes all live or stillborn infants delivered to women with untreated or inadequately treated syphilis.

One-third to one-half of individuals named as sexual contacts of persons with infectious syphilis become infected. Many will have already developed manifestations of syphilis when they are first seen, and ~30% of asymptomatic contacts examined within 30 days of exposure actually have incubating infection and will later develop infectious syphilis if not treated. Thus, identification and treatment of all recently exposed sexual contacts continue to be important aspects of syphilis control.

GLOBAL SYPHILIS

Syphilis remains a significant health problem globally; the number of new infections is estimated at nearly 12 million per year. The regions that are most affected include sub-Saharan Africa, South America, China, and Southeast Asia **(Fig. 74-1)**. During the past decade, the number of reported cases in China has increased 10-fold, and higher rates have been reported among MSM in many European countries. Worldwide, congenital syphilis has been reported to account for up to 50% of stillbirths, and between 500,000 and 1.5 million cases of congenital syphilis are estimated to occur annually.

NATURAL COURSE AND PATHOGENESIS OF UNTREATED SYPHILIS

T. pallidum rapidly penetrates intact mucous membranes or microscopic abrasions in skin and, within a few hours, enters the lymphatics and blood to produce systemic infection and metastatic foci long before the appearance of a primary lesion. Blood from a patient with incubating or early syphilis is infectious. The generation time of *T. pallidum* during early active disease in vivo is estimated

FIGURE 74-1
Estimated annual new cases of syphilis among adults, 1999. (*Courtesy of the World Health Organization.*)

to be ~30 h, and the incubation period of syphilis is inversely proportional to the number of organisms inoculated. The 50% infectious dose for intradermal inoculation in humans has been calculated to be 57 organisms, and the treponeme concentration generally reaches 10^7/g of tissue before a clinical lesion appears. The median incubation period in humans (~21 days) suggests an average inoculum of 500–1000 infectious organisms for naturally acquired disease; the incubation period rarely exceeds 6 weeks.

The primary lesion appears at the site of inoculation, usually persists for 4–6 weeks, and then heals spontaneously. Histopathologic examination shows perivascular infiltration, chiefly by CD4+ and CD8+ T lymphocytes, plasma cells, and macrophages, with capillary endothelial proliferation and subsequent obliteration of small blood vessels. The cellular infiltration displays a T_H1-type cytokine profile consistent with the activation of macrophages. Phagocytosis of opsonized organisms by activated macrophages ultimately causes their destruction, resulting in spontaneous resolution of the chancre.

The generalized parenchymal, constitutional, and mucocutaneous manifestations of secondary syphilis usually appear ~6–8 weeks after the chancre heals. Approximately 15% of patients with secondary syphilis still have persisting or healing chancres, and the stages may overlap more frequently in persons with concurrent HIV infection. In other patients, secondary lesions may appear several months after the chancre has healed, and some patients may enter the latent stage without ever recognizing secondary lesions. The histopathologic features of secondary maculopapular skin lesions include hyperkeratosis of the epidermis, capillary proliferation with endothelial swelling in the superficial corium, dermal papillae with transmigration of polymorphonuclear leukocytes, and—in the deeper corium—perivascular infiltration by CD8+ T lymphocytes, CD4+ T lymphocytes, macrophages, and plasma cells. Treponemes are found in many tissues, including the aqueous humor of the eye and the cerebrospinal fluid (CSF). Invasion of the CNS by *T. pallidum* occurs during the first weeks or months of infection, and CSF abnormalities are detected in as many as 40% of patients during the secondary stage. Clinical hepatitis and immune complex–induced glomerulonephritis are relatively rare but recognized manifestations of secondary syphilis; liver function tests may yield abnormal results in up to one-quarter of patients with early syphilis. Generalized nontender lymphadenopathy is noted in 85% of patients with secondary syphilis. The paradoxical appearance of secondary manifestations despite high titers of antibody (including immobilizing antibody) to *T. pallidum* may result from antigenic variation or changes in expression of surface antigens. Secondary lesions subside within 2–6 weeks, and the infection enters the latent stage, which is detectable only by serologic testing. In the preantibiotic era, up to 25% of untreated patients experienced at least one generalized or localized mucocutaneous relapse, usually during the first year. Therefore, identification and examination of sexual contacts are most important for patients with syphilis of <1 year's duration.

About one-third of patients with untreated latent syphilis developed clinically apparent tertiary disease in the preantibiotic era. In industrialized countries today, specific treatment for early and latent syphilis and coincidental therapy have nearly eliminated tertiary disease except for cases of neurosyphilis in HIV-infected persons. In the past, the most common types of tertiary disease were the gumma (a usually benign granulomatous lesion), cardiovascular syphilis (usually involving the vasa vasorum of the ascending aorta and resulting in aneurysm), and late symptomatic neurosyphilis (tabes dorsalis and paresis). Asymptomatic CNS involvement, however, is still demonstrable in up to 25% of patients with late latent syphilis. The factors that contribute to the development and progression of tertiary disease are unknown.

The course of untreated syphilis was studied retrospectively in a group of nearly 2000 patients with primary or secondary disease diagnosed clinically (the Oslo Study, 1891–1951) and was assessed prospectively in 431 African-American men with seropositive latent syphilis of ≥3 years' duration (the notorious Tuskegee Study, 1932–1972). In the Oslo Study, 24% of patients developed relapsing secondary lesions within 4 years, and 28% eventually developed one or more manifestations of tertiary syphilis. Cardiovascular syphilis, including aortitis, was detected in 10% of patients; 7% of patients developed symptomatic neurosyphilis, and 16% developed benign tertiary gummatous syphilis. Syphilis was the primary cause of death in 15% of men and 8% of women. Cardiovascular syphilis was documented in 35% of men and 22% of women who eventually came to autopsy. In general, serious late complications were nearly twice as common among men as among women.

The Tuskegee Study showed that the death rate among untreated African-American men with syphilis (25–50 years old) was 17% higher than the rate among uninfected subjects and that 30% of all deaths were attributable to cardiovascular or, to a lesser extent, CNS syphilis. Anatomic evidence of aortitis was found in 40–60% of autopsied subjects with syphilis (vs. 15% of control subjects), whereas CNS syphilis was found in only 4%. Rates of hypertension were also higher among the infected subjects. The ethical issues eventually raised by this study, begun in the preantibiotic era but continuing into the early 1970s, had a major influence on the development of current guidelines for human medical experimentation, and the history of the study may still contribute to a reluctance of some African Americans to participate as subjects in clinical research.

CLINICAL MANIFESTATIONS

Primary syphilis

The typical primary chancre usually begins as a single painless papule that rapidly becomes eroded and usually becomes indurated, with a characteristic cartilaginous consistency on palpation of the edge and base of

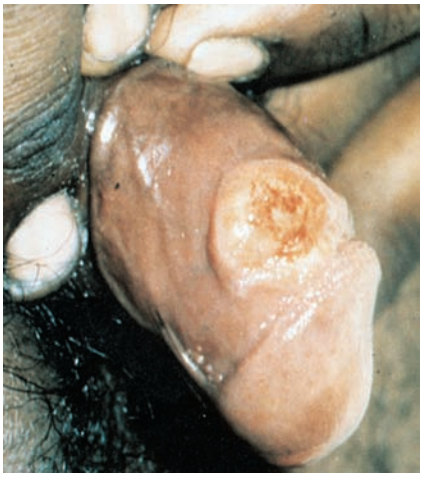


FIGURE 74-2
Primary syphilis with a firm, nontender chancre.

the ulcer. Multiple primary lesions are seen in a minority of patients. In heterosexual men the chancre is usually located on the penis (Fig. 74-2), whereas in homosexual men it may be found in the anal canal or rectum, in the mouth, or on the external genitalia. In women, common primary sites are the cervix and labia. Consequently, primary syphilis goes unrecognized in women and homosexual men more often than in heterosexual men.

Atypical primary lesions are common. The clinical appearance depends on the number of treponemes inoculated and on the immunologic status of the patient. A large inoculum produces a dark-field-positive ulcerative lesion in nonimmune volunteers but may produce a small dark-field-negative papule, an asymptomatic but seropositive latent infection, or no response at all in some individuals with a history of syphilis. A small inoculum may produce only a papular lesion, even in nonimmune individuals. Therefore, syphilis should be considered even in the evaluation of trivial or atypical dark-field-negative genital lesions. The genital lesions that most commonly must be differentiated from those of primary syphilis include those caused by herpes simplex virus infection (Chap. 84), chancroid (Chap. 50), traumatic injury, and donovanosis (Chap. 66). Regional (usually inguinal) lymphadenopathy accompanies the primary syphilitic lesion, appearing within 1 week of lesion onset. The nodes are firm, nonsuppurative, and painless. Inguinal lymphadenopathy is bilateral and may occur with anal as well as with external genital chancres. The chancre generally heals within 4–6 weeks (range, 2–12 weeks), but lymphadenopathy may persist for months.

Secondary syphilis

The protean manifestations of the secondary stage usually include mucocutaneous lesions and generalized nontender lymphadenopathy. The healing primary chancre may still be present in ~15% of cases, and the stages may overlap more frequently in persons with concurrent HIV infection. The skin rash consists of macular, papular, papulosquamous, and occasionally pustular syphilides; often more than one form is present simultaneously. The eruption may be very subtle, and 25% of patients with a discernible rash may be unaware that they have dermatologic manifestations. Initial lesions are pale red or pink, nonpruritic, discrete macules distributed on the trunk and proximal extremities; these macules progress to papular lesions that are distributed widely and that frequently involve the palms and soles (Fig. 74-3; see also Figs. 11-18 and 11-19). Rarely, severe necrotic lesions (*lues maligna*) may appear; they are more commonly reported in HIV-infected individuals. Involvement of the hair follicles may result in patchy alopecia of the scalp hair, eyebrows, or beard in up to 5% of cases.

In warm, moist, intertriginous areas (commonly the perianal region, vulva, and scrotum), papules can enlarge to produce broad, moist, pink or gray-white, highly infectious lesions (*condylomata lata* [see Fig. 11-20]) in 10% of patients with secondary syphilis. Superficial mucosal erosions (*mucous patches*) occur in 10–15% of patients and commonly involve the oral or genital mucosa. The typical mucous patch is a painless silver-gray erosion surrounded by a red periphery.

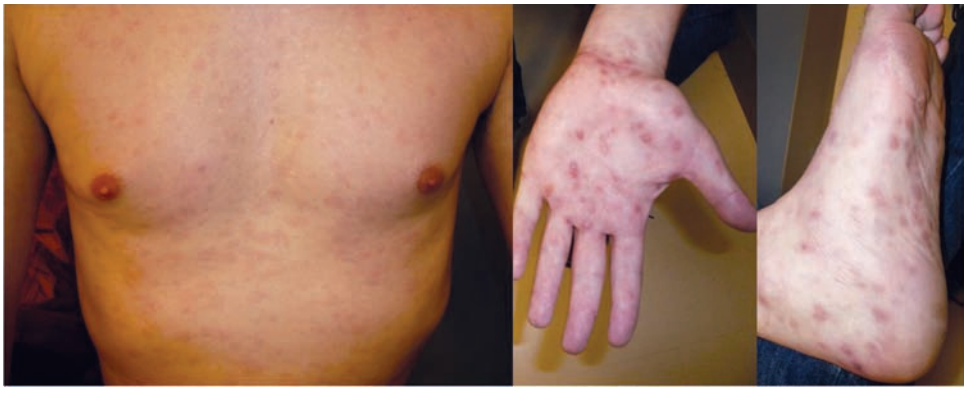


FIGURE 74-3
Secondary syphilis. *Left*: Maculopapular truncal eruption. *Middle*: Papules on the palms. *Right*: Papules on the soles. (*Courtesy of Jill McKenzie and Christina Marra.*)

Constitutional symptoms that may accompany or precede secondary syphilis include sore throat (15–30%), fever (5–8%), weight loss (2–20%), malaise (25%), anorexia (2–10%), headache (10%), and meningismus (5%). *Acute meningitis* occurs in only 1–2% of cases, but CSF cell and protein concentrations are increased in up to 40% of cases, and *T. pallidum* has been recovered from CSF during primary and secondary syphilis in 30% of cases; the latter finding is often but not always associated with other CSF abnormalities.

Less common complications of secondary syphilis include hepatitis, nephropathy, gastrointestinal involvement (hypertrophic gastritis, patchy proctitis, or a rectosigmoid mass), arthritis, and periostitis. Ocular findings that suggest secondary syphilis include pupillary abnormalities and optic neuritis as well as the classic iritis or uveitis. The diagnosis of secondary syphilis is often considered in affected patients only after they fail to respond to steroid therapy. Anterior uveitis has been reported in 5–10% of patients with secondary syphilis, and *T. pallidum* has been demonstrated in aqueous humor from such patients. Hepatic involvement is common in syphilis; although usually asymptomatic, up to 25% of patients may have abnormal liver function tests. Frank *syphilitic hepatitis* may be seen. *Renal involvement* usually results from immune complex deposition and produces proteinuria associated with an acute nephrotic syndrome. Like those of primary syphilis, the manifestations of the secondary stage resolve spontaneously, usually within 1–6 months.

Latent syphilis

Positive serologic tests for syphilis, together with a normal CSF examination and the absence of clinical manifestations of syphilis, indicate a diagnosis of latent syphilis in an untreated person. The diagnosis is often suspected on the basis of a history of primary or secondary lesions, a history of exposure to syphilis, or the delivery of an infant with congenital syphilis. A previous negative serologic test or a history of lesions or exposure may help establish the duration of latent infection, which is an important factor in the selection of appropriate therapy. *Early latent* syphilis is limited to the first year after infection, whereas *late latent* syphilis is defined as that of ≥1 year's (or unknown) duration. *T. pallidum* may still seed the bloodstream intermittently during the latent stage, and pregnant women with latent syphilis may infect the fetus in utero. Moreover, syphilis has been transmitted through blood transfusion or organ donation from patients with latent syphilis. It was previously thought that untreated late latent syphilis had three possible outcomes: (1) persistent lifelong infection; (2) development of late syphilis; or (3) spontaneous cure, with reversion of serologic tests to negative. It is now apparent, however, that the more sensitive treponemal antibody tests rarely, if ever, become negative without treatment. Although progression to clinically evident late syphilis is very rare today, the occurrence of spontaneous cure is in doubt.

Involvement of the CNS

Traditionally, neurosyphilis has been considered a late manifestation of syphilis, but this view is inaccurate. CNS syphilis represents a continuum encompassing early invasion (usually within the first weeks or months of infection), months to years of asymptomatic involvement, and, in some cases, development of early or late neurologic manifestations.

Asymptomatic neurosyphilis

The diagnosis of asymptomatic neurosyphilis is made in patients who lack neurologic symptoms and signs but who have CSF abnormalities including mononuclear pleocytosis, increased protein concentrations, or CSF reactivity in the Venereal Disease Research Laboratory test. CSF abnormalities are demonstrated in up to 40% of cases of primary or secondary syphilis and in 25% of cases of latent syphilis. *T. pallidum* has been recovered by CSF inoculation into rabbits from up to 30% of patients with primary or secondary syphilis but rarely from those with latent syphilis. The presence of *T. pallidum* in CSF is often associated with other CSF abnormalities, but organisms can be recovered from patients with otherwise-normal CSF. Although the prognostic implications of these findings in early syphilis are uncertain, it may be appropriate to conclude that even patients with early syphilis who have such findings do indeed have asymptomatic neurosyphilis and should be treated for neurosyphilis; such treatment is particularly important in patients with concurrent HIV infection. Before the advent of penicillin, the risk of development of clinical neurosyphilis in untreated asymptomatic persons was roughly proportional to the intensity of CSF changes, with the overall cumulative probability of progression to clinical neurosyphilis ~20% in the first 10 years but increasing with time. Most experts agree that neurosyphilis is more common in HIV-infected persons, while immunocompetent patients with untreated latent syphilis and normal CSF probably run a very low risk of subsequent neurosyphilis. In several recent studies, neurosyphilis was associated with a rapid plasma reagin titer of ≥1:32, regardless of clinical stage or HIV infection status.

Symptomatic neurosyphilis

The major clinical categories of symptomatic neurosyphilis include meningeal, meningovascular, and parenchymatous syphilis. The last category includes general paresis and tabes dorsalis. The onset of symptoms usually occurs <1 year after infection for meningeal syphilis, up to 10 years after infection for meningovascular syphilis, at ~20 years for general paresis, and at 25–30 years for tabes dorsalis. However, symptomatic neurosyphilis, particularly in the antibiotic era, often presents not as a classic picture but rather as mixed and subtle or incomplete syndromes.

Meningeal syphilis may present as headache, nausea, vomiting, neck stiffness, cranial nerve involvement, seizures, and changes in mental status. This condition may be concurrent with or may follow the secondary stage.

Patients presenting with uveitis, iritis, or hearing loss often have meningeal syphilis, but these clinical findings can also be seen in patients with normal CSF.

Meningovascular syphilis reflects meningitis together with inflammatory vasculitis of small, medium, or large vessels. The most common presentation is a stroke syndrome involving the middle cerebral artery of a relatively young adult. However, unlike the usual thrombotic or embolic stroke syndrome of sudden onset, meningovascular syphilis often becomes manifest after a subacute encephalitic prodrome (with headaches, vertigo, insomnia, and psychological abnormalities), which is followed by a gradually progressive vascular syndrome.

The manifestations of *general paresis* reflect widespread late parenchymal damage and include abnormalities corresponding to the mnemonic *paresis: p*ersonality, *a*ffect, *r*eflexes (hyperactive), *e*ye (e.g., Argyll Robertson pupils), *s*ensorium (illusions, delusions, hallucinations), *i*ntellect (a decrease in recent memory and in the capacity for orientation, calculations, judgment, and insight), and *s*peech. *Tabes dorsalis* is a late manifestation of syphilis that presents as symptoms and signs of demyelination of the posterior columns, dorsal roots, and dorsal root ganglia. Symptoms include ataxic wide-based gait and foot drop; paresthesia; bladder disturbances; impotence; areflexia; and loss of positional, deep-pain, and temperature sensations. Trophic joint degeneration (Charcot's joints) and perforating ulceration of the feet can result from loss of pain sensation. The small, irregular Argyll Robertson pupil, a feature of both tabes dorsalis and paresis, reacts to accommodation but not to light. *Optic atrophy* also occurs frequently in association with tabes.

Other manifestations of late syphilis

The slowly progressive inflammatory disease leading to tertiary disease begins early during infection, although these manifestations may not become clinically apparent for years or decades. Early syphilitic aortitis becomes evident soon after secondary lesions subside, and treponemes that trigger the development of gummas may have seeded the tissue years earlier.

Cardiovascular syphilis

Cardiovascular manifestations, usually appearing 10–40 years after infection, are attributable to endarteritis obliterans of the vasa vasorum, which provide the blood supply to large vessels; *T. pallidum* DNA has been detected by PCR in aortic tissue. Cardiovascular involvement results in uncomplicated aortitis, aortic regurgitation, saccular aneurysm (usually of the ascending aorta), or coronary ostial stenosis. In the preantibiotic era, symptomatic cardiovascular complications developed in ~10% of persons with late untreated syphilis, although syphilitic aortitis was demonstrated at autopsy in about one-half of African-American men with untreated syphilis. Today, this form of late syphilis is rarely seen in the developed world. Linear calcification of the ascending aorta on chest x-ray films suggests asymptomatic syphilitic aortitis, as arteriosclerosis seldom produces this sign. Syphilitic aneurysms—usually saccular, occasionally fusiform—do not lead to dissection. Only 1 in 10 aortic aneurysms of syphilitic origin involves the abdominal aorta.

Late benign syphilis (gumma)

Gummas are usually solitary lesions ranging from microscopic to several centimeters in diameter. Histologic examination shows a granulomatous inflammation, with a central area of necrosis due to endarteritis obliterans. Although rarely demonstrated microscopically, *T. pallidum* has been detected by PCR or recovered from these lesions, and penicillin treatment results in rapid resolution, confirming the treponemal stimulus for the inflammation. Common sites include the skin and skeletal system; however, any organ (including the brain) may be involved. Gummas of the skin produce indolent, painless, indurated nodular or ulcerative lesions that may resemble other chronic granulomatous conditions, including tuberculosis, sarcoidosis, leprosy, and deep fungal infections. Skeletal gummas most frequently involve the long bones, although any bone may be affected. Upper respiratory gummas can lead to perforation of the nasal septum or palate.

Congenital syphilis

Transmission of *T. pallidum* across the placenta from a syphilitic woman to her fetus may occur at any stage of pregnancy, but fetal damage generally does not occur until after the fourth month of gestation, when fetal immunologic competence begins to develop. This timing suggests that the pathogenesis of congenital syphilis, like that of adult syphilis, depends on the host immune response rather than on a direct toxic effect of *T. pallidum*. The risk of fetal infection during untreated early maternal syphilis is ~75–95%, decreasing to ~35% for maternal syphilis of >2 years' duration. Adequate treatment of the woman before the 16th week of pregnancy should prevent fetal damage, and treatment before the third trimester should adequately treat the infected fetus. Untreated maternal infection may result in a rate of fetal loss of up to 40% (with stillbirth more common than abortion because of the late onset of fetal pathology), prematurity, neonatal death, or nonfatal congenital syphilis. Among infants born alive, only fulminant congenital syphilis is clinically apparent at birth, and these babies have a very poor prognosis. The most common clinical problem is the healthy-appearing baby born to a mother with a positive serologic test. Routine serologic testing in early pregnancy is considered cost-effective in virtually all populations, even in areas with a low prenatal prevalence of syphilis. Low-tech point-of-care tests are being developed to facilitate antenatal testing in resource-poor settings. Where the prevalence of syphilis is high or when the patient is at high risk of re-infection, serologic testing should be repeated in the third trimester and at delivery. Neonatal congenital syphilis must be differentiated from other generalized congenital infections, including rubella,

cytomegalovirus or herpes simplex virus infection, and toxoplasmosis, as well as from erythroblastosis fetalis.

The manifestations of congenital syphilis include (1) early manifestations, which appear within the first 2 years of life (often at 2–10 weeks of age), are infectious, and resemble the manifestations of secondary syphilis in the adult; (2) late manifestations, which appear after 2 years and are noninfectious; and (3) residual stigmata. The earliest manifestations of congenital syphilis (appearing 2–6 weeks after birth) include rhinitis, or "snuffles" (23%); mucocutaneous lesions (35–41%); bone changes (61%), including osteochondritis, osteitis, and periostitis detectable by x-ray examination of long bones; hepatosplenomegaly (50%); lymphadenopathy (32%); anemia (34%); jaundice (30%); thrombocytopenia; and leukocytosis. CNS invasion by *T. pallidum* is detectable in 22% of infected neonates. Neonatal death is usually due to pulmonary hemorrhage, secondary bacterial infection, or severe hepatitis.

Late congenital syphilis (untreated after 2 years of age) is subclinical in 60% of cases; the clinical spectrum in the remainder of cases may include interstitial keratitis (which occurs at 5–25 years of age), eighth-nerve deafness, and recurrent arthropathy. Bilateral knee effusions are known as *Clutton's joints*. Asymptomatic neurosyphilis is present in about one-third of untreated patients, and clinical neurosyphilis occurs in one-quarter of untreated individuals >6 years old. Gummatous periostitis occurs at 5–20 years of age and, as in nonvenereal endemic syphilis, tends to cause destructive lesions of the palate and nasal septum.

Classic stigmata include *Hutchinson's teeth* (centrally notched, widely spaced, peg-shaped upper central incisors), "mulberry" molars (sixth-year molars with multiple, poorly developed cusps), saddle nose, and saber shins.

LABORATORY EXAMINATIONS

Demonstration of the organism

T. pallidum cannot be detected by culture. Historically, dark-field microscopy and immunofluorescence antibody staining have been used to identify this spirochete in samples from moist lesions such as chancres or condylomata lata, but these tests are rarely available today outside of research laboratories. More sensitive PCR tests have been developed but are not commercially available, although some laboratories perform in-house PCR testing.

T. pallidum can be found in tissue with appropriate silver stains, but these results should be interpreted with caution because artifacts resembling *T. pallidum* are often seen. Tissue treponemes can be demonstrated more reliably in research laboratories by PCR or by immunofluorescence or immunohistochemical methods using specific monoclonal or polyclonal antibodies to *T. pallidum*.

Serologic tests for syphilis

There are two types of serologic test for syphilis: nontreponemal and treponemal. Both are reactive in persons with any treponemal infection, including yaws, pinta, and endemic syphilis.

The most widely used nontreponemal antibody tests for syphilis are the rapid plasma reagin (RPR) and Venereal Disease Research Laboratory (VDRL) tests, which measure IgG and IgM directed against a cardiolipin-lecithin-cholesterol antigen complex. The RPR test is easier to perform and uses unheated serum; it is the test of choice for rapid serologic diagnosis in a clinical setting and can be automated. The VDRL test remains the standard for examining CSF. The RPR and VDRL tests are recommended for screening or for quantitation of serum antibody. The titer reflects disease activity, rising during the evolution of early syphilis and often exceeding 1:32 in secondary syphilis. After therapy for early syphilis, a persistent fall by fourfold or more (e.g., a decline from 1:32 to 1:8) is considered an adequate response. VDRL titers do not correspond directly to RPR titers, and sequential quantitative testing (as for response to therapy) must employ a single test. As will be discussed (see "Evaluation for Neurosyphilis," later), the RPR titer may be useful in determining which patients will benefit from CSF examination.

Treponemal tests measure antibodies to native or recombinant *T. pallidum* antigens and include the fluorescent treponemal antibody–absorbed (FTA-ABS) test and the *T. pallidum* particle agglutination (TPPA) test, both of which are more sensitive for primary syphilis than the previously used hemagglutination tests. The *T. pallidum* hemagglutination (TPHA) test is widely used in Europe but is not available in the United States. When used to confirm positive nontreponemal test results, treponemal tests have a very high positive predictive value for diagnosis of syphilis. In a screening setting, however, these tests give false-positive results at rates as high as 1–2%. Treponemal tests are likely to remain reactive even after adequate treatment and cannot differentiate past from current *T. pallidum* infection.

Treponemal immunochromatographic strip (ICS) tests and enzyme immunoassays (EIAs), based largely on reactivity to recombinant antigens, have also been developed. Treponemal EIAs have been approved as confirmatory tests and, because of their ease of automation, are now used for screening purposes by some large laboratories. Because treponemal tests cannot distinguish between current and treated syphilis or may be falsely reactive, clinicians may be uncertain about how to interpret reactive EIA screening results. **Figure 74-4** provides a suggested algorithm for management of such cases.

Considerable interest has recently been focused on point-of-care ICS tests that can be used in the field or in resource-poor settings. These treponemal tests are not yet approved for use in the United States but have been assessed in antenatal clinics in a number of developing countries.

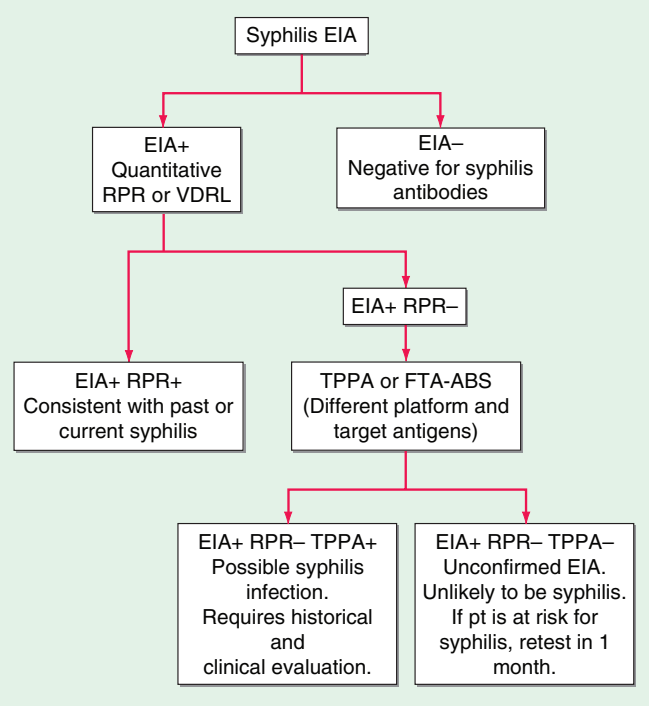


FIGURE 74-4
Algorithm for interpretation of results from syphilis enzyme immunoassays (EIAs) used for screening. RPR, rapid plasma reagin; VDRL, Venereal Disease Research Laboratory; TPPA, *T. pallidum* particle agglutination; FTA-ABS, fluorescent treponemal antibody–absorbed. (*Based on the 2010 Sexually Transmitted Diseases Treatment Guidelines from the Centers for Disease Control and Prevention.*)

Both nontreponemal and treponemal tests may be nonreactive in early primary syphilis, although treponemal tests are slightly more sensitive (85–90%) during this stage than nontreponemal tests (~80%). All tests are reactive during secondary syphilis. (Fewer than 1% of patients with high titers have a nontreponemal test that is nonreactive or weakly reactive with undiluted serum but is reactive with diluted serum—the *prozone phenomenon*.) VDRL and RPR sensitivity and titers may decline in untreated persons with late latent or late syphilis, but treponemal tests remain sensitive in these stages. Whereas nontreponemal test titers will decline or the tests will become nonreactive after therapy for early syphilis, treponemal tests often remain reactive after therapy and are not helpful in determining the infection status of persons with past syphilis.

For practical purposes, most clinicians need to be familiar with three uses of serologic tests for syphilis: (1) screening or diagnosis (RPR or VDRL), (2) quantitative measurement of antibody to assess clinical syphilis activity or to monitor response to therapy (RPR or VDRL), and (3) confirmation of a syphilis diagnosis in a patient with a reactive RPR or VDRL test (FTA-ABS, TPPA, EIA). Studies have not demonstrated the utility of IgM testing for adult syphilis. While IgM titers appear to decline after therapy, the presence or absence of specific IgM does not strictly correlate with *T. pallidum* infection. Moreover, no commercially available IgM test is recommended for evaluation of infants with suspected congenital syphilis.

False-positive serologic tests for syphilis

The lipid antigens of nontreponemal tests are similar to those found in human tissues, and the tests may be reactive (usually with titers ≤1:8) in persons without treponemal infection. Among patients being screened for syphilis because of risk factors, clinical suspicion, or history of exposure, ~1% of reactive tests are falsely positive. Modern VDRL and RPR tests are highly specific, and false-positive reactions are largely limited to persons with autoimmune conditions or injection drug use. The prevalence of false-positive results increases with advancing age, approaching 10% among persons >70 years old. In a patient with a false-positive nontreponemal test, syphilis is excluded by a nonreactive treponemal test.

Evaluation for neurosyphilis

Involvement of the CNS is detected by examination of CSF for pleocytosis (>5 white blood cells/μL), increased protein concentration (>45 mg/dL), or VDRL reactivity. Elevated CSF cell counts and protein

concentrations are not specific for neurosyphilis and may be confounded by HIV co-infection. Because CSF pleocytosis may also be due to HIV, some studies have suggested using a CSF white-cell cutoff of 20 cells/μL as diagnostic of neurosyphilis in HIV-infected patients with syphilis. The CSF VDRL test is highly specific and, when reactive, is considered diagnostic of neurosyphilis; however, this test is insensitive and may be nonreactive even in cases of symptomatic neurosyphilis. The FTA-ABS test on CSF is reactive far more often than the VDRL test on CSF in all stages of syphilis, but reactivity may reflect passive transfer of serum antibody into the CSF. A nonreactive FTA-ABS test on CSF, however, may be used to rule out asymptomatic neurosyphilis. A recent study demonstrated the utility of measuring CXCL13 in CSF to distinguish between neurosyphilis and HIV-related CSF abnormalities.

Clearly, all *T. pallidum*–infected patients who have signs or symptoms consistent with neurologic disease (e.g., meningitis, hearing loss) or ophthalmic disease (e.g., uveitis, iritis) should have a CSF examination, regardless of disease stage. The appropriate management of asymptomatic persons is less clear. Lumbar puncture on all asymptomatic patients with untreated syphilis is impractical and unnecessary. Because standard therapy with penicillin G benzathine fails to result in treponemicidal drug levels in CSF, it is important to identify those persons at higher risk for having or developing neurosyphilis so that appropriate therapy may be given. Large-scale prospective studies have now provided evidence-based guidelines for determining which syphilis patients may benefit most from CSF examination for evidence of neurosyphilis. Specifically, patients with RPR titers of ≥1:32 are at higher risk of having neurosyphilis (11-fold and 6-fold higher in HIV-infected and HIV-uninfected persons, respectively), as are HIV-infected patients with CD4+ T cell counts of ≤350/μL. Current recommendations for CSF examination are shown in **Table 74-1**.

TABLE 74-1

INDICATIONS FOR CSF EXAMINATION IN ADULTS WITH ALL STAGES OF SYPHILIS

All Patients
Signs or symptoms of nervous system involvement [e.g., meningitis, hearing loss, cranial nerve dysfunction, altered mental status, ophthalmic disease (e.g., uveitis, iritis, pupillary abnormalities), ataxia, loss of vibration sense], *or*
RPR or VDRL titer ≥1:32, *or*
Suspected treatment failure
Additional Indications in HIV-Infected Persons
CD4+ T cell count ≤350/μL, *or*
CSF examination is recommended by some experts for all HIV-infected persons.

Source: Adapted from the 2010 Sexually Transmitted Diseases Treatment Guidelines from the Centers for Disease Control and Prevention.

Evaluation of HIV-infected patients for syphilis

Because persons at highest risk for syphilis are also at increased risk for HIV infection, these two infections frequently coexist. There is evidence that syphilis and other genital ulcer diseases may be important risk factors in the acquisition and transmission of HIV infection. Some manifestations of syphilis may be altered in patients with concurrent HIV infection, and multiple cases of neurologic relapse after standard therapy have been reported in these patients. *T. pallidum* has been isolated from the CSF of several patients (with and without concurrent HIV infection) after penicillin G benzathine therapy for early syphilis.

Persons with newly diagnosed HIV infection should be tested for syphilis; conversely, all patients with newly diagnosed syphilis should be tested for HIV infection. Some authorities, persuaded by reports of persistent *T. pallidum* in CSF of HIV-infected persons after standard therapy for early syphilis, recommend CSF examination for evidence of neurosyphilis for all co-infected patients, regardless of the stage of syphilis, with treatment for neurosyphilis if CSF abnormalities are found. Others, on the basis of their own clinical experience, believe that standard therapy—without CSF examination—is sufficient for all cases of early syphilis in HIV-infected patients without neurologic signs or symptoms. As described earlier, RPR titer and CD4+ T cell count can be used to identify patients at higher risk of neurosyphilis for lumbar puncture, although some cases of neurosyphilis will not be identified by these criteria. Table 74-1 summarizes guidelines suggested by published studies. Serologic testing after treatment is important for all patients with syphilis, particularly for those also infected with HIV.

TREATMENT Syphilis

TREATMENT OF ACQUIRED SYPHILIS The CDC's 2010 guidelines for the treatment of syphilis are summarized in **Table 74-2** and are discussed later. Penicillin G is the drug of choice for all stages of syphilis. *T. pallidum* is killed by very low concentrations of penicillin G, although a long period of exposure to penicillin is required because of the unusually slow rate of multiplication of the organism. The efficacy of penicillin against syphilis remains undiminished after 60 years of use, and there is no evidence of penicillin resistance in *T. pallidum*. Other antibiotics effective in syphilis include the tetracyclines and the cephalosporins. Aminoglycosides and spectinomycin inhibit *T. pallidum* only in very large doses, and the sulfonamides and the quinolones are inactive. Azithromycin has shown significant promise as an effective oral agent against *T. pallidum*; however, strains harboring 23S rRNA mutations that confer macrolide resistance are widespread; such strains represent >50% of recent isolates from Seattle and San Francisco and have now been identified in

TABLE 74-2

RECOMMENDATIONS FOR THE TREATMENT OF SYPHILIS[a]

STAGE OF SYPHILIS	PATIENTS WITHOUT PENICILLIN ALLERGY	PATIENTS WITH CONFIRMED PENICILLIN ALLERGY[b]
Primary, secondary, or early latent	*CSF normal or not examined:* Penicillin G benzathine (single dose of 2.4 mU IM) *CSF abnormal:* Treat as neurosyphilis	*CSF normal or not examined:* Tetracycline HCl (500 mg PO qid) or doxycycline (100 mg PO bid) for 2 weeks *CSF abnormal:* Treat as neurosyphilis
Late latent (or latent of uncertain duration), cardiovascular, or benign tertiary	*CSF normal or not examined:* Penicillin G benzathine (2.4 mU IM weekly for 3 weeks) *CSF abnormal:* Treat as neurosyphilis	*CSF normal and patient not infected with HIV:* Tetracycline HCl (500 mg PO qid) or doxycycline (100 mg PO bid) for 4 weeks *CSF normal and patient infected with HIV:* Desensitization and treatment with penicillin if compliance cannot be ensured *CSF abnormal:* Treat as neurosyphilis
Neurosyphilis (asymptomatic or symptomatic)	Aqueous crystalline penicillin G (18–24 mU/d IV, given as 3–4 mU q4h or continuous infusion) for 10–14 days *or* Aqueous procaine penicillin G (2.4 mU/d IM) plus oral probenecid (500 mg qid), both for 10–14 days	Desensitization and treatment with penicillin[c]
Syphilis in pregnancy	According to stage	Desensitization and treatment with penicillin

[a]See Table 74-1 and text for indications for CSF examination.
[b]Because of the documented presence of macrolide resistance in many *T. pallidum* strains in North America, Europe, and China, azithromycin should be used with caution only when treatment with penicillin or doxycycline is not feasible. Azithromycin should not be used for men who have sex with men or for pregnant women.
[c]Limited data suggest that ceftriaxone (2 g/d either IM or IV for 10–14 days) can be used; however, cross-reactivity between penicillin and ceftriaxone is possible.
Abbreviations: CSF, cerebrospinal fluid; mU, million units.
Source: Based on the 2010 Sexually Transmitted Diseases Treatment Guidelines from the Centers for Disease Control and Prevention.

multiple North American and European sites. Macrolide resistance mutations have been identified in nearly all samples reported from China. In contrast, three studies conducted in Africa (Uganda, Tanzania, and Madagascar) have documented the clinical efficacy of azithromycin and, for the subset of samples examined, have found no molecular evidence of the mutation. In short, the prevalence of resistant strains varies widely by geographic location, and routine treatment of syphilis with azithromycin is not recommended. In all cases, careful follow-up of any patient treated for syphilis with azithromycin must be ensured.

Early Syphilis Patients and Their Contacts Penicillin G benzathine is the most widely used agent for the treatment of early syphilis; a single dose of 2.4 million units is recommended. Preventive treatment is also recommended for individuals who have been exposed to infectious syphilis within the previous 3 months. *The regimens recommended for prevention are the same as those recommended for early syphilis*. Penicillin G benzathine cures >95% of cases of early syphilis, although clinical relapse can follow treatment, particularly in patients with concurrent HIV infection. Because the risk of neurologic relapse may be higher in HIV-infected patients, CSF examination is recommended in HIV-seropositive individuals with syphilis of any stage, particularly those with a serum RPR titer of ≥1:32 or a CD4+ T cell count of ≤350/μL. Therapy appropriate for neurosyphilis should be given if there is any evidence of CNS disease.

Late Latent and Late Syphilis If CSF abnormalities are found, the patient should be treated for neurosyphilis. If CSF is normal, the recommended treatment is penicillin G benzathine (7.2 million units total; Table 74-2). The clinical response to treatment for benign tertiary syphilis is usually impressive. However, responses to therapy for cardiovascular syphilis are not dramatic because aortic aneurysm and aortic regurgitation cannot be reversed by antibiotics.

Penicillin-Allergic Patients For penicillin-allergic patients with syphilis, a 2-week (early syphilis) or 4-week (late or late latent syphilis) course of therapy with

doxycycline or tetracycline is recommended. These regimens appear to be effective in early syphilis but have not been tested for late or late latent syphilis, and compliance may be problematic. Limited studies suggest that ceftriaxone (1 g/d, given IM or IV, for 8–10 days) is effective for early syphilis. These nonpenicillin regimens have not been carefully evaluated in HIV-infected individuals and should be used with caution. If compliance and follow-up cannot be ensured, penicillin-allergic HIV-infected persons with late latent or late syphilis should be desensitized and treated with penicillin.

Neurosyphilis Penicillin G benzathine, given in total doses of up to 7.2 million units, does not produce detectable concentrations of penicillin G in CSF and should not be used for treatment of neurosyphilis. Asymptomatic neurosyphilis may relapse into symptomatic disease following treatment with benzathine penicillin, and the risk of relapse may be higher in HIV-infected patients. Both symptomatic and asymptomatic neurosyphilis should be treated with aqueous penicillin. Administration either of IV aqueous crystalline penicillin G or of aqueous procaine penicillin G plus probenecid in recommended doses is thought to ensure treponemicidal concentrations of penicillin G in CSF. The clinical response to penicillin therapy for meningeal syphilis is dramatic, but treatment of neurosyphilis with existing parenchymal damage may only arrest disease progression. Neurologic relapse has been reported after high-dose IV penicillin therapy for neurosyphilis in an HIV-infected patient. No alternative therapies have been studied, but careful follow-up is essential, and re-treatment is warranted in such patients. No data suggest that additional therapy (e.g., penicillin G benzathine for 3 weeks) is beneficial after treatment for neurosyphilis.

The use of antibiotics other than penicillin G for the treatment of neurosyphilis has not been studied, although very limited data suggest that ceftriaxone may be used. In patients with penicillin allergy demonstrated by skin testing, desensitization and treatment with penicillin are recommended.

Management of Syphilis in Pregnancy Every pregnant woman should undergo a nontreponemal test at her first prenatal visit and, if at high risk of exposure, again in the third trimester and at delivery. In the untreated pregnant patient with presumed syphilis, expeditious treatment appropriate to the stage of the disease is essential. Patients should be warned of the risk of a Jarisch-Herxheimer reaction, which may be associated with mild premature contractions but rarely results in premature delivery.

Penicillin is the only recommended agent for the treatment of syphilis in pregnancy. If the patient has a documented penicillin allergy, desensitization and penicillin therapy should be undertaken according to the CDC's 2010 guidelines. After treatment, a quantitative nontreponemal test should be repeated monthly throughout pregnancy to assess therapeutic efficacy. Treated women whose antibody titers rise by fourfold or whose titers do not decrease by fourfold over a 3-month period should be re-treated.

EVALUATION AND MANAGEMENT OF CONGENITAL SYPHILIS Whether or not they are infected, newborn infants of mothers with reactive serologic tests may themselves have reactive tests because of transplacental transfer of maternal IgG antibody. For asymptomatic infants born to women treated adequately with penicillin during the first or second trimester of pregnancy, monthly quantitative nontreponemal tests may be performed to monitor for appropriate reduction in antibody titers. Rising or persistent titers indicate infection, and the infant should be treated. Detection of neonatal IgM antibody may be useful, but no commercially available test is currently recommended.

An infant should be treated at birth if the treatment status of the seropositive mother is unknown; if the mother has received inadequate or nonpenicillin therapy or has received penicillin therapy in the third trimester; or if the infant may be difficult to follow. The CSF should be examined to obtain baseline values before treatment. Penicillin is the only recommended drug for the treatment of syphilis in infants. Specific recommendations for the treatment of infants and older children are included in the CDC's 2010 treatment guidelines.

JARISCH-HERXHEIMER REACTION A dramatic though usually mild reaction consisting of fever, chills, myalgias, headache, tachycardia, increased respiratory rate, increased circulating neutrophil count, and vasodilation with mild hypotension may follow the initiation of treatment for syphilis. This reaction is thought to be a response to lipoproteins released by dying *T. pallidum* organisms. The Jarisch-Herxheimer reaction occurs in ~50% of patients with primary syphilis, 90% of those with secondary syphilis, and a lower proportion of persons with later-stage disease. Defervescence takes place within 12–24 h. In patients with secondary syphilis, erythema and edema of the mucocutaneous lesions may increase. Patients should be warned to expect such symptoms, which can be managed with symptom-based treatment. Steroid and other anti-inflammatory therapy is not required for this mild transient reaction.

FOLLOW-UP EVALUATION OF RESPONSES TO THERAPY Efficacy of treatment should be assessed by clinical evaluation and monitoring of the quantitative VDRL or RPR titer for a fourfold decline (e.g., from 1:32 to 1:8). Patients with primary or secondary syphilis should be examined 6 and 12 months after treatment and persons with latent or late syphilis at 6, 12, and 24 months. More frequent clinical and serologic examination (3, 6, 9, 12, and 24 months) is recommended for patients concurrently infected with HIV, regardless of the stage of syphilis.

After successful treatment of seropositive first-episode primary or secondary syphilis, the VDRL or RPR titer progressively declines, becoming negative by 12 months in 40–75% of seropositive primary cases and in 20–40% of secondary cases. Patients with HIV

infection or a history of prior syphilis are less likely to become nonreactive in the VDRL or RPR test. Rates of decline of serologic titers appear to be slower and serologically defined treatment failures more common among HIV-infected patients than among those without HIV co-infection; however, effective antiretroviral therapy may reduce these differences. Re-treatment should be considered if serologic responses are not adequate or if clinical signs persist or recur. Because it is difficult to differentiate treatment failure from reinfection, the CSF should be examined, with treatment for neurosyphilis if CSF is abnormal and treatment for late latent syphilis if CSF is normal. Patients treated for late latent syphilis frequently have low initial VDRL or RPR titers and may not have a fourfold decline after therapy with penicillin. In such patients, re-treatment is not warranted unless the titer rises or signs and symptoms of syphilis appear. Because treponemal tests may remain positive despite treatment for seropositive syphilis, these tests are not useful in following the response to therapy.

The activity of neurosyphilis (symptomatic or asymptomatic) correlates best with CSF pleocytosis, and this measure provides the most sensitive index of response to treatment. Repeat CSF examinations should be performed every 6 months until the cell count is normal. An elevated CSF cell count falls to normal in 3–12 months in adequately treated HIV-uninfected patients. The persistence of mild pleocytosis in HIV-infected patients may be due to the presence of HIV in CSF; this scenario may be difficult to distinguish from treatment failure. Elevated levels of CSF protein fall more slowly, and the CSF VDRL titer declines gradually over several years. In patients treated for neurosyphilis, a fourfold reduction in serum RPR titer has been positively correlated with normalization of CSF abnormalities; this correlation is stronger in HIV-uninfected patients and in HIV-infected patients receiving effective antiretroviral therapy.

IMMUNITY TO SYPHILIS

The rate of development of acquired resistance to *T. pallidum* after natural or experimental infection is related to the size of the antigenic stimulus, which depends on both the size of the infecting inoculum and the duration of infection before treatment. Both humoral and cellular responses are considered to be of major importance in immunity and in the healing of early lesions. Cellular infiltration, predominantly by T lymphocytes and macrophages, produces a T_H1 cytokine milieu consistent with the clearance of organisms by activated macrophages. Specific antibody enhances phagocytosis and is required for macrophage-mediated killing of *T. pallidum*. Recent studies demonstrate antigenic variation of the TprK protein, which may lead to persistence of infection and determine susceptibility to reinfection with another strain. Comparative genomic studies have revealed some sequence variations among *T. pallidum* strains. Strains can be differentiated by molecular typing methods, and a possible correlation between molecular type and clinical manifestations is being examined.

CHAPTER 75

ENDEMIC TREPONEMATOSES

Sheila A. Lukehart

The endemic, or nonvenereal, treponematoses are bacterial infections caused by close relatives of *Treponema pallidum* subspecies *pallidum*, the etiologic agent of venereal syphilis (Chap. 74). Yaws, pinta, and endemic syphilis are traditionally distinguished from venereal syphilis by mode of transmission, age of acquisition, geographic distribution, and clinical features. These infections are limited to rural areas of developing nations and are seen in developed countries only among recent immigrants from endemic regions. Our "knowledge" about the endemic treponematoses is based on observations by health care workers who have visited endemic areas; virtually no well-designed studies of the natural history, diagnosis, or treatment of these infections have been conducted. The treponemal infections are compared and contrasted in **Table 75-1**.

TABLE 75-1

COMPARISON OF THE TREPONEMES AND ASSOCIATED DISEASES

FEATURE	VENEREAL SYPHILIS	YAWS	ENDEMIC SYPHILIS	PINTA
Organism	*T. pallidum* subsp. *pallidum*	*T. pallidum* subsp. *pertenue*	*T. pallidum* subsp. *endemicum*	*T. carateum*
Modes of transmission	Sexual, transplacental	Skin-to-skin	Household contacts: mouth-to-mouth or via shared drinking/ eating utensils	Skin-to-skin
Usual age of acquisition	Adulthood or in utero	Early childhood	Early childhood	Late childhood
Primary lesion	Cutaneous ulcer (chancre)	Papilloma, often ulcerative	Rarely seen	Nonulcerating papule with satellites, pruritic
Location	Genital, oral, anal	Extremities	Oral	Extremities, face
Secondary lesions	Mucocutaneous lesions; condylomata lata	Cutaneous papulosquamous lesions; osteoperiostitis	Florid mucocutaneous lesions (mucous patch, split papule, condyloma latum); osteoperiostitis	Pintides, pigmented, pruritic
Infectious relapses	~25%	Common	Unknown	None
Late complications	Gummas, cardiovascular and CNS involvement[a]	Destructive gummas of skin, bone, cartilage	Destructive gummas of skin, bone, cartilage	Nondestructive, dyschromic, achromic macules

[a]CNS involvement in the endemic treponematoses has been postulated by some investigators (see text).

EPIDEMIOLOGY

The endemic treponematoses are chronic diseases transmitted by direct contact during childhood and, like syphilis, can cause severe late manifestations years after initial infection. In a World Health Organization (WHO)–sponsored mass eradication campaign from 1952 to 1969, more than 160 million people in Africa, Asia, and South America were examined for treponemal infections, and more than 50 million cases, contacts, and latent infections were treated. This campaign reduced the prevalence of active yaws from >20% to <1% in many areas. In recent decades, lack of focused surveillance and diversion of resources have resulted in documented resurgence of these infections in some regions. The estimated geographic distribution of the endemic treponematoses in the 1990s is shown in Fig. 75-1. The most recent WHO estimate (1997) suggested that there are 460,000 new cases per year and a prevalence of 2.5 million infected persons; during the subsequent decade, an increased incidence was documented in some countries. Areas of resurgent yaws morbidity include West Africa (Ivory Coast, Ghana, Togo, Benin), the Central African Republic, Nigeria, and rural Democratic Republic of Congo. The prevalence of endemic syphilis is estimated to be >10% in some regions of Ghana, Mali, Niger, Burkina Faso, and Senegal. In Asia and the Pacific Islands, reports suggest active outbreaks of yaws in Indonesia, Papua New Guinea, East Timor, Vanuatu, Laos, and Kampuchea. India actively renewed its focus on yaws eradication in 1996 and has reported no new cases since 2003. In the Americas, foci of yaws are thought to persist in Haiti and other Caribbean islands, Peru, Colombia, Ecuador, Brazil, Guyana, and Surinam. Pinta is limited to Central America and northern South America, where it is found rarely and only in remote villages. Evidence of yaws-like disease and seroreactivity in wild gorillas and baboons in Africa has led to speculation that there may be an animal reservoir for yaws, although strains recently obtained from humans and nonhuman primates have not been subjected to molecular comparison. A single strain isolated from a baboon in 1966 contains several identified genetic differences from available yaws isolates from humans.

MICROBIOLOGY

The etiologic agents of the endemic treponematoses are *T. pallidum* subspecies *pertenue* (yaws), *T. pallidum* subspecies *endemicum* (endemic syphilis), and *T. carateum* (pinta). These little-studied organisms are morphologically identical to *T. pallidum* subspecies *pallidum*, and no definitive antigenic differences among them have been identified to date. A controversy has existed about whether the pathogenic treponemes are truly different organisms. Three of the four organisms are classified as subspecies of *T. pallidum*; the fourth (*T. carateum*) remains a separate species simply because no organisms have been available for genetic studies. A number of genetic loci distinguish the agents of venereal

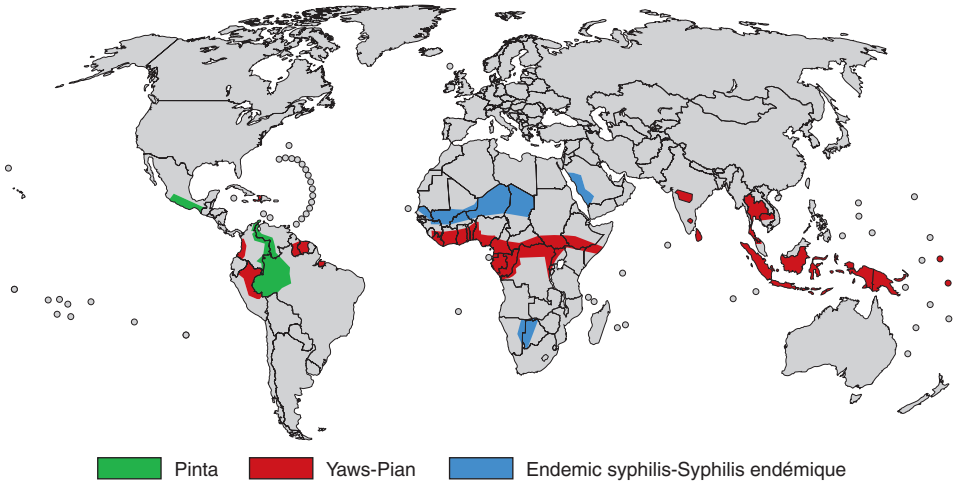


FIGURE 75-1
Geographic distribution of endemic treponematoses in the 1990s. (*Courtesy of the World Health Organization; www.who.int/yaws/epidemiology/Map_yaws_90s.jpg.*)

and nonvenereal treponemal infections, and molecular signatures (assessed by polymerase chain reaction amplification of *tpr* genes and restriction digestion) can differentiate the individual agents of venereal syphilis, yaws, and bejel. Whether these genetic differences are related to the distinct clinical courses of these diseases has not been determined.

CLINICAL FEATURES

All of the treponemal infections are chronic and are characterized by defined disease stages, with a localized primary lesion, disseminated secondary lesions, periods of latency, and possible late lesions. Primary and secondary stages are more frequently overlapping in yaws and endemic syphilis than in venereal syphilis, and the late manifestations of pinta are very mild relative to the destructive lesions of the other treponematoses. The current preference is to divide the clinical course of the endemic treponematoses into "early" and "late" stages.

The major clinical distinctions made between venereal syphilis and the nonvenereal infections are the apparent lack of congenital transmission and of central nervous system (CNS) involvement in the nonvenereal infections. It is not known whether these distinctions are entirely accurate. Because of the high degree of genetic relatedness among the organisms, there is little biological reason to think that *T. pallidum* subspecies *endemicum* and *T. pallidum* subspecies *pertenue* would be unable to cross the blood-brain barrier or to invade the placenta. These organisms are like *T. pallidum* subspecies *pallidum* in that they can disseminate from the site of primary infection and can persist for decades. The lack of recognized congenital infection may be due to the fact that childhood infections are often in the latent stage (low bacterial load) before girls reach sexual maturity. Neurologic involvement may go unrecognized because of the lack of trained medical personnel in endemic regions, the delay of many years between infection and possible CNS manifestations, or a low rate of symptomatic CNS disease. Some published evidence supports congenital transmission as well as cardiovascular, ophthalmologic, and CNS involvement in yaws. Although the reported studies have been small, have failed to control for other causes of CNS abnormalities, have not included specific treponemal serologic tests, and have not analyzed the response to therapy, it may be erroneous to accept unquestioningly the frequently repeated belief that these organisms fail to cause such manifestations.

Yaws

Also known as *pian*, *framboesia*, or *bouba*, yaws is characterized by the development of one or several primary lesions ("mother yaw") followed by multiple disseminated skin lesions. All early skin lesions are infectious and may persist for many months; cutaneous relapses are common during the first 5 years. Late manifestations, affecting 10% of untreated persons, are destructive and can involve skin, bone, and joints.

The infection is transmitted by direct contact with infectious lesions, often during play or group sleeping, and may be enhanced by disruption of the skin by insect bites or abrasions. After an average of 3–4 weeks, the first lesion begins as a papule—usually on an extremity—and then enlarges (particularly during moist warm weather) to become papillomatous or "raspberry-like" (thus the name "framboesia") (**Fig. 75-2**, left). Regional lymphadenopathy develops, and the lesion usually heals within 6 months; dissemination is thought to occur during the early weeks of infection. A generalized secondary eruption, accompanied by generalized lymphadenopathy, appears either concurrent with or following the primary lesion, may take several forms (macular, papular, or papillomatous), and may become secondarily infected with other bacteria. Painful papillomatous lesions on the soles of the feet result in a crablike gait ("crab yaws"), and periostitis may result in nocturnal bone pain and

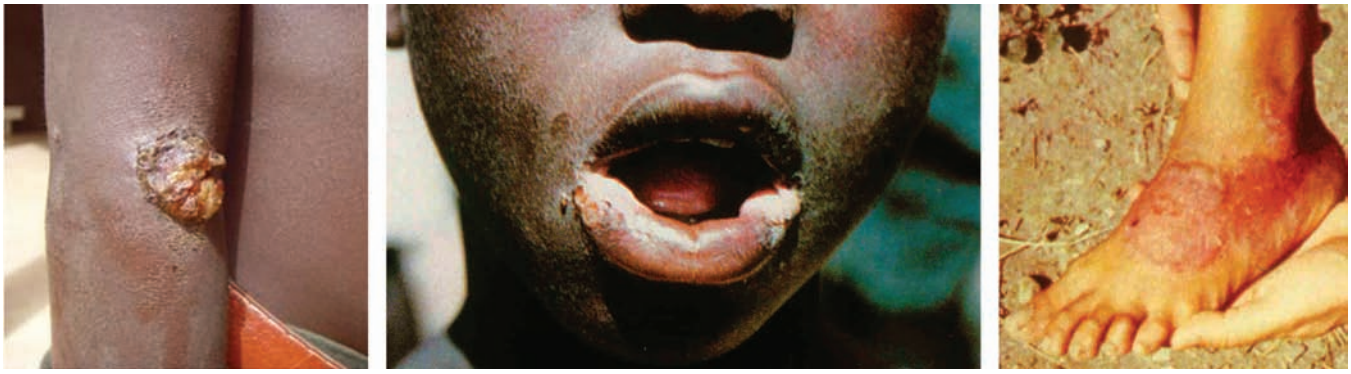


FIGURE 75-2
Clinical manifestations of endemic treponematoses. ***Left:*** Papillomatous primary lesion of yaws. ***Center:*** Split papules of early endemic syphilis. ***Right:*** Pigmented macules of pinta. (*Photos published with permission from Professor H. Assé, Côte d'Ivoire [left] and from PL Perine et al: Handbook of Endemic Treponematoses, Geneva, World Health Organization, 1984 [center and right]*).

polydactylitis. Late yaws is manifested by gummas of the skin and long bone, hyperkeratoses of the palms and soles, osteitis and periostitis, and hydrarthrosis. The late gummatous lesions are characteristically extensive. Destruction of the nose, maxilla, palate, and pharynx is termed *gangosa* and is similar to the destructive lesions seen in leprosy and leishmaniasis.

Endemic syphilis

The early lesions of endemic syphilis (*bejel*, *siti*, *dichuchwa*, *njovera*, *skerljevo*) are localized primarily to mucocutaneous and mucosal surfaces. The infection is reported to be transmitted by direct contact, by kissing, or by sharing drinking and eating utensils. A role for insects in transmission has been suggested but is unproven. The initial lesion, usually an intraoral papule (Fig. 75-2, center), often goes unrecognized and is followed by mucous patches on the oral mucosa and mucocutaneous lesions resembling the condylomata lata of secondary syphilis. This eruption may last for months or even years, and treponemes can readily be demonstrated in early lesions. Periostitis and regional lymphadenopathy are common. After a variable period of latency, late manifestations may appear, including osseous and cutaneous gummas. Destructive gummas, osteitis, and gangosa are more common in endemic syphilis than in late yaws.

Pinta

Pinta (*mal del pinto*, *carate*, *azul*, *purupuru*) is the most benign of the treponemal infections. This disease has three stages that are characterized by marked changes in skin color (Fig. 75-2, right), but pinta does not appear to cause destructive lesions or to involve other tissues. The initial papule is most often located on the extremities or face and is pruritic. After one to many months of infection, numerous disseminated secondary lesions (*pintides*) appear. These lesions are initially red but become deeply pigmented, ultimately turning a dark slate blue. The secondary lesions are infectious and highly pruritic and may persist for years. Late pigmented lesions are called *dyschromic macules* and contain treponemes. Over time, most pigmented lesions show varying degrees of depigmentation, becoming brown and eventually white and giving the skin a mottled appearance. White achromic lesions are characteristic of the late stage.

DIAGNOSIS

Diagnosis of the endemic treponematoses is based on clinical manifestations and, when available, darkfield microscopy and serologic testing. The same serologic tests that are used for venereal syphilis (Chap. 74) become reactive during all treponemal infections. Although several targets have been evaluated for specific serodiagnosis, to date there is no test that can discriminate among the different infections. The nonvenereal treponemal infections should be considered in the evaluation of a reactive syphilis serology in any person who has emigrated from an endemic area.

TREATMENT **Endemic Treponematoses**

The WHO-recommended therapy for patients and their contacts is benzathine penicillin (1.2 million units IM for adults; 600,000 units for children <10 years old). This dose is half of that recommended for early venereal syphilis, and no controlled efficacy studies have been conducted. Definitive evidence of resistance to penicillin is lacking, although relapsing lesions have been reported after penicillin treatment in Papua New Guinea. Limited data suggest the efficacy of tetracycline for treatment of yaws, but no data exist for other endemic treponematoses. Solely on the basis of experience with venereal syphilis, it is thought that doxycycline or tetracycline (at doses appropriate for syphilis; Chap. 74) are alternatives for patients allergic to penicillin. Macrolide resistance mutations have been

identified in *T. pallidum* subspecies *pallidum*, but no data are available on possible mutations in the nonvenereal treponemes. A Jarisch-Herxheimer reaction (Chap. 74) may follow treatment of endemic treponematoses. Nontreponemal serologic titers (in the Venereal Disease Research Laboratory [VDRL] slide test or the rapid plasma reagin [RPR] test) usually decline after effective therapy, but patients may not become seronegative.

CONTROL

Because of lack of ongoing surveillance for the endemic treponematoses, these potentially destructive diseases are not recognized by public health decision-makers and control efforts are rarely undertaken, even though penicillin therapy is inexpensive and effective. There is concern that, as HIV spreads throughout developing countries, it may markedly affect the manifestations and transmission of the endemic treponematoses.

CHAPTER 76

LEPTOSPIROSIS

Joseph M. Vinetz

Leptospirosis is a globally important zoonotic disease caused by spirochetes of the genus *Leptospira* **(Fig. 76-1)**. In 1885, Adolf Weil described the clinical hallmarks of this disease as an acute process characterized by splenomegaly, jaundice, and nephritis. With time, the designation *Weil's disease* came to signify severe leptospirosis characterized by diverse clinical findings, particularly fever, jaundice, acute renal injury, refractory shock, and hemorrhage (especially pulmonary hemorrhage). The global burden of leptospirosis is hard to quantify because of the difficulties encountered in its clinical diagnosis and the lack of efficient confirmatory laboratory testing, which limits public health reporting.

ETIOLOGIC AGENT

The genus *Leptospira* (order Spirochetales, family Leptospiraceae) constitutes the most ancient lineage of spirochetes pathogenic for humans and the only spirochetes that can live both in animals and free in the environment. This genus includes 20 named species, 9 of which are classified as pathogenic, 5 as intermediately pathogenic, and 6 as nonpathogenic (saprophytic) based on molecular phylogenetic analysis **(Fig. 76-2)**. Of the pathogenic and intermediate *Leptospira* species, more than 250 serovars—classified on the basis of agglutination testing with specific antisera—cause disease in humans and animals. New species and serovars continue to be discovered. Although all species, serovars, and strains are morphologically

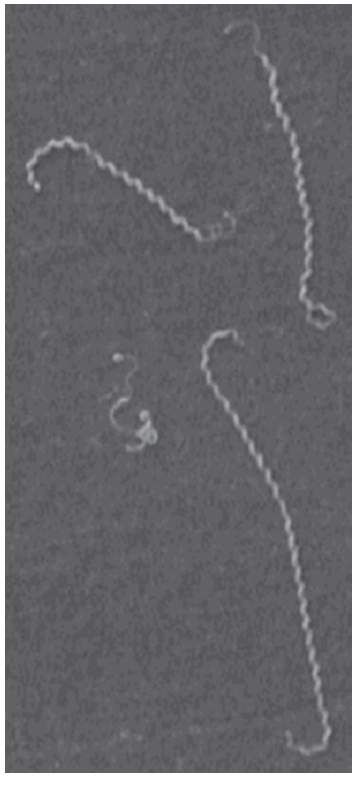


FIGURE 76-1
Transmission electron micrograph of *Leptospira interrogans* serovar Icterohaemorrhagiae.

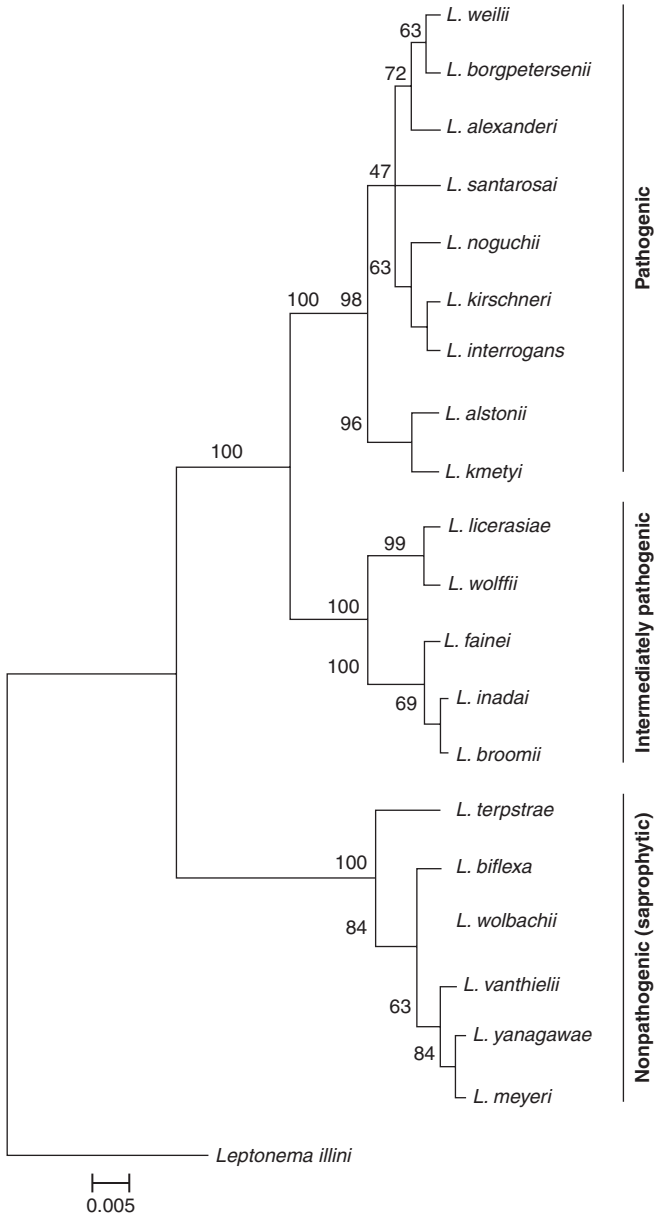


FIGURE 76-2
Differentiation of pathogenic, intermediately pathogenic, and nonpathogenic (saprophytic) *Leptospira* species based on molecular phylogenetic analysis using the 16S rRNA gene. Scale bar indicates rate of nucleotide substitution per base pair.

identical, leptospires are described by serovar for clinical and epidemiologic reasons.

The dimensions and motility of leptospires (~0.1 × 6–20 μm) allow them to pass through filters used to sterilize culture medium. Leptospires are tightly and regularly coiled, with characteristic hooked ends (hence the species name *interrogans*), and are highly motile, spinning around their longitudinal axis and darting back and forth. The organisms cannot be seen by direct light microscopy. To visualize the spirochetes directly in culture or in clinical specimens, dark-field or phase-contrast microscopy must be used. Small protein strands that appear motile by Brownian movement can easily be confused with leptospires. In tissues, leptospires can be visualized by silver impregnation (i.e., Warthin-Starry staining), immunohistochemistry, or immunofluorescence microscopy.

Leptospires are difficult to isolate in pure culture from clinical specimens such as blood, urine, and cerebrospinal fluid (CSF), although certain species and serovars (e.g., *L. interrogans* serovar Copenhageni) are grown more easily than others. The organisms have peculiar nutritional requirements, particularly their inability to ferment glucose and their apparently exclusive use of long-chain fatty acids to generate energy and metabolites for cell division and growth. Standard leptospiral culture medium (Ellinghausen–McCullough–Johnson–Harris [EMJH]) contains oleic acid polymers (Tween60 and Tween40) as fatty acid sources. These spirochetes do not grow in medium typically used in automated blood culture systems but can be recovered if specimens are subcultured within ~1 week onto EMJH, Stuart, Fletcher's, or Korthoff's medium. EMJH, the standard for isolation of *Leptospira* from clinical specimens, is a liquid polysorbate-Tween medium to which 0.1% agar is added (sometimes supplemented with antibiotics to prevent growth of contaminants). The primary isolation of *Leptospira* requires the presence of a solid phase in the medium, which is provided by the agar particles. Cultures are maintained in the dark at 28–30°C and are examined at weekly intervals by dark-field microscopy for up to 3 months. After some weeks, florid growth sometimes produces a dense ring of organisms—Dinger's ring—just under the surface of the medium.

EPIDEMIOLOGY

Leptospirosis is a zoonotic disease. Human-to-human transmission does not occur. Although more than 100 different mammals can be infected, the most important sources of transmission to humans are rats, dogs, cattle, and pigs. Rats do not become ill from leptospiral infection, but dogs often develop severe disease similar to that in humans; infection can cause reproductive failure in cattle and pigs. Even when vaccinated, asymptomatic dogs, cattle, and pigs can be leptospiruric and thus transmit infection to humans. Classic (but not exclusive) serovar-animal associations include Icterohaemorrhagiae and Copenhageni in domestic rats (*Rattus norvegicus, R. rattus*), Grippotyphosa in opossums and raccoons (emerging in the United States and Canada in the absence of a vaccine that covers this serovar), Canicola in dogs, Hardjo in cattle and buffalo, and Pomona in pigs.

Patterns of leptospirosis transmission are characterized as epidemic, endemic, and sporadic. Factors that facilitate human infection are those that bring susceptible persons into indirect contact with contaminated animal urine through surface waters, moist soil, or other wet environments or into direct contact with urine and other excreta (e.g., products of parturition, placenta) of infected animals. In recent years, fewer occupation-related cases and more cases related to environmental exposure have been seen.

Seasonal rains and seasonal flooding are the most important factors in the occurrence of epidemic leptospirosis. Tropical humid environments, poor sanitation leading to rodent infestation, and uncontrolled dog populations are important for endemic transmission. Sporadic leptospirosis is associated with human contact with contaminated environments in various settings: on the job (veterinary, sewer, and slaughterhouse workers), in unhygienic inner-city alleys and slums, during adventure travel and other non-work-related outdoor activities, and during military training exercises in endemic regions.

Reliable data on the incidence of leptospirosis and on rates of associated morbidity and mortality remain scant and are generally drawn from biased hospital-based series or from governmental registries including passively reported serologic results. In the United States, leptospirosis was removed from the list of notifiable diseases in the 1990s. The ~50–100 cases passively reported annually to the Centers for Disease Control and Prevention (CDC) clearly represent an underestimate; the majority of these cases are from Hawaii, and others are sporadically acquired in inner-city settings or in association with environments such as farms, lakes, and adventure-sport locales. In large urban centers in Brazil that are subject to seasonal flooding (e.g., São Paulo, Rio de Janeiro, and Salvador), tens of thousands of cases are estimated to occur annually. Prospective, population-based cohort studies in Salvador indicate that 5% of slum dwellers are infected annually and that some people are reinfected. Case-fatality rates among hospitalized patients in São Paulo can be as high as ~20% despite state-of-the-art intensive care unit and supportive care. In the Peruvian Amazon, ~30–50% of patients with acute undifferentiated fever have been identified as having leptospirosis; the disease is severe in a small minority of such cases (<2%), and these severe cases are often associated with urban acquisition of infection. Men are affected more often by clinical disease than are women.

Infection by *Leptospira* does not occur via inhalation, and leptospirosis is a rare cause of laboratory-acquired infection. Laboratory strains usually used for serologic diagnosis have been serially passaged for long periods and usually have lost their virulence.

Leptospirosis affects urban and rural populations in industrialized and developing countries alike. The highest burden of disease falls upon those at lower socioeconomic levels whose activities of daily living bring them into contact with surface waters contaminated with the urine of animals carrying the infection. High rates of endemic leptospirosis, associated with both mild and severe disease, are found throughout tropical regions. Torrential seasonal flooding in areas of high population density (e.g., in urban slums in Brazil, India, and Thailand) is the major risk factor for epidemic severe disease. In 2009, outbreaks after typhoons in the Philippines affected large populations, prompting the Ministry of Health to provide antimicrobial chemoprophylaxis to millions of people; the efficacy of this intervention remains unknown.

Military training, outdoor athletic activities, and adventure travel have led to recognized outbreaks and sporadic cases of leptospirosis. Now-classic examples include the frequent occurrence of leptospirosis in U.S. soldiers undergoing jungle training in Panama (in which context the first clinical trial of antibiotic prophylaxis was carried out), whitewater rafters in Costa Rica, and almost half of the participants in Eco-Challenge Sabah in Borneo, Malaysia, in 2000.

Sporadic leptospirosis, which is likely to be common but underrecognized in urban and rural settings, is generally identified when the manifestations of disease are severe and the index of suspicion is high.

PATHOGENESIS

Leptospires infect humans through the mucosa (usually conjunctival and possibly oral or tonsillar) or through macerated, punctured, or abraded skin. The organisms resist innate immune defenses (e.g., complement), proliferate in the bloodstream or extracellularly within organs, and then disseminate hematogenously to all organs. The incubation period averages 5–14 days (range, 2–30 days); leptospires can be isolated from blood during the first 3–10 days of clinical illness **(Fig. 76-3)**. As antibodies develop, leptospires disappear from the blood but persist in various organs, including brain (the meninges and possibly other sites), liver, lung, heart, and kidney. The life cycle is completed as leptospires traverse the interstitial spaces of the kidney, penetrate the basement membrane of the proximal renal tubules, cross through proximal renal tubule epithelial cells, and become adherent to the proximal renal tubular brush border, whence they are excreted in the urine. In humans, as in other mammalian hosts, chronic and persistent renal colonization can last for weeks or years, with unknown pathophysiologic consequences.

Although severe human disease due to a wide variety of leptospires has been reported, some of the leptospires involved are thought to be more intrinsically pathogenic than others. Rat-associated *L. interrogans* serovars Icterohaemorrhagiae and Copenhageni are mostly commonly associated with Weil's disease; jaundice, renal failure, shock, and hemorrhage due to other species and serovars have been reported as well. Specific molecular determinants and virulencemechanisms responsible for disease manifestations have not been identified. An unusual lipid A structure renders the leptospiral lipopolysaccharide of low endotoxic potential in experimental systems. Multiple in vitro studies have shown that leptospires and their extracts cause cellular toxicity; however, the biochemical nature of damage to host cells and the underlying mechanisms remain unclear.

Pathologic findings are organ specific. Acute and chronic inflammation within the kidney is associated with acute tubular necrosis and interstitial nephritis. Autopsy studies have revealed abnormal regulation of fluid and electrolyte transporters—including the endogenous sodium/hydrogen exchanger isoform 3 (NHE 3), aquaporins 1 and 2, α-Na+K+ATPase, and sodium–potassium–chloride cotransporter (NKCC2 isoform)—in both the presence and the absence of

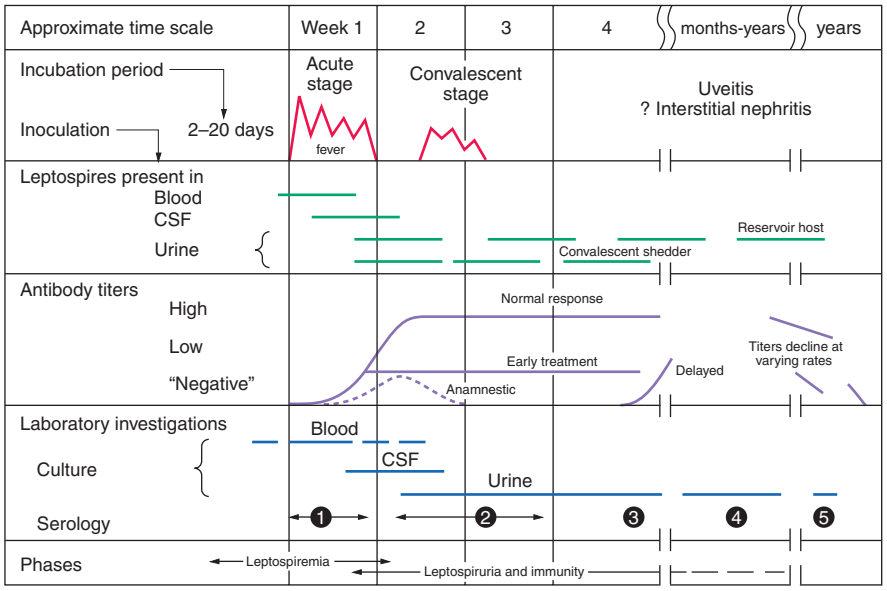


FIGURE 76-3

Biphasic nature of leptospirosis and relevant investigations at different stages of disease. Specimens 1 and 2 for serology are acute-phase serum samples; specimen 3 is a convalescent-phase serum sample that may facilitate detection of a delayed immune response; and specimens 4 and 5 are follow-up serum samples that can provide epidemiologic information, such as the presumptive infecting serogroup. (*Reprinted as adapted by Levitt [from LH Turner: Leptospirosis. BMJ 1:231, 1969] with permission from the American Society for Microbiology and the BMJ Publishing Group.*)

acute tubular necrosis. Primary injury of the proximal convoluted tubules is the primary renal pathophysiologic lesion in acute leptospirosis, with secondary increased distal tubular potassium excretion, hypokalemia, and polyuria.

Hepatic histopathology in fatal cases is associated with disruption of cellular cohesion, plugging of bile canaliculi, occasional acute inflammatory infiltrates, and focal periportal cellular necrosis and steatosis; widespread hepatocellular necrosis is not found. Cases of severe pulmonary hemorrhage syndrome that come to autopsy are characterized by the absence of inflammation, the paucity of organisms visible by silver or immunohistochemical staining, and grossly obvious frank hemorrhage **(Fig. 76-4)**. Ultrastructural features of the lung in the few fatal cases reported include swelling, increased pinocytotic vesicles, and giant dense bodies in the cytoplasm of epithelial cells; these abnormalities are limited to hemorrhagic areas, and the intercellular junctions are preserved. Platelets are adherent to activated but abnormal-appearing endothelial cells. Septal capillary lesions seem to be causally related to death, leading

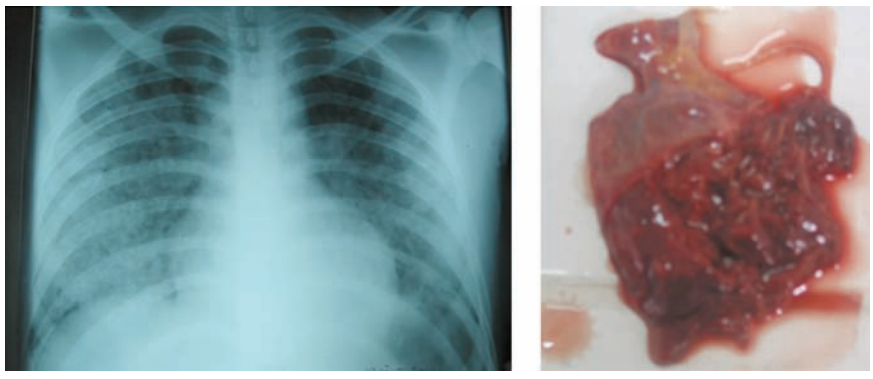


FIGURE 76-4

Severe pulmonary hemorrhage in leptospirosis. ***Left:*** Chest x-ray. ***Right:*** Gross appearance of right lower lobe of lung at autopsy. This patient, a 15-year-old in the Peruvian Amazonian city of Iquitos, died several days after presentation with acute illness, jaundice, and hemoptysis. Blood culture yielded *Leptospira interrogans* serovar Copenhageni/Icterohaemorrhagiae. (*Adapted with permission from E Segura et al: Clin Infect Dis 40:343, 2005. ©2005 by the Infectious Diseases Society of America.*)

to pulmonary hemorrhage; in both animal models and human cases, immunoglobulin and complement deposition have been demonstrated in lung tissue involved in leptospiral pulmonary hemorrhage.

The relation of disseminated intravascular coagulation to leptospirosis has long been debated. The prothrombin and activated partial thromboplastin times are not necessarily elevated in severe leptospirosis, and fibrinogen levels are typically elevated. Thrombocytopenia is characteristic, probably reflecting platelet consumption in the activated endothelial surface; platelet counts are lower in severe than in mild leptospirosis. Nonetheless, proteolytic products of fibrinogen (e.g., d-dimers), thrombin–antithrombin III complexes, and prothrombin fragment 1,2 have been found to be elevated in cases of leptospirosis in Thailand (but with no difference between severe and nonsevere cases), a finding indicating pathologic activation of the coagulation system in leptospirosis.

In the heart, pericardial and endocardial hemorrhage, disruption of myocardial fiber organization, and scattered myocyte necrosis (accompanied, grossly, by dilation of both right and left ventricles) are pathological lesions associated with severe leptospirosis.

Despite the traditional view that leptospirosis is characterized by vasculitis, formal demonstration of inflammatory infiltrates within any blood vessel has not been shown to be involved in the pathogenesis of this disease. A more likely possibility is that leptospires induce endothelial cell dysfunction with organ dysfunction and systemic disease, but this hypothesis remains to be validated.

CLINICAL MANIFESTATIONS

The clinical expression of infection by *Leptospira*, which is related to diverse focal organ dysfunction, includes subclinical infection, an undifferentiated febrile illness, and Weil's disease—the most severe form. Leptospirosis is classically described as biphasic (Fig. 76-3). Acute fever in the initial leptospiremic phase lasts for 3–10 days, during which period the organism may be cultured from blood. In a later immune phase, fever is not responsive to antibiotic therapy but leptospires can be isolated from urine. Unlike milder forms, Weil's disease may also be monophasic and fulminant.

Physical examination may include any of the following findings, none of which is pathognomonic for leptospirosis: conjunctival suffusion (dilated conjunctival blood vessels in the absence of discharge); pharyngeal erythema without exudate; muscle tenderness; rales on lung auscultation or dullness on chest percussion over areas of pleural hemorrhage; rash (which may be macular, maculopapular, erythematous, petechial, or ecchymotic); jaundice; meningismus; and hypo- or areflexia, particularly in the legs.

The natural course of mild uncomplicated leptospirosis usually ends in spontaneous resolution within 7–10 days without sequelae, but the difficulties of rapid diagnosis do not permit the initiation of specific antimicrobial therapy. Biomarkers to predict progression to severe disease are not available. Some patients experience a return of fever, headache, and other systemic symptoms after 3–10 days (the immune phase) in association with the clearance of leptospires from the blood and the appearance of antibodies; this phase of illness does not respond to antibiotic therapy.

Weil's disease is characterized by variable combinations of jaundice, acute kidney injury, hypotension, and hemorrhage—mostcommonly involving the lungs (Fig. 76-4) but also potentially affecting the gastrointestinal tract, retroperitoneum, pericardium, and brain. Other syndromes include aseptic meningitis, uveitis, cholecystitis, acute abdomen, and pancreatitis (with hypo- or hyperglycemia). Jaundice is not associated with fulminant hepatic necrosis or hepatocellular damage, but rather with abnormal laboratory values (see "Diagnosis," next). The liver can be enlarged and tender; splenomegaly is reported in a minority of cases. Acute kidney injury manifests after several days of illness and can be nonoliguric or oliguric, with serum electrolyte abnormalities reflecting proximal renal tubular dysfunction. Hypokalemia and hypomagnesemia are common in nonoliguric renal failure; hypomagnesemia can cause severe muscle weakness. Hypotension is associated with acute tubular necrosis and oliguria, requiring fluid resuscitation, sometimes pressors, and hemodialysis. Renal function typically returns to normal in survivors of severe disease. Severe pulmonary hemorrhage in leptospirosis is a clinical problem wherever the disease is endemic, manifesting with cough, chest pain, and hemoptysis but without purulent sputum.

Cardiac involvement is commonly reflected on the electrocardiogram as nonspecific ST and T wave changes, but also as right-bundle-branch block and right- and/or left-sided ventricular dilation indicating myocarditis. Skeletal muscle involvement manifests as severe myalgia, typically of the legs (especially the calves) but also of the abdominal muscles (mimicking acute abdomen); these symptoms are associated with a moderately elevated serum concentration of creatine kinase that, by itself, is not sufficient to result in acute kidney injury. Skin abnormalities include petechiae and ecchymosis as well as macular and maculopapular rash. Neurologic findings include aseptic meningitis (in which CSF pleocytosis can range from a few cells to >1000 cells/μL, with a polymorphonuclear cell predominance) and hypo- or areflexia, especially of the legs.

DIAGNOSIS

Leptospirosis should be suspected on the basis of an appropriate exposure history combined with any of the infection's protean manifestations. A high index of suspicion prompting elicitation of a detailed exposure history is critical and guides confirmatory testing (see later). Leptospiral infection is usually associated with obvious exposure events that go beyond casual activities such as simply having been on a farm or in an urban alley. An infected person usually has been immersed in or has

had mucosal or percutaneous exposure to contaminated animal urine. Leptospiral infection resulting from the bite of a rat or another animal is rare.

Biochemical, hematologic, and urinalysis findings in acute leptospirosis are not specific, but certain patterns suggest the diagnosis. In the context of an appropriate exposure history and in the absence of a more likely explanation, classic Weil's disease is suggested by elevated levels of blood urea nitrogen and serum creatinine in conjunction with mixed conjugated and unconjugated hyperbilirubinemia with aminotransferase elevation to less than five times the upper limit of normal. In all forms of leptospirosis (not just Weil's disease), a variety of abnormalities can occur. Urinalysis may show abnormalities of the sediment (leukocytes, erythrocytes, hyaline and granular cases). Elevation of the noncardiac isoform of creatine kinase may indicate skeletal muscle damage. Troponin levels indicative of myocarditis have not been adequately studied in leptospirosis. Hematologic abnormalities are variable but common: leukocytosis (typical in severe disease), leukopenia, hemolytic anemia, mild to moderate anemia, and thrombocytopenia.

On chest radiography, the appearance of the lungs varies. Alveolar infiltrates predominate and are associated with hemoptysis, but not with purulent sputum. Other findings include diffuse interstitial infiltrate patterns corresponding to hyaline membrane disease (acute respiratory distress syndrome) and small nodular infiltrates and pleural-based densities representing hemorrhage.

The confirmation of leptospirosis requires laboratory testing. Definitive diagnosis rests on demonstrating the presence of the organism by culture isolation, detection of nucleic acids or antigen in body fluids, or immunohistochemical visualization in tissue. Direct examination of urine or blood by dark-field microscopy has the potential to provide a rapid diagnosis but is not recommended because of complicating artifacts. Leptospiral cultures do not become positive for weeks and therefore cannot guide clinical care. Polymerase chain reaction–based assays have been used in research laboratories to detect leptospiral DNA but are not clinically available. Moreover, a negative result does not rule out the diagnosis: the assays' sensitivity is insufficient when the level of bacteremia is below a detectable threshold, and inhibitors in blood and urine can interfere with these tests.

Serologic assays are the diagnostic mainstay in leptospirosis. In the United States, the gold standard—the microscopic agglutination test (MAT)—is performed only at the CDC; likewise, in other countries, performance of the MAT is generally limited to reference laboratories. The MAT entails growth of a battery of serovars representing the 26 leptospiral serogroups, incubation of a standard quantity of leptospires with the patient's serum on a microtiter plate, and detection of agglutination by dark-field microscopy. The highest dilution of serum that yields significant (50%) agglutination is reported as the titer. Although antibody titers are reported by serovar, a positive MAT result reflects the presence only of *Leptospira*-specific antibodies and cannot be used to precisely identify the infecting serovar because one serovar may induce antibodies that cross-react with other serovars. When patients have a high pretest probability of leptospirosis, a single antibody titer >1:200 is considered strong evidence of infection; however, in regions where leptospirosis transmission and subclinical disease are common, higher titers are generally required for a confident diagnosis because of long-lasting antibodies after a previous infection. Because the MAT is generally negative in the first 7–10 days after the onset of infection, paired acute- and convalescent-phase serum samples are preferred to document seroconversion or a fourfold rise in titer.

Other serologic tests for leptospirosis (e.g., enzyme-linked immunosorbent assay, indirect hemagglutination, dot-blot, and lateral flow) are based on solid-phase assays; some of these tests are commercially available. Such assays use the saprophytic (non-disease-associated) leptospire *L. biflexa* as antigen. *L. biflexa* has lipopolysaccharide epitopes in common with pathogenic *Leptospira* species. While useful in some regions of the world, *L. biflexa*–based tests are relatively insensitive (because of regional variation of leptospires) and nonspecific (because of previous exposure) and must be interpreted with caution.

Leptospires can be cultured from blood and CSF during the first 7–10 days of illness and from urine beginning in the second week. Cultures usually become positive after 2–4 weeks (range, 1 week to 6 months). Urine cultures can remain positive for months or years despite antibiotic therapy. Because leptospires can remain viable for as long as ~10 days at room temperature, specimens can be shipped to reference laboratories in anticoagulated blood (heparin, citrate, EDTA). Although leptospires do not grow in medium used in automated blood culture detection systems, inoculated bottles can be subcultured into leptospiral culture medium within 1 week after inoculation for attempted isolation.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of acute leptospirosis is broad, reflecting its diverse clinical presentations and depending on the patient's travel and exposure history and geographic region of presentation. When fever and severe myalgia predominate, influenza is often considered, although the absence of coryza, sore throat, and cough is not consistent with this diagnosis. Other important possibilities include malaria, rickettsial diseases, arboviral infections (e.g., dengue and chikungunya), typhoid fever, hantavirus infection (hemorrhagic fever with renal syndrome or hantavirus cardiopulmonary syndrome), and viral hepatitis.

TREATMENT Leptospirosis

Although the value of antimicrobial treatment (Table 76-1) has not been proven in clinical trials, its prompt initiation probably shortens the course of severe leptospirosis and prevents the progression of mild disease. Despite debates

TABLE 76-1

TREATMENT AND CHEMOPROPHYLAXIS OF LEPTOSPIROSIS IN ADULTS[a]

INDICATION	REGIMEN
Treatment	
Mild leptospirosis	Doxycycline (100 mg PO bid) *or* Amoxicillin (500 mg PO tid) *or* Ampicillin (500 mg PO tid)
Moderate/severe leptospirosis	Penicillin (1.5 million units IV or IM q6h) *or* Ceftriaxone (1 g/d IV) *or* Cefotaxime (1 g IV q6h)
Chemoprophylaxis[b]	
	Doxycycline (200 mg PO once a week) *or* Azithromycin (250 mg PO once or twice a week)

[a]All regimens are given for 7 days.
[b]The efficacy of doxycycline prophylaxis in endemic or epidemic settings remains unclear. Experiments in animal models and a cost-effectiveness model indicate that azithromycin has a number of characteristics that may make it efficacious in treatment and prophylaxis, but clinical trials have not been performed.

about efficacy, antimicrobial drugs (typically penicillin, ceftriaxone, or cefotaxime) should be used to treat severe later-stage leptospirosis. Mild leptospirosis often is not specifically identified and typically resolves without antibiotic treatment. If clinical suspicion is high or the diagnosis is suggested or confirmed by laboratory findings in an appropriate context (e.g., clinical presentation, exposure history), mild disease should be treated with oral antibiotics—in particular, doxycycline, especially where rickettsial infections (including scrub typhus) are coendemic. Solid data from studies of animals indicate that oral azithromycin is also likely to be useful in mild leptospirosis. Like many acute bacterial diseases manifesting as multiorgan system dysfunction, severe leptospirosis frequently requires empirical initiation of broad-spectrum parenteral therapy before the diagnosis can be confirmed.

In rare instances, acute decompensation after the initiation of antimicrobial therapy occurs in association with a Jarisch-Herxheimer response and should be managed supportively. Fresh-frozen plasma, plasmapheresis, glucocorticoids, and activated protein C have no demonstrated role in the treatment of leptospirosis. Anecdotal reports in which inhaled nitric oxide was successfully used by leptospirosis patients with severe pulmonary involvement must be confirmed before such treatment can be recommended.

PROGNOSIS

The severity of illness in terms of pulmonary and renal dysfunction is the most important determinant of prognosis. Advanced age, clinically evident pulmonary involvement, elevated serum creatinine level, oliguria, and thrombocytopenia are associated with a poor prognosis; liver dysfunction in acute leptospirosis has not been confirmed to be an independent risk factor for death. Chronic alcoholism seems to be associated with severe disease. Reported mortality rates among hospitalized patients have varied from <5% to >20%.

Leptospirosis is generally considered to leave no permanent sequelae, although renal dysfunction, as manifested by electrolyte imbalances, may persist for days or weeks after acute illness resolves. Severe pulmonary hemorrhage and liver disease are not known to lead to persistent or progressive organ dysfunction. Some authorities have suggested that neuropsychiatric disturbance may follow severe disease; such conclusions must be assessed in a prospective clinical investigation.

PREVENTION

No vaccine is available for human leptospirosis. Preventive strategies, including prophylaxis with doxycycline, have been variably effective in different settings. Antibiotic prophylaxis can be considered for anticipated short-term, well-defined exposures, such as those incurred during military training or specific adventure travel (with, for example, fresh-water swimming). Long-term antibiotic prophylaxis has not been shown to be effective in preventing infection in high-transmission endemic settings. General sanitation approaches (e.g., rodent control) and avoidance of swimming in potentially contaminated places (e.g., for recreational use) are recommended, but these measures are difficult to apply consistently.

CHAPTER 77

RELAPSING FEVER

Mark S. Dworkin

Relapsing fever is an illness characterized by recurring episodes of fever and nonspecific symptoms (e.g., headache, myalgia, arthralgia, shaking chills, and abdominal symptoms) after infection with one of several species of *Borrelia*.

GLOBAL FEATURES

In North America, relapsing fever (a zoonosis) is transmitted by the bite of an *Ornithodoros* tick. In many other parts of the world, including Africa and Asia, relapsing fever is endemic and occurs after the bite of a tick or the human body louse (*Pediculus humanus*). Tick-borne relapsing fever (TBRF) is also reported from countries in the Middle East, including Israel, Iran, and Jordan. Louse-borne relapsing fever (LBRF) is occasionally imported into the United States by a traveler. TBRF is rarely fatal in North America, where it is most often sporadic; in some African countries (e.g., Senegal and Tanzania), TBRF is a more significant bacterial infection, causing morbidity and death. Conditions that favor infestation with *P. humanus*, such as living in refugee camps or other stressful situations in which many people are crowded together without access to good hygiene and nutrition, have led to large outbreaks of LBRF with substantial rates of morbidity and death; thus, LBRF is also known as *epidemic relapsing fever*.

ETIOLOGY AND PATHOGENESIS

The borreliae are helical or wavy motile spirochetes whose length ranges from 3 to 25 μm and whose width is usually 0.2–0.3 μm. In fixed Wright-stained differential smears, the organisms appear as loose coils **(Fig. 77-1)**. Borreliae are transmitted to humans by exposure to the bite of an infected *Ornithodoros* tick (TBRF) or to the hemolymph of an infected human body louse, which may be found on clothing (LBRF). For louse-borne disease, it is not the louse's bite that causes transmission; rather, spirochetes are introduced when the louse is crushed (e.g., by scratching) and the insect's infected hemolymph is released and contaminates abraded or normal skin and mucous membranes. Relapsing fever results when variation in borrelial surface antigens leads to repeated bacteremia and stimulation of the immune system by each new antigen. Each time the organism changes its surface antigens, thus evading the immune system, another febrile response occurs. LBRF is caused by *Borrelia recurrentis*, whereas TBRF is caused by a variety of *Borrelia* species whose names sometimes correspond to their tick vectors. For example, *B. hermsii* is transmitted by the tick *O. hermsi*, and *B. turicatae* is transmitted by *O. turicata* **(Fig. 77-2)**.

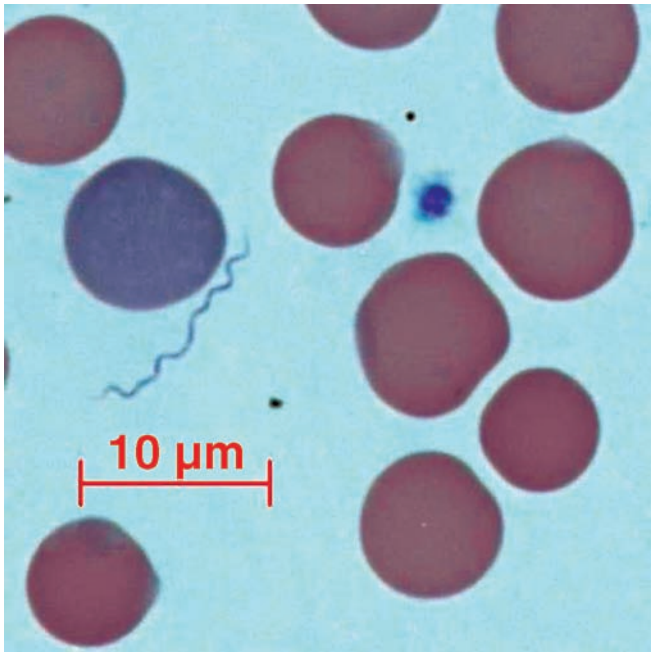


FIGURE 77-1
Photomicrograph of tick-borne relapsing fever spirochete (*Borrelia hermsii*) in a Wright-Giemsa–stained peripheral blood film. (*Reprinted with permission from DT Dennis: Relapsing fever, in Harrison's Principles of Internal Medicine, 17th ed, AF Fauci et al [eds]. New York, McGraw-Hill, 2008, p 1054.*)

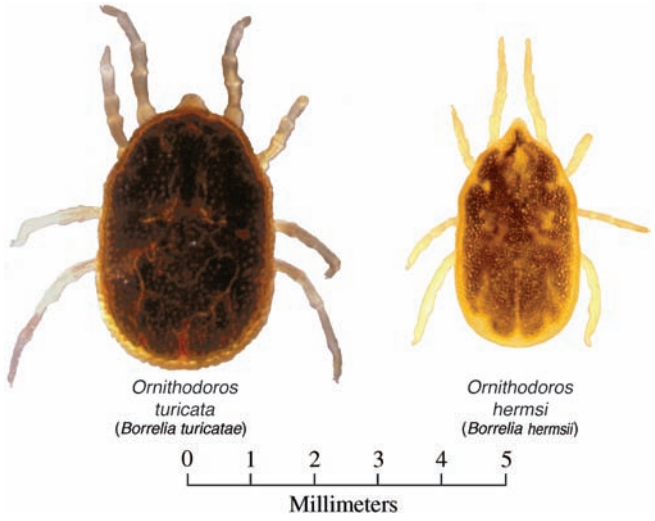


FIGURE 77-2
Ornithodoros turicata* and *O. hermsi, two of the many species of blood-feeding soft ticks responsible for transmitting tick-borne relapsing fever. (*Reprinted from MS Dworkin et al: Infect Dis Clin North Am 22:449, 2008, with permission from Elsevier.*)

EPIDEMIOLOGY

TBRF is endemic in the western United States, southern British Columbia, the plateau regions of Mexico, Central and South America, the Mediterranean, Central Asia, and throughout much of Africa. In the United States, it typically is not reported farther east than Montana, Colorado, New Mexico, and Texas, although cases have been acquired in Oklahoma, Kansas, and Ohio and one case has been reported from Wyoming. A relapsing fever spirochete has been described as far east as Florida, although human infections have not yet been reported in that state. In the United States, exposure sites typically are forested areas at various elevations in mountainous regions (the Cascade, Rocky Mountain, San Bernardino, and Sierra Nevada ranges) and limestone caves in central Texas. Caves may likewise be an important source of TBRF in other areas of the world, such as Israel and Jordan. Houses, cabins, and cowsheds have been implicated as sources of infection because of tick-infested rodent nesting. The most common vector in the United States, *O. hermsi,* is often found in coniferous forests at elevations of 1500–8000 ft, where it feeds primarily on ground squirrels, tree squirrels, and chipmunks dwelling near freshwater lakes that attract humans who may live in or rent nearby cabins. The disease tends to be most common where humans come into contact with diurnal rodents and their ticks. Only 13 counties have accounted for ~50% of all U.S. cases. Surveillance of TBRF is not performed in all states where the disease is endemic, and substantial underreporting is likely where the disease is reportable. Therefore, the precise distribution of disease is not known.

Many cases of TBRF in West Africa have been attributed to infection with *B. crocidurae* transmitted by the tick *O. sonrai*. In Senegal, this disease has been identified as the most common bacterial infection causing febrile illness. Thus this infection is an important factor in the differential diagnosis of suspected malaria in West Africa, where LBRF has not been described in many decades. Co-infection with *Plasmodium* species was reported in more than one-third of blood films from Senegalese TBRF patients. In eastern sub-Saharan Africa, *B. duttonii* is more prevalent. TBRF has been detected (albeit less commonly) in northern Africa (e.g., in Morocco), where *B. hispanica* and *B. crocidurae* have been identified.

The epidemiology of LBRF is not as well characterized as that of TBRF, probably in part because of the higher prevalence of the former in regions with relatively few resources for communicable disease surveillance. Historically, LBRF has been described in North America and Europe, but it is now only uncommonly reported in these regions. LBRF is relatively well described in East Africa. Outbreaks have been reported in Sudan and Ethiopia. Reports of disease in the highlands of Ethiopia have included many documented cases, despite a recent decline; in that country, more cases have occurred in male than in female patients. Seasonality has not been reported consistently.

APPROACH TO THE PATIENT **Relapsing Fever**

Recurring febrile episodes in a patient who lives in or has recently traveled to a geographic location where relapsing fever is known to occur should lead to consideration of relapsing fever. Diagnosis has sometimes been delayed because of a focus on symptoms other than the recurrence of fever, such as diarrhea, thrombocytopenia, and cranial nerve palsy. Failure to diagnose relapsing fever promptly can lead to prolonged (untreated) illness and can incur excessive (preventable) medical costs. One patient may present with illness resembling meningitis, another with illness resembling influenza, and others with a febrile gastrointestinal illness or no physical findings. In all these instances, the patient may undergo a variety of unnecessary invasive and noninvasive tests. In addition, some patients may have more than one diagnosis (e.g., LBRF and typhus); therefore, other local tick-borne or louse-borne diseases should be kept in mind during evaluation.

CLINICAL MANIFESTATIONS

The mean incubation period is 7 days for TBRF (range, 4–18 days or longer) and 8 days for LBRF (range, 5–15 days; sometimes a shorter period in North Africa). Regardless of the tick or louse vector, the clinical manifestations of relapsing fever are similar, although not identical. The signs and symptoms documented in a large series of cases of TBRF are listed with their frequencies in **Table 77-1**. Alteration of sensorium, abdominal pain, and vomiting are common. Diarrhea may develop in 25%

TABLE 77-1

MANIFESTATIONS OF TICK-BORNE RELAPSING FEVER ACQUIRED IN THE NORTHWESTERN UNITED STATES AND SOUTHWESTERN BRITISH COLUMBIA

SIGN OR SYMPTOM	%	SIGN OR SYMPTOM	%
Headache	94	Photophobia	25
Myalgia	92	Neck pain	24
Chills	88	Rash	18
Nausea	76	Dysuria	13
Arthralgia	73	Jaundice	10
Vomiting	71	Hepatomegaly	10
Abdominal pain	44	Splenomegaly	6
Confusion	38	Conjunctival injection	5
Dry cough	27	Eschar	2
Eye pain	26	Meningitis	2
Diarrhea	25	Nuchal rigidity	2
Dizziness	25		

Source: From a review of 182 cases reported during 1980–1995 (MS Dworkin et al: Clin Infect Dis 26:122, 1998. ©1998 Clinical Infectious Diseases).

of cases. Jaundice; central nervous system (CNS) involvement; petechiae on the trunk, extremities, and mucous membranes; epistaxis; and blood-tinged sputum are more likely in LBRF. Uncommon manifestations of relapsing fever include iritis, acute respiratory distress syndrome, uveitis, iridocyclitis, myocarditis, and splenic rupture. Cranial nerve palsy and other neurologic manifestations are often reversible. Neurologic findings may occur in 10–30% of cases and are more common in LBRF. These findings may include signs of meningitis with or without cerebrospinal fluid abnormalities, seizure, focal deficits, hemiplegia, paraplegia, paresthesias, psychosis, hallucinations, and delirium. Certain species of tick-borne *Borrelia* have been reported with particular frequency in cases with neurologic complications (*B. duttonii* and *B. turicatae*).

The average duration of the first episode of TBRF is 3 days (range, 12 h to 17 days), and the episode terminates in a crisis. In contrast, the average duration of the first episode of LBRF is 5.5 days (range, 4–10 days). Subsequent relapsing febrile episodes are typically of shorter duration. The average time between the first episode and the first relapse is 7 days for TBRF and 9 days for LBRF. During afebrile intervals, the patient may have symptoms (e.g., malaise) or may feel well.

The differential diagnosis of infectious diseases causing fevers that may relapse or have biphasic patterns includes but is not limited to Colorado tick fever, yellow fever, dengue fever, lymphocytic choriomeningitis, brucellosis, malaria, leptospirosis, chronic meningococcemia, rat-bite fever, and infection with echovirus 9 or *Bartonella* species. The many other diagnoses that may overlap with relapsing fever in terms of other manifestations include typhus and typhoid fever. A history of travel, place of residence, and animal exposures is useful when patients have these fever patterns.

DIAGNOSIS

Detection and isolation of spirochetes

During asymptomatic intervals, relapsing fever borreliae are undetectable in the bloodstream by microscopy. Laboratory confirmation is made by the detection or isolation of spirochetes from blood during a febrile episode. Spirochetal counts may be high in the blood. Typically, an average of five organisms per oil-immersion field are observed in routine differential fixed smears of blood obtained from patients during the acute febrile phase of illness. A thin smear or a thick drop of blood is applied to a standard glass microscope slide, stained with Wright or Giemsa, and examined with a bright-field microscope at 1000x with oil immersion. Spirochetes also may be visualized by direct or indirect immunofluorescent staining and fluorescence microscopy. A dark-field microscope may be used to observe spirochetes in the blood. However, microscopic observation of spirochetes is relatively insensitive. Quantitative buffy coat analysis is an alternative method. Other available methods are most often used in research settings. Polymerase chain reaction (PCR) and monoclonal antibody can be used to determine the species of *Borrelia*. For laboratories with PCR technology and expertise, this method is more sensitive than microscopy.

Serology

Serologic confirmation of TBRF is demonstrated by a fourfold rise in antibody titer between acute- and convalescent-phase serum samples or by the diagnostic reactivity of a single convalescent-phase serum sample. However, serology may not be reliable because of lack of standardization. Patients infected previously with other species of spirochetes may have false-positive reactions in the enzyme-linked immunosorbent assay (ELISA) and the indirect fluorescence antibody (IFA) assay. The most reliable method—the recombinant GlpQ assay—is not widely available. Therefore, blood samples are often screened with ELISA or IFA, and, if the result is positive (e.g., an IFA titer of 1:128–1:256 or higher), an immunoblot can be performed to determine the pattern of reactivity. This procedure has led to recognition of patients erroneously diagnosed with Lyme disease who actually have TBRF.

TREATMENT **Relapsing Fever**

Treatment options for adults with relapsing fever are summarized in Fig. 77-3. Relapsing fever spirochetes are commonly sensitive to antibiotics such as doxycycline and erythromycin. Single-dose therapy is generally recommended for LBRF, while a 7-day (or 10-day) course is usually used for TBRF. Insufficient information is available on the efficacy of single-dose therapy for TBRF.

Lumbar puncture should be considered when signs of meningitis or encephalitis are present; cerebrospinal fluid evidence of these neurologic conditions

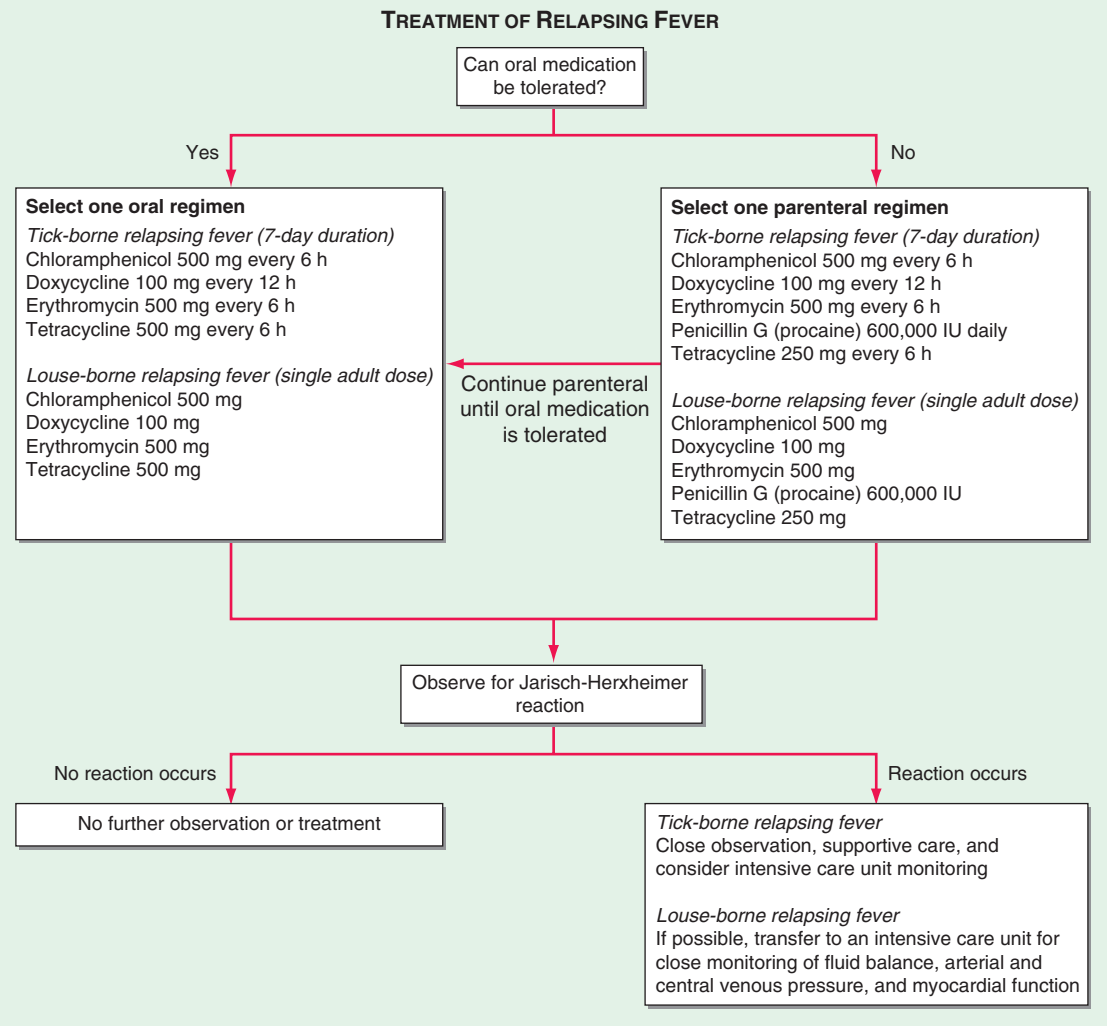


FIGURE 77-3
Treatment of relapsing fever and approach to the Jarisch-Herxheimer reaction.

suggests the need for treatment with an IV antibiotic regimen. This issue is especially relevant in TBRF due to certain species such as *B. duttonii* in Africa and *B. turicatae* in the southwestern United States because these species are more prone to invade the CNS and can reenter the bloodstream after antibiotic treatment if a regimen with good CNS penetration is not used.

Children <8 years of age and pregnant women with relapsing fever should be treated with penicillin or erythromycin. When a Jarisch-Herxheimer reaction occurs (and its occurrence is unpredictable), it may be milder in children than in adults. Monitoring of patients for this reaction for the first 12 h after the first dose of antibiotic is recommended (see following).

COMPLICATIONS

Moderate to severe thrombocytopenia, although not associated with a fatal outcome, is a typical finding in acute TBRF. Bleeding complications, such as epistaxis, purpura, hemoptysis, hematemesis, bloody diarrhea, hematuria, subarachnoid and cerebral hemorrhages, splenic rupture, and retinal hemorrhage, are more common with LBRF. Although death from TBRF in North America is rare, this infection has been associated with complications during pregnancy, including spontaneous abortion, premature birth, or neonatal death.

The Jarisch-Herxheimer reaction is an acute exacerbation of symptoms that may occur on initial treatment of relapsing fever with an effective antibiotic. During this reaction, spirochetes disappear rapidly from the circulation and there is massive cytokine release. The likelihood of a Jarisch-Herxheimer reaction is not reliably predictable in TBRF; the reaction is common in LBRF treated with tetracycline. Treatment with penicillin rapidly alters the morphology of the dividing spirochetes, making them susceptible to phagocytosis. Symptoms of the Jarisch-Herxheimer reaction often include hypotension, tachycardia, chills, rigors, diaphoresis, and marked elevation of body temperature. The reaction typically begins within 1–4 h of the first dose of antibiotic, and the symptoms may be extremely severe. When possible, patients with LBRF

who develop the Jarisch-Herxheimer reaction should be transferred to an intensive care unit for close monitoring of fluid balance, arterial and central venous pressure, and myocardial function. Death (most often secondary to cardiovascular collapse) has been reported as a complication of the reaction in patients with LBRF. Patients with TBRF and the Jarisch-Herxheimer reaction also should be monitored closely; however, death from the Jarisch-Herxheimer reaction from relapsing fever acquired in North America has not been reported despite the severity of this reaction. An opioid partial agonist, meptazinol, has been shown to reduce the severity of symptoms, but this treatment has not been thoroughly studied.

PROGNOSIS

Death is more likely if relapsing fever is acquired from a louse rather than a tick. Nutritional status may play a significant role in outcome. LBRF often occurs in settings of famine or overcrowding, where nutrition may be poor and additional diseases may complicate the diagnosis or the disease course. Among treated individuals, the fatality rate is 5% for LBRF and much lower for TBRF. Two *Borrelia* species associated with a relatively high fatality rate from relapsing fever are *B. recurrentis* (louse-borne) and *B. duttonii* (tick-borne).

PREVENTION

Prevention of TBRF includes the avoidance of rodent- and tick-infested dwellings as well as infested natural sites, such as animal burrows or caves. Environmental health specialists from local health departments and pest removal services may be consulted about rodent-proofing of homes and vacation cabins and reduction of rodent habitat around homes (e.g., by removal of rodent nesting material from walls, ceilings, and floors). Chemical treatment of rodent-infested areas should be undertaken only by pest control specialists. Contact with ticks and potential animal hosts should occur only while gloves are worn, given that TBRF has been contracted through skin contact with contaminated blood (e.g., in laboratory accidents and blood transfusions). Wearing clothing that protects the skin (e.g., long pants and long-sleeved shirts) and applying insect repellents such as DEET and permethrin to exposed skin and clothing, respectively, can prevent transmission of disease by hard ticks and possibly by soft ticks in some settings (e.g., in caves or—as a partial measure of protection—during sleep). Protection while sleeping in a potentially infested dwelling may best be provided by topical repellents. Sleeping on the floor or on a bed positioned directly against a wall should be avoided.

To prevent LBRF, it is necessary to prevent louse infestation by promoting personal hygiene (e.g., bathing) and systematic delousing (e.g., application of permethrin to clothing). Laundering or disposal of infested clothing and bedding is another important measure. Control of epidemics may involve widespread antibiotic use.

TBRF is reportable through local health departments in some states where the disease is endemic. (State health departments maintain a list of reportable diseases.) Reporting is encouraged for cases diagnosed in these states; surveillance data derived from reported cases are vital for an enhanced understanding of this tick-borne disease. Reporting of cases of TBRF may result in prevention and education of the public and physicians about the epidemiology and clinical presentation of the disease.

CHAPTER 78

LYME BORRELIOSIS

Allen C. Steere

DEFINITION

Lyme borreliosis is caused by a spirochete, *Borrelia burgdorferi sensu lato*, that is transmitted by ticks of the *Ixodes ricinus* complex. The infection usually begins with a characteristic expanding skin lesion, erythema migrans (EM; stage 1, localized infection). After several days or weeks, the spirochete may spread to many different sites (stage 2, disseminated infection). Possible manifestations of disseminated infection include secondary annular skin lesions, meningitis, cranial neuritis, radiculoneuritis, peripheral neuritis, carditis, atrioventricular nodal block,

or migratory musculoskeletal pain. Months or years later (usually after periods of latent infection), intermittent or persistent arthritis, chronic encephalopathy or polyneuropathy, or acrodermatitis may develop (stage 3, persistent infection). Most patients experience early symptoms of the illness during the summer, but the infection may not become symptomatic until it progresses to stage 2 or 3.

Lyme disease was recognized as a separate entity in 1976 because of geographic clustering of children in Lyme, Connecticut, who were thought to have juvenile rheumatoid arthritis. It became apparent that Lyme disease was a multisystemic illness that affected primarily the skin, nervous system, heart, and joints. Epidemiologic studies of patients with EM implicated certain *Ixodes* ticks as vectors of the disease. Early in the twentieth century, EM had been described in Europe and attributed to *I. ricinus* tick bites. In 1982, a previously unrecognized spirochete, now called *Borrelia burgdorferi*, was recovered from *Ixodes scapularis* ticks and then from patients with Lyme disease. The entity is now called Lyme disease or Lyme borreliosis.

ETIOLOGIC AGENT

B. burgdorferi, the causative agent of Lyme disease, is a fastidious microaerophilic bacterium. The spirochete's genome is quite small (~1.5 Mb) and consists of a highly unusual linear chromosome of 950 kb as well as 17–21 linear and circular plasmids. The most remarkable aspect of the *B. burgdorferi* genome is that there are sequences for more than 100 known or predicted lipoproteins—a larger number than in any other organism. The spirochete has few proteins with biosynthetic activity and depends on its host for most of its nutritional requirements. It has no sequences for recognizable toxins.

Currently, 13 closely related borrelial species are collectively referred to as *Borrelia burgdorferi sensu lato* (i.e., *B. burgdorferi* in the general sense). The human infection Lyme borreliosis is caused primarily by three pathogenic genospecies: *B. burgdorferi sensu stricto* (*B. burgdorferi* in the strict sense, hereafter referred to as *B. burgdorferi*), *Borrelia garinii*, and *Borrelia afzelii*. *B. burgdorferi* is the sole cause of the infection in the United States; all three genospecies are found in Europe, and the latter two species occur in Asia.

Strains of *B. burgdorferi* have been subdivided according to several typing schemes, including one based on sequence variation of outer-surface protein C (OspC) and a second based on differences in the 16S–23S rRNA intergenic spacer region (RST or IGS). From these typing systems, it is apparent that strains of *B. burgdorferi* differ in pathogenicity. OspC type A (RST1) strains seem to be particularly virulent and may have played a role in the emergence of Lyme disease in epidemic form in the late twentieth century.

EPIDEMIOLOGY

The 13 known genospecies of *B. burgdorferi sensu lato* live in nature in enzootic cycles involving 14 species of ticks that are part of the *I. ricinus* complex. *I. scapularis* (Fig. 132-1) is the principal vector in the eastern United States from Maine to Georgia and in the midwestern states of Wisconsin, Minnesota, and Michigan. *I. pacificus* is the vector in the western states of California and Oregon. The disease is acquired throughout Europe (from Great Britain to Scandinavia to European Russia), where *I. ricinus* is the vector, and in Asian Russia, China, and Japan, where *I. persulcatus* is the vector. These ticks may transmit other diseases as well. In the United States, *I. scapularis* also transmits babesiosis and human anaplasmosis; in Europe and Asia, *I. ricinus* and *I. persulcatus* also transmit tick-borne encephalitis.

Ticks of the *I. ricinus* complex have larval, nymphal, and adult stages. They require a blood meal at each stage. The risk of infection in a given area depends largely on the density of these ticks as well as their feeding habits and animal hosts, which have evolved differently in different locations. For *I. scapularis* in the northeastern United States, the white-footed mouse and certain other rodents are the preferred hosts of the immature larvae and nymphs. It is critical that both of the tick's immature stages feed on the same host because the life cycle of the spirochete depends on horizontal transmission: in early summer from infected nymphs to mice and in late summer from infected mice to larvae, which then molt to become the infected nymphs that will begin the cycle again the following year. It is the tiny nymphal tick that is primarily responsible for transmission of the disease to humans during the early summer months. White-tailed deer, which are not involved in the life cycle of the spirochete, are the preferred host for the adult stage of *I. scapularis* and seem to be critical to the tick's survival.

Lyme disease is now the most common vector-borne infection in the United States and Europe. Since surveillance was begun by the Centers for Disease Control and Prevention (CDC) in 1982, the number of cases in the United States has increased dramatically. More than 25,000 new cases are now reported each summer. In Europe, the highest reported frequencies of the disease are in the middle of the continent and in Scandinavia.

PATHOGENESIS AND IMMUNITY

To maintain its complex enzootic cycle, *B. burgdorferi* must adapt to two markedly different environments: the tick and the mammalian host. The spirochete expresses outer-surface protein A (OspA) in the midgut of the tick, whereas OspC is upregulated as the organism travels to the tick's salivary gland. There, OspC binds a tick salivary-gland protein (Salp15), which is required for infection of the mammalian host. The tick must usually be attached for at least 24 h for transmission of *B. burgdorferi*.

After injection into the human skin, *B. burgdorferi* may migrate outward, producing EM, and may spread hematogenously or in the lymph to other organs. The only known virulence factors of *B. burgdorferi* are surface proteins that allow the spirochete to attach to mammalian proteins, integrins, glycosaminoglycans, or glycoproteins. For example, spread through the skin and

other tissue matrices may be facilitated by the binding of human plasminogen and its activators to the surface of the spirochete. Some *Borrelia* strains bind complement regulator–acquiring surface proteins (FHL-1/reconectin, or factor H), which help to protect spirochetes from complement-mediated lysis. Dissemination of the organism in the blood is facilitated by binding to the fibrinogen receptor on activated platelets ($\alpha_{IIb}\beta_3$) and the vitronectin receptor ($\alpha_v\beta_3$) on endothelial cells. As the name indicates, spirochetal decorin-binding proteins A and B bind decorin, a glycosaminoglycan on collagen fibrils; this binding may explain why the organism is commonly aligned with collagen fibrils in the extracellular matrix in the heart, nervous system, or joints.

To control and eradicate *B. burgdorferi*, the host mounts both innate and adaptive immune responses, resulting in macrophage- and antibody-mediated killing of the spirochete. As part of the innate immune response, complement may lyse the spirochete in the skin. Chemokines released by constituent cells in the skin lead to the recruitment of neutrophils and macrophages; the latter release potent proinflammatory cytokines. The purpose of the adaptive immune response appears to be the production of specific antibodies, which opsonize the organism—a step necessary for optimal spirochetal killing. Studies with protein arrays expressing ~1400 *B. burgdorferi* proteins detected antibody responses to a total of 89 spirochetal proteins (primarily outer-surface lipoproteins) in a population of patients with Lyme arthritis. Histologic examination of all affected tissues reveals an infiltration of lymphocytes, macrophages, and plasma cells with some degree of vascular damage (including mild vasculitis or hypervascular occlusion). These findings suggest that the spirochete may have been present in or around blood vessels.

In enzootic infection, *B. burgdorferi* spirochetes must survive this immune assault only during the summer months before returning to larval ticks to begin the cycle again the following year. In contrast, infection of humans is a dead-end event for the spirochete. Within several weeks or months, innate and adaptive immune mechanisms—even without antibiotic treatment—control widely disseminated infection, and generalized systemic symptoms wane. However, without antibiotic therapy, spirochetes may survive in localized niches for several more years. For example, *B. burgdorferi* infection in the United States may cause persistent arthritis or, in rare cases, subtle encephalopathy or polyneuropathy. Thus, immune mechanisms seem to succeed eventually in the near or total eradication of *B. burgdorferi* from selected niches, including the joints or nervous system.

CLINICAL MANIFESTATIONS

Early infection: stage 1 (localized infection)

Because of the small size of nymphal ixodid ticks, most patients do not remember the preceding tick bite. After an incubation period of 3–32 days, EM, which occurs at the site of the tick bite, usually begins as a red macule or papule that expands slowly to form a large annular lesion **(Fig. 78-1)**. As the lesion increases in size, it often develops a bright red outer border and partial central clearing. The center of the lesion sometimes becomes intensely erythematous and indurated, vesicular, or necrotic. In other instances, the expanding lesion remains an even, intense red; several red rings are found within an outside ring; or the central area turns blue before the lesion clears. Although EM can be located anywhere, the thigh, groin, and axilla are particularly common sites. The lesion is warm but not often painful. Approximately 20% of patients do not exhibit this characteristic skin manifestation.

Early infection: stage 2 (disseminated infection)

In cases in the United States, *B. burgdorferi* often spreads hematogenously to many sites within days or weeks after the onset of EM. In these cases, patients may develop secondary annular skin lesions similar in appearance to the initial lesion. Skin involvement is commonly accompanied by severe headache, mild stiffness of the neck, fever, chills, migratory musculoskeletal pain, arthralgias, and profound malaise and fatigue. Less common manifestations include generalized lymphadenopathy or splenomegaly, hepatitis, sore throat, nonproductive cough, conjunctivitis, iritis, or testicular swelling. Except for fatigue and lethargy, which are often constant, the early signs and symptoms of Lyme disease are typically intermittent and changing. Even in untreated patients, the early symptoms usually become less severe or disappear within several weeks. In ~15% of patients, the infection presents with these nonspecific systemic symptoms.

Symptoms suggestive of meningeal irritation may develop early in Lyme disease when EM is present but usually are not associated with cerebrospinal fluid (CSF) pleocytosis or an objective neurologic deficit. After several weeks or months, ~15% of untreated

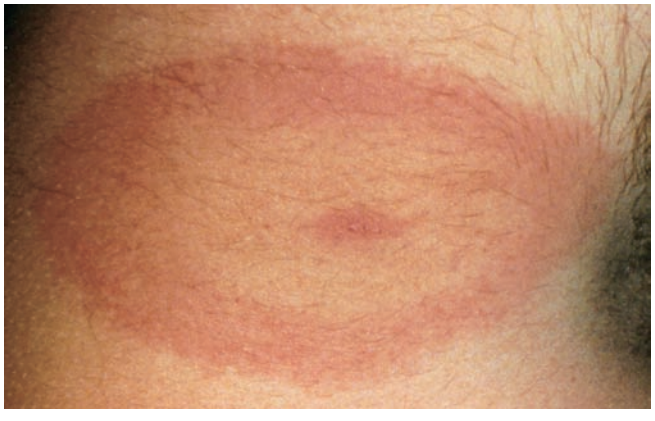


FIGURE 78-1
A classic erythema migrans lesion (9 cm in diameter) is shown near the right axilla. The lesion has partial central clearing, a bright red outer border, and a target center. (*Courtesy of Vijay K. Sikand, MD; with permission.*)

patients develop frank neurologic abnormalities, including meningitis, subtle encephalitic signs, cranial neuritis (including bilateral facial palsy), motor or sensory radiculoneuropathy, peripheral neuropathy, mononeuritis multiplex, cerebellar ataxia, or myelitis—alone or in various combinations. In the United States, the usual pattern consists of fluctuating symptoms of meningitis accompanied by facial palsy and peripheral radiculoneuropathy. Lymphocytic pleocytosis (~100 cells/μL) is found in CSF, often along with elevated protein levels and normal or slightly low glucose concentrations. In Europe and Asia, the first neurologic sign is characteristically radicular pain, which is followed by the development of CSF pleocytosis (called meningopolyneuritis, or *Bannwarth's syndrome*); meningeal or encephalitic signs are frequently absent. In children, the optic nerve may be affected because of inflammation or increased intracranial pressure, which may lead to blindness. These early neurologic abnormalities usually resolve completely within months, but in rare cases chronic neurologic disease may occur later.

Within several weeks after the onset of illness, ~8% of patients develop cardiac involvement. The most common abnormality is a fluctuating degree of atrioventricular block (first-degree, Wenckebach, or complete heart block). Some patients have more diffuse cardiac involvement, including electrocardiographic changes indicative of acute myopericarditis, left ventricular dysfunction evident on radionuclide scans, or (in rare cases) cardiomegaly or pancarditis. Cardiac involvement usually lasts for only a few weeks but may recur. Chronic cardiomyopathy caused by *B. burgdorferi* has been reported in Europe.

During this stage, musculoskeletal pain is common. The typical pattern consists of migratory pain in joints, tendons, bursae, muscles, or bones (usually without joint swelling) lasting for hours or days and affecting one or two locations at a time.

Late infection: stage 3 (persistent infection)

Months after the onset of infection, ~60% of patients in the United States who have received no antibiotic treatment develop frank arthritis. The typical pattern comprises intermittent attacks of oligoarticular arthritis in large joints (especially the knees), lasting for weeks or months in a given joint. A few small joints or periarticular sites may also be affected, primarily during early attacks. The number of patients who continue to have recurrent attacks decreases each year. However, in a small percentage of cases, involvement of large joints—usually one or both knees—is persistent and may lead to erosion of cartilage and bone.

White cell counts in joint fluid range from 500 to 110,000/μL (average, 25,000/μL); most of these cells are polymorphonuclear leukocytes. Tests for rheumatoid factor or antinuclear antibodies usually give negative results. Examination of synovial biopsy samples reveals fibrin deposits, villous hypertrophy, vascular proliferation, microangiopathic lesions, and a heavy infiltration of lymphocytes and plasma cells.

Although most patients with Lyme arthritis respond well to antibiotic therapy, a small percentage in the northeastern United States have persistent arthritis for months or even for several years after the near or total eradication of spirochetes from the joints by antibiotic therapy. Compared with antibiotic-responsive patients, those with antibiotic-refractory arthritis are more often infected with RST1 strains of *B. burgdorferi*; have a higher frequency of certain class II major histocompatibility complex molecules (particularly HLA-DRBI*0401 or -*0101 molecules) that bind an epitope of OspA ($OspA_{163–175}$); and often exhibit T cell recognition of this epitope. In addition, these patients have significantly higher levels of proinflammatory chemokines and cytokines in joint fluid (especially CXCL9 and interferon γ) than do antibiotic-responsive patients; these higher levels persist during the postantibiotic period, when polymerase chain reaction (PCR) results for *B. burgdorferi* DNA are uniformly negative. It has been postulated that, in these genetically susceptible individuals, *B. burgdorferi* may trigger localized, tissue-specific autoimmunity within the proinflammatory milieu of the joints.

Although rare, chronic neurologic involvement may also become apparent from months to several years after the onset of infection, sometimes following long periods of latent infection. The most common form of chronic central nervous system involvement is subtle encephalopathy affecting memory, mood, or sleep, and the most common form of peripheral neuropathy is an axonal polyneuropathy manifested as either distal paresthesia or spinal radicular pain. Patients with encephalopathy frequently have evidence of memory impairment in neuropsychological tests and abnormal results in CSF analyses. In cases of polyneuropathy, electromyography generally shows extensive abnormalities of proximal and distal nerve segments. Encephalomyelitis or leukoencephalitis, a rare manifestation of Lyme borreliosis associated primarily with *B. garinii* infection in Europe, is a severe neurologic disorder that may include spastic paraparesis, upper motor-neuron bladder dysfunction, and, rarely, lesions in the periventricular white matter.

Acrodermatitis chronica atrophicans, the late skin manifestation of Lyme borreliosis, has been associated primarily with *B. afzelii* infection in Europe and Asia. It has been observed especially often in elderly women. The skin lesions, which are usually found on the acral surface of an arm or leg, begin insidiously with reddish-violaceous discoloration; they become sclerotic or atrophic over a period of years.

The basic patterns of Lyme borreliosis are similar worldwide, but there are regional variations, primarily between the illness found in North America, which is caused exclusively by *B. burgdorferi*, and that found in Europe, which is caused primarily by *B. afzelii* and *B. garinii*. With each of the *Borrelia* species, the infection usually begins with EM. However, *B. burgdorferi* often disseminates widely; it is particularly arthritogenic, and it may cause antibiotic-refractory arthritis. *B. garinii* typically disseminates less widely, but it is especially neurotropic and may cause borrelial encephalomyelitis.

B. afzelii often infects only the skin but may persist in that site, where it may cause several different dermatoborrelioses, including acrodermatitis chronica atrophicans.

Post–Lyme syndrome (chronic Lyme disease)

Despite resolution of the objective manifestations of the infection with antibiotic therapy, a small percentage of patients have pain, neurocognitive manifestations, or fatigue symptoms for months or years afterward. This syndrome is similar to or indistinguishable from chronic fatigue syndrome (Chap. 33) and fibromyalgia. Compared with symptoms of active Lyme disease, post-Lyme symptoms tend to be more generalized or disabling. They include marked fatigue, severe headache, diffuse musculoskeletal pain, multiple symmetric tender points in characteristic locations, pain and stiffness in many joints, diffuse paresthesias, difficulty with concentration, and sleep disturbances. Patients with this condition lack evidence of joint inflammation, have normal neurologic test results, and may exhibit anxiety and depression. In contrast, late manifestations of Lyme disease, including arthritis, encephalopathy, and neuropathy, are usually associated with minimal systemic symptoms. Currently, no evidence indicates that persistent subjective symptoms after recommended courses of antibiotic therapy are caused by active infection.

DIAGNOSIS

The culture of *B. burgdorferi* in Barbour-Stoenner-Kelly (BSK) medium permits definitive diagnosis, but this method has been used primarily in research studies. Moreover, with a few exceptions, positive cultures have been obtained only early in the illness—particularly from biopsy samples of EM skin lesions, less often from plasma samples, and occasionally from CSF samples. Later in the infection, PCR is greatly superior to culture for the detection of *B. burgdorferi* DNA in joint fluid—the major use for PCR testing in Lyme disease. However, the sensitivity of PCR determinations in CSF from patients with neuroborreliosis has been much lower. There seems to be little if any role for PCR in the detection of *B. burgdorferi* DNA in blood or urine samples. Moreover, this procedure must be carefully controlled to prevent contamination.

Because of the problems associated with direct detection of *B. burgdorferi*, Lyme disease is usually diagnosed by the recognition of a characteristic clinical picture with serologic confirmation. Although serologic testing may yield negative results during the first several weeks of infection, most patients have a positive antibody response to *B. burgdorferi* after that time. The limitation of serologic tests is that they do not clearly distinguish between active and inactive infection. Patients with previous Lyme disease—particularly in cases progressing to late stages—often remain seropositive for years, even after adequate antibiotic treatment. In addition, ~10% of patients are seropositive because of asymptomatic infection. If these individuals subsequently develop another illness, the positive serologic test for Lyme disease may cause diagnostic confusion. According to an algorithm published by the American College of Physicians **(Table 78-1)**, serologic testing for Lyme disease is recommended only for patients with at least an intermediate pretest probability of Lyme disease, such as those with oligoarticular arthritis. It should not be used as a screening procedure in patients with pain or fatigue syndromes. In such patients, the probability of a false-positive serologic result is higher than that of a true-positive result.

For serologic analysis of Lyme disease in the United States, the CDC recommends a two-step approach in which samples are first tested by enzyme-linked immunosorbent assay (ELISA) and equivocal or positive results are then tested by western blotting. During the first month of infection, both IgM and IgG responses to the spirochete should be determined, preferably in both acute- and convalescent-phase serum samples. Approximately 20–30% of patients have a positive response detectable in acute-phase samples, whereas ~70–80% have a positive response during convalescence (2–4 weeks later). After 4–8 weeks of infection (by which time most patients with active Lyme disease have disseminated infection), the sensitivity and specificity of the IgG response to the spirochete are both very high—in the range of 99%—as determined by the two-test approach of ELISA and western blot. At this point and thereafter, a single test (that for IgG) is usually sufficient. In persons with illness of >2 months' duration, a positive IgM test result alone is likely

TABLE 78-1

ALGORITHM FOR TESTING FOR AND TREATING LYME DISEASE

PRETEST PROBABILITY	EXAMPLE	RECOMMENDATION
High	Patients with erythema migrans	Empirical antibiotic treatment without serologic testing
Intermediate	Patients with oligoarticular arthritis	Serologic testing and antibiotic treatment if test results are positive
Low	Patients with nonspecific symptoms (myalgias, arthralgias, fatigue)	Neither serologic testing nor antibiotic treatment

Source: Adapted from the recommendations of the American College of Physicians (G Nichol et al: Ann Intern Med 128:37, 1998, with permission).

to be false-positive and therefore should not be used to support the diagnosis.

According to current criteria adopted by the CDC, an IgM western blot is considered positive if two of the following three bands are present: 23, 39, and 41 kDa. However, the combination of the 23- and 41-kDa bands may still represent a false-positive result. Misuse or misinterpretation of IgM blots has been a factor in the incorrect diagnosis of Lyme disease in patients with other illnesses. An IgG blot is considered positive if 5 of the following 10 bands are present: 18, 23, 28, 30, 39, 41, 45, 58, 66, and 93 kDa. In European cases, there is less expansion of the antibody response, and no single set of criteria for the interpretation of immunoblots results in high levels of sensitivity and specificity in all countries.

The most promising second-generation serologic test is the C6 peptide IgG ELISA, which employs a 26-mer of the sixth invariant region of the VlsE lipoprotein of *B. burgdorferi*. The results achieved with this test are similar to those obtained with the standard two-test approach (sonicate IgM and IgG ELISA and western blot). The principal advantage of the C6 peptide ELISA is the early detection of an IgG response, which renders an IgM test unnecessary. However, not all patients with late Lyme disease have a response to the C6 peptide, and this test is not quite as specific as sonicate western blot. Thus, at present, a two-test approach that includes western blot is still recommended. Like sonicate test responses, the response to the VlsE peptide may persist for months or years after successful antibiotic treatment; therefore, persistence of antibody to VlsE cannot be equated with spirochetal persistence in Lyme disease.

DIFFERENTIAL DIAGNOSIS

Classic EM is a slowly expanding erythema, often with partial central clearing. If the lesion expands little, it may represent the red papule of an uninfected tick bite. If the lesion expands rapidly, it may represent cellulitis (e.g., streptococcal cellulitis) or an allergic reaction, perhaps to tick saliva. Patients with secondary annular lesions may be thought to have erythema multiforme, but neither the development of blistering mucosal lesions nor the involvement of the palms or soles is a feature of *B. burgdorferi* infection. In the southeastern United States, an EM-like skin lesion, sometimes with mild systemic symptoms, may be associated with *Amblyomma americanum* tick bites. However, the cause of this Southern tick-associated rash illness (STARI) has not yet been identified.

In the United States, *I. scapularis* ticks may transmit not only *B. burgdorferi* but also *Babesia microti*, a red blood cell parasite (Chap. 120), or *Anaplasma phagocytophilum*, the agent of human granulocytotropic anaplasmosis (formerly human granulocytotropic ehrlichiosis; Chap. 79). Although babesiosis and anaplasmosis are most often asymptomatic, infection with any of these three agents may cause nonspecific systemic symptoms, and co-infected patients may have more severe or persistent symptoms than patients infected with a single agent. Standard blood counts may yield clues regarding the presence of co-infection. Anaplasmosis may cause leukopenia or thrombocytopenia, and babesiosis may cause thrombocytopenia or (in severe cases) hemolytic anemia. IgM serologic responses may confuse the diagnosis. For example, *A. phagocytophilum* may elicit a positive IgM response to *B. burgdorferi*. The frequency of co-infection in different studies has been variable. In one prospective study, 4% of patients with EM had evidence of co-infection.

Facial palsy caused by *B. burgdorferi*, which occurs in the early disseminated phase of the infection (often in July, August, or September), is usually recognized by its association with EM. However, in rare cases, facial palsy without EM may be the presenting manifestation of Lyme disease. In such cases, both the IgM and the IgG responses to the spirochete are usually positive. The most common infectious agents that cause facial palsy are herpes simplex virus type 1 (Bell's palsy; Chap. 84) and varicella-zoster virus (Ramsay Hunt syndrome; Chap. 85).

Later in the infection, oligoarticular Lyme arthritis most resembles reactive arthritis in an adult or the pauciarticular form of juvenile idiopathic arthritis in a child. Patients with Lyme arthritis usually have the strongest IgG antibody responses seen in Lyme borreliosis, with reactivity to many spirochetal proteins.

The most common problem in diagnosis is to mistake Lyme disease for chronic fatigue syndrome (Chap. 33) or fibromyalgia. This difficulty is compounded by the fact that a small percentage of patients do in fact develop these chronic pain or fatigue syndromes in association with or soon after Lyme disease. Moreover, a counterculture has emerged that ascribes pain and fatigue syndromes to chronic Lyme disease when there is little or no evidence of *B. burgdorferi* infection. In such cases, the term *chronic Lyme disease*, which is equated with chronic *B. burgdorferi* infection, is a misnomer, and the use of prolonged, dangerous, and expensive antibiotic treatment is not warranted.

TREATMENT Lyme Borreliosis

ANTIBIOTIC TREATMENT As outlined in the algorithm in Fig. 78-2, the various manifestations of Lyme disease can usually be treated successfully with orally administered antibiotics; the exceptions are objective neurologic abnormalities and third-degree atrioventricular heart block, which are generally treated with IV antibiotics. For early Lyme disease, doxycycline is effective and can be administered to men and nonpregnant women. An advantage of this regimen is that it is also effective against *A. phagocytophilum*, which is transmitted by the same tick that transmits the Lyme disease agent. Amoxicillin, cefuroxime axetil, and erythromycin or its congeners are second-, third-, and fourth-choice alternatives, respectively. In children, amoxicillin is effective (not more than 2 g/d); in cases of penicillin allergy, cefuroxime axetil or erythromycin may be used. In contrast to second- or third-generation cephalosporin antibiotics, first-generation cephalosporins, such as cephalexin, are not effective.

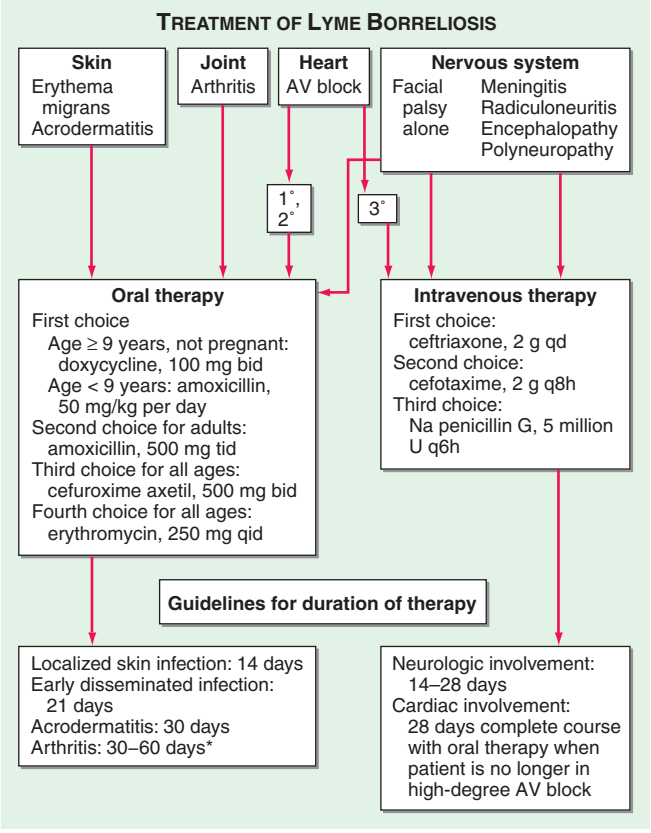


FIGURE 78-2
Algorithm for the treatment of the various acute or chronic manifestations of Lyme borreliosis. AV, atrioventricular. *For Lyme arthritis, IV ceftriaxone (2 g given once a day for 14–28 days) is also effective and is necessary for a small percentage of patients; however, compared with oral treatment, this regimen is less convenient to administer, has more side effects, and is more expensive.

For patients with infection localized to the skin, a 14-day course of therapy is generally sufficient; in contrast, for patients with disseminated infection, a 21-day course is recommended. Approximately 15% of patients experience a Jarisch-Herxheimer-like reaction during the first 24 h of therapy. In multicenter studies, >90% of patients whose early Lyme disease was treated with these regimens had satisfactory outcomes. Although some patients reported symptoms after treatment, objective evidence of persistent infection or relapse was rare, and re-treatment was usually unnecessary.

Oral administration of doxycycline or amoxicillin for 30 days is recommended for the initial treatment of Lyme arthritis in patients who do not have concomitant neurologic involvement. Among patients with arthritis who do not respond to oral antibiotics, re-treatment with IV ceftriaxone for 28 days is appropriate. In patients with arthritis in whom—despite a negative PCR result for *B. burgdorferi* DNA in joint fluid—joint inflammation persists for months or even several years after both oral and IV antibiotics, treatment with anti-inflammatory agents or synovectomy may be successful.

In the United States, parenteral antibiotic therapy is usually used for objective neurologic abnormalities (with the possible exception of facial palsy alone). Patients with neurologic involvement are most commonly treated with IV ceftriaxone for 14–28 days, but IV cefotaxime or IV penicillin G for the same duration may also be effective. In Europe, similar results have been achieved with oral doxycycline and IV antibiotics in the treatment of acute neuroborreliosis. In patients with high-degree atrioventricular block or a PR interval of >0.3 s, IV therapy for at least part of the course and cardiac monitoring are recommended, but the insertion of a permanent pacemaker is not necessary.

It is unclear how and whether asymptomatic infection should be treated, but patients with such infection are often given a course of oral antibiotics. Because maternal-fetal transmission of *B. burgdorferi* seems to occur rarely (if at all), standard therapy for the manifestations of the illness is recommended for pregnant women. Long-term persistence of *B. burgdorferi* has not been documented in any large series of patients after treatment with currently recommended regimens. Although an occasional patient requires a second course of antibiotics, there is no indication for multiple, repeated antibiotic courses in the treatment of Lyme disease.

CHRONIC LYME DISEASE After appropriately treated Lyme disease, a small percentage of patients continue to have subjective symptoms, primarily musculoskeletal pain, neurocognitive difficulties, or fatigue. This *chronic Lyme disease* or *post–Lyme syndrome* is a disabling condition that is similar to chronic fatigue syndrome or fibromyalgia. In a large study, one group of patients with post–Lyme syndrome received IV ceftriaxone for 30 days followed by oral doxycycline for 60 days, while another group received IV and oral placebo preparations for the same durations. No significant differences were found between groups in the numbers of patients reporting that their symptoms had improved, become worse, or stayed the same. Such patients are best treated for the relief of symptoms rather than with prolonged courses of antibiotics.

PROPHYLAXIS AFTER A TICK BITE The risk of infection with *B. burgdorferi* after a recognized tick bite is so low that antibiotic prophylaxis is not routinely indicated. However, if an attached, engorged *I. scapularis* nymph is found or if follow-up is anticipated to be difficult, a single 200-mg dose of doxycycline, which usually prevents Lyme disease when given within 72 h after the tick bite, may be administered.

PROGNOSIS

The response to treatment is best early in the disease. Later treatment of Lyme borreliosis is still effective, but the period of convalescence may be longer. Eventually, most patients recover with minimal or no residual deficits.

REINFECTION

Reinfection may occur after EM when patients are treated with antimicrobial agents. In such cases, the immune response is not adequate to provide protection from subsequent infection. However, patients who develop an expanded immune response to the spirochete over a period of months (e.g., those with Lyme arthritis) have protective immunity for a period of years and do not acquire the infection again.

PREVENTION

Protective measures for the prevention of Lyme disease may include the avoidance of tick-infested areas, the use of repellents and acaricides, tick checks, and modification of landscapes in or near residential areas. Although a vaccine for Lyme disease used to be available, the manufacturer has discontinued its production. Therefore, no vaccine is now commercially available for the prevention of this infection.

CHAPTER 79

RICKETTSIAL DISEASES

David H. Walker ■ J. Stephen Dumler ■ Thomas Marrie

The rickettsiae are a heterogeneous group of small, obligately intracellular, gram-negative coccobacilli and short bacilli, most of which are transmitted by a tick, mite, flea, or louse vector. Except in the case of louse-borne typhus, humans are incidental hosts. Among rickettsiae, *Coxiella burnetii, Rickettsia prowazekii,* and *R. typhi* have the well-documented ability to survive for an extended period outside the reservoir or vector and to be extremely infectious: inhalation of a single *Coxiella* microorganism can cause pneumonia. High infectivity and severe illness after inhalation make *R. prowazekii, R. rickettsii, R. typhi, R. conorii,* and *C. burnetii* bioterrorism threats.

Clinical infections with rickettsiae can be classified according to (1) the taxonomy and diverse microbial characteristics of the agents, which belong to six genera (*Rickettsia, Orientia, Ehrlichia, Anaplasma, Neorickettsia,* and *Coxiella*); (2) epidemiology; or (3) clinical manifestations. The clinical manifestations of all the acute presentations are similar during the first 5 days: fever, headache, and myalgias with or without nausea, vomiting, and cough. As the course progresses, clinical manifestations—including occurrence of a macular, maculopapular, or vesicular rash; eschar; pneumonitis; and meningoencephalitis—vary from one disease to another. Given the 14 etiologic agents with varied mechanisms of transmission, geographic distributions, and associated disease manifestations, the consideration of rickettsial diseases as a single entity poses complex challenges **(Table 79-1)**.

Establishing the etiologic diagnosis of rickettsioses is very difficult during the acute stage of illness, and definitive diagnosis usually requires the examination of paired serum samples after convalescence. Heightened clinical suspicion is based on epidemiologic data, history of exposure to vectors or reservoir animals, travel to endemic locations, clinical manifestations (sometimes including rash or eschar), and characteristic laboratory findings [including thrombocytopenia, normal or low white blood cell (WBC) counts, elevated hepatic enzyme levels, and hyponatremia]. Such suspicion should prompt empirical treatment. Doxycycline is the drug of choice for most of these infections. Only one agent, *C. burnetii*, has been documented to cause chronic illness. One other, *R. prowazekii*, causes recrudescent illness (Brill-Zinsser disease) when latent infection is reactivated years after resolution of the acute illness.

Rickettsial infections dominated by fever may resolve without further clinical evolution. However, after nonspecific early manifestations, the illnesses can also evolve along one or more of several principal clinical lines: (1) development of a macular or maculopapular rash; (2) development of an eschar at the site of tick or mite feeding; (3) development of a vesicular rash (often in rickettsialpox and African tick-bite fever); (4) development of pneumonitis with chest radiographic opacities and/or rales (Q fever and severe cases of Rocky Mountain spotted fever [RMSF], Mediterranean spotted fever [MSF], louse-borne typhus, human monocytotropic ehrlichiosis [HME], human granulocytotropic anaplasmosis [HGA], scrub typhus, and murine typhus); (5) development of meningoencephalitis (louse-borne typhus and severe cases

TABLE 79-1

FEATURES OF SELECTED RICKETTSIAL INFECTIONS

DISEASE	ORGANISM	TRANSMISSION	GEOGRAPHIC RANGE	INCUBATION PERIOD, DAYS	DURATION, DAYS	RASH, %	ESCHAR, %	LYMPHADENOPATHY[a]
Rocky Mountain spotted fever	*Rickettsia rickettsii*	Tick bite: *Dermacentor andersoni, D. variabilis*	United States	2–14	10–20	90	<1	+
		Amblyomma cajennense, A. aureolatum	Central/South America					
		Rhipicephalus sanguineus	Mexico, Brazil, United States					
Mediterranean spotted fever	*R. conorii*	Tick bite: *R. sanguineus, R. pumilio*	Southern Europe, Africa, Middle East, Central Asia	5–7	7–14	97	50	+
African tick-bite fever	*R. africae*	Tick bite: *A. hebraeum, A. variegatum*	Sub-Saharan Africa, West Indies	4–10	?	50	90	++++
Maculatum disease	*R. parkeri*	*A. maculatum*	United States, South America	2–10	?	88	94	++
Rickettsialpox	*R. akari*	Mite bite: *Liponyssoides sanguineus*	United States, Ukraine, Turkey, Mexico, Croatia	10–17	3–11	100	90	+++
Tick-borne lymphadenopathy	*R. slovaca*	Tick bite: *Dermacentor marginatus, D. reticularis*	Europe	7–9	17–180	5	100	++++
Flea-borne spotted fever	*R. felis*	Flea (mechanism undetermined): *Ctenocephalides felis*	Worldwide	8–16	8–16	80	15	—
Epidemic typhus	*R. prowazekii*	Louse feces: *Pediculus humanus corporis,* fleas and lice of flying squirrels, or recrudescence	Worldwide	7–14	10–18	80	None	—
Murine typhus	*R. typhi*	Flea feces: *Xenopsylla cheopis, C. felis,* others	Worldwide	8–16	9–18	80	None	—
Human monocytotropic ehrlichiosis	*Ehrlichia chaffeensis*	Tick bite: *Amblyomma americanum, D. variabilis*	United States	1–21	3–21	26	None	++
Ewingii ehrlichiosis	*E. ewingii*	Tick bite: *A. americanum*	United States				None	
Human granulocytotropic anaplasmosis	*Anaplasma phagocytophilum*	Tick bite: *Ixodes scapularis, I. ricinus, I. pacificus, I. persulcatus*	United States, Europe, Asia	4–8	3–14	Rare	None	—

(*continued*)

TABLE 79-1

FEATURES OF SELECTED RICKETTSIAL INFECTIONS (*CONTINUED*)

DISEASE	ORGANISM	TRANSMISSION	GEOGRAPHIC RANGE	INCUBATION PERIOD, DAYS	DURATION, DAYS	RASH, %	ESCHAR, %	LYMPHADENOPATHY[a]
Scrub typhus	*Orientia tsutsugamushi*	Mite bite: *Leptotrombidium deliense,* others	Asia, Australia, New Guinea, Pacific Islands	9–18	6–21	50	35	+++
Q fever	*Coxiella burnetii*	Inhalation of aerosols of infected parturition material (sheep, dogs, others), ingestion of infected milk or milk products	Worldwide	3–30	5–57	<1	None	—

[a]++++, severe; +++, marked; ++, moderate; +, present in a small portion of cases; —, not a noted feature.

of RMSF, scrub typhus, HME, murine typhus, MSF, and [rarely] Q fever); and (6) progressive hypotension and multiorgan failure as seen with sepsis or toxic shock syndrome (RMSF, MSF, louse-borne typhus, murine typhus, scrub typhus, HME, and HGA).

Epidemiologic clues to the transmission of a particular pathogen include (1) environmental exposure to ticks, fleas, or mites during the season of activity of the vector species for the disease in the appropriate geographic region (spotted fever and typhus rickettsioses, scrub typhus, ehrlichioses, anaplasmosis); (2) travel to or residence in an endemic geographic region during the incubation period (Table 79-1); (3) exposure to parturient ruminants, cats, and dogs (Q fever); (4) exposure to flying squirrels (*R. prowazekii* infection); and (5) history of previous louse-borne typhus (recrudescent typhus).

Clinical laboratory findings, such as thrombocytopenia (particularly in spotted fever and typhus rickettsioses, ehrlichioses, anaplasmosis, and scrub typhus), normal or low WBC counts, mild to moderate serum elevations of hepatic aminotransferases, and hyponatremia suggest some common pathophysiologic mechanisms.

Application of these clinical, epidemiologic, and laboratory principles requires consideration of a rickettsial diagnosis and knowledge of the individual diseases.

TICK-, MITE-, LOUSE-, AND FLEA-BORNE RICKETTSIOSES

These diseases, caused by organisms of the genera *Rickettsia* and *Orientia* in the family Rickettsiaceae, result from endothelial infection and increased vascular permeability. Pathogenic rickettsial species are very closely related, have small genomes (as a result of reductive evolution, which eliminated many genes for biosynthesis of intracellularly available molecules), and are traditionally separated into typhus and spotted fever groups on the basis of lipopolysaccharide antigens. Some diseases and their agents (e.g., *R. africae, R. parkeri*, and *R. sibirica*) are too similar to require separate descriptions. Indeed, the similarities among MSF (*R. conorii* [all strains]) and *R. massiliae*, North Asian tick typhus (*R. sibirica*), Japanese spotted fever (*R. japonica*), and Flinders Island spotted fever (*R. honei*) far outweigh the minor variations. The Rickettsiaceae that cause life-threatening infections are, in order of decreasing case-fatality rate, *R. rickettsii* (RMSF); *R. prowazekii* (louse-borne typhus); *Orientia tsutsugamushi* (scrub typhus); *R. conorii* (MSF); *R. typhi* (murine typhus); and, in rare cases, other spotted fever–group organisms. Some agents (e.g., *R. parkeri*, *R. africae*, *R. akari*, *R. slovaca*, *R. honei*, *R. felis*, *R. massiliae, R. helvetica, R. heilongjiangensis, R. aeschlimannii*, and *R. monacensis*) have never been documented to cause a fatal illness.

ROCKY MOUNTAIN SPOTTED FEVER

RMSF occurs in 47 states (with the highest prevalence in the south-central and southeastern states) as well as in Canada, Mexico, and Central and South America. The infection is transmitted by *Dermacentor variabilis*, the American dog tick, in the eastern two-thirds of the United States and California; by *D. andersoni*, the Rocky Mountain wood tick, in the western United States; by *Rhipicephalus sanguineus* in Mexico, Arizona, and probably Brazil; and by *Amblyomma cajennense* in Central and South America. Maintained principally by transovarian transmission from one generation of ticks to the next, *R. rickettsii* can be acquired by uninfected ticks through the ingestion of a blood meal from rickettsemic small mammals.

Humans become infected during tick season (in the Northern Hemisphere, from May to September), although some cases occur in winter. The mortality rate was 20–25% in the preantibiotic era and remains

at ~3–5% principally because of delayed diagnosis and treatment. The case-fatality ratio increases with each decade of life above age 20.

Pathogenesis

R. rickettsii organisms are inoculated into the dermis along with secretions of the tick's salivary glands after ≥6 h of feeding. The rickettsiae spread lymphohematogenously throughout the body and infect numerous foci of contiguous endothelial cells. The dose-dependent incubation period is ~1 week (range, 2–14 days). Occlusive thrombosis and ischemic necrosis are not the fundamental pathologic basis for tissue and organ injury. Instead, increased vascular permeability, with resulting edema, hypovolemia, and ischemia, is responsible. Consumption of platelets results in thrombocytopenia in 32–52% of patients, but disseminated intravascular coagulation with hypofibrinogenemia is rare. Activation of platelets, generation of thrombin, and activation of the fibrinolytic system all appear to be homeostatic physiologic responses to endothelial injury.

Clinical manifestations

Early in the illness, when medical attention usually is first sought, RMSF is difficult to distinguish from many self-limiting viral illnesses. Fever, headache, malaise, myalgia, nausea, vomiting, and anorexia are the most common symptoms during the first 3 days. The patient becomes progressively more ill as vascular infection and injury advance. In one large series, only one-third of patients were diagnosed with presumptive RMSF early in the clinical course and treated appropriately as outpatients. In the tertiary-care setting, RMSF is all too often recognized only when late severe manifestations, developing at the end of the first week or during the second week of illness in patients without appropriate treatment, prompt return to a physician or hospital and admission to an intensive care unit.

The progressive nature of the infection is clearly manifested in the skin. Rash is evident in only 14% of patients on the first day of illness and in only 49% during the first 3 days. Macules (1–5 mm) appear first on the wrists and ankles and then on the remainder of the extremities and the trunk. Later, more severe vascular damage results in frank hemorrhage at the center of the maculopapule, producing a petechia that does not disappear upon compression **(Fig. 79-1)**. This sequence of events is sometimes delayed or aborted by effective treatment. However, the rash is a variable manifestation, appearing on day 6 or later in 20% of cases and not appearing at all in 9–16% of cases. Petechiae occur in 41–59% of cases, appearing on or after day 6 in 74% of cases that manifest a rash. Involvement of the palms and soles, often considered diagnostically important, usually develops relatively late in the course (after day 5 in 43% of cases) and does not develop at all in 18–64% of cases.

Hypovolemia leads to prerenal azotemia and (in 17% of cases) hypotension. Infection of the pulmonary microcirculation leads to noncardiogenic pulmonary edema;

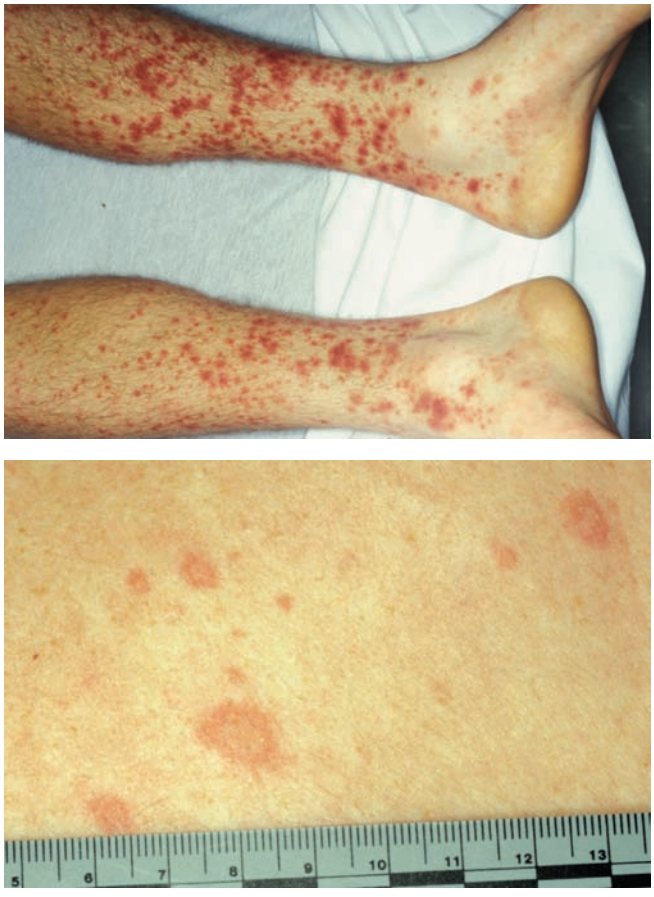


FIGURE 79-1
Top: **Petechial lesions of Rocky Mountain spotted fever** on the lower legs and soles of a young, previously healthy patient. ***Bottom:*** **Close-up of lesions** from the same patient. (*Photos courtesy of Dr. Lindsey Baden; with permission.*)

12% of patients have severe respiratory disease, and 8% require mechanical ventilation. Cardiac involvement manifests as dysrhythmia in 7–16% of cases.

Besides respiratory failure, central nervous system (CNS) involvement is the other important determinant of the outcome of RMSF. Encephalitis, presenting as confusion or lethargy, is apparent in 26–28% of cases. Progressively severe encephalitis manifests as stupor or delirium in 21–26% of cases, ataxia in 18%, coma in 10%, and seizures in 8%. Numerous focal neurologic deficits have been reported. Meningoencephalitis results in cerebrospinal fluid (CSF) pleocytosis in 34–38% of cases; usually there are 10–100 cells/μL and a mononuclear predominance, but occasionally there are >100 cells/μL and a polymorphonuclear predominance. The CSF protein concentration is increased in 30–35% of cases, but the CSF glucose concentration is usually normal.

Renal failure, often reversible with rehydration, is caused by acute tubular necrosis in severe cases with shock. Hepatic injury with increased serum aminotransferase concentrations (38% of cases) is due to focal death of individual hepatocytes without hepatic failure. Jaundice is recognized in 9% of cases and an elevated serum bilirubin concentration in 18–30%.

Life-threatening bleeding is rare. Anemia develops in 30% of cases and is severe enough to require transfusions in 11%. Blood is detected in the stools or vomitus of 10% of patients, and death has followed massive upper gastrointestinal hemorrhage.

Other characteristic clinical laboratory findings include increased plasma levels of proteins of the acute-phase response (C-reactive protein, fibrinogen, ferritin, and others), hypoalbuminemia, and hyponatremia (in 56% of cases) due to the appropriate secretion of antidiuretic hormone in response to the hypovolemic state. Myositis occurs occasionally, with marked elevations in serum creatine kinase levels and multifocal rhabdomyonecrosis. Ocular involvement includes conjunctivitis in 30% of cases and retinal vein engorgement, flame hemorrhages, arterial occlusion, and papilledema with normal CSF pressure in some instances.

In untreated cases, the patient usually dies 8–15 days after onset. A rare presentation, fulminant RMSF, is fatal within 5 days after onset. This fulminant presentation is seen most often in male black patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency and may be related to an undefined effect of hemolysis on the rickettsial infection. Although survivors of RMSF usually return to their previous state of health, permanent sequelae, including neurologic deficits and gangrene necessitating amputation of extremities, may follow severe illness.

Diagnosis

The diagnosis of RMSF during the acute stage is more difficult than is generally appreciated. The most important epidemiologic factor is a history of exposure to a potentially tick-infested environment within the 12 days preceding disease onset during a season of possible tick activity. However, only 60% of patients actually recall being bitten by a tick during the incubation period.

The differential diagnosis for early clinical manifestations of RMSF (fever, headache, and myalgia without a rash) includes influenza, enteroviral infection, infectious mononucleosis, viral hepatitis, leptospirosis, typhoid fever, gram-negative or gram-positive bacterial sepsis, HME, HGA, murine typhus, sylvatic flying-squirrel typhus, and rickettsialpox. Enterocolitis may be suggested by nausea, vomiting, and abdominal pain; prominence of abdominal tenderness has resulted in exploratory laparotomy. CNS involvement may masquerade as bacterial or viral meningoencephalitis. Cough, pulmonary signs, and chest radiographic opacities may lead to a diagnostic consideration of bronchitis or pneumonia.

At presentation during the first 3 days of illness, only 3% of patients exhibit the classic triad of fever, rash, and history of tick exposure. When a rash appears, a diagnosis of RMSF should certainly be considered. However, many illnesses considered in the differential diagnosis may also be associated with a rash, including rubeola, rubella, meningococcemia, disseminated gonococcal infection, secondary syphilis, toxic shock syndrome, drug hypersensitivity, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, Kawasaki syndrome, and immune complex vasculitis. Conversely, any person in an endemic area with a provisional diagnosis of one of the illnesses mentioned earlier may have RMSF. Thus, if a viral infection is suspected during RMSF season in an endemic area, it should always be kept in mind that RMSF can mimic viral infection early in the course; if the illness worsens over the next couple of days after initial presentation, the patient should return for reevaluation.

The most common serologic test for confirmation of the diagnosis is the indirect immunofluorescence assay. Not until 7–10 days after onset is a diagnostic titer of ≥1:64 usually detectable. The sensitivity and specificity of the indirect immunofluorescence assay are 94–100% and 100%, respectively. It is important to understand that serologic tests for RMSF are usually negative at the time of presentation for medical care and that treatment should not be delayed while a positive serologic result is awaited.

The only diagnostic test that is useful during the acute illness is immunohistologic examination of a cutaneous biopsy sample from a rash lesion for *R. rickettsii*. Examination of a 3-mm punch biopsy from such a lesion is 70% sensitive and 100% specific. The sensitivity of polymerase chain reaction (PCR) amplification and detection of *R. rickettsii* DNA in peripheral blood is improving. However, although rickettsiae are present in large quantities in heavily infected foci of endothelial cells, there are relatively low quantities in the circulation. Cultivation of rickettsiae in cell culture is feasible but is seldom undertaken because of biohazard concerns. The recent dramatic increase in the reported incidence of RMSF correlates with the use of single-titer spotted fever–group cross-reactive enzyme immunoassay serology, with which few cases are specifically determined to be caused by *R. rickettsii*.

TREATMENT **Rocky Mountain Spotted Fever**

The drug of choice for the treatment of both children and adults with RMSF is doxycycline, except when the patient is pregnant or allergic to this drug (see later). Because of the severity of RMSF, immediate empirical administration of doxycycline should be strongly considered for any patient with a consistent clinical presentation in the appropriate epidemiologic setting. Doxycycline is administered orally (or, in the presence of coma or vomiting, intravenously) at 200 mg/d in two divided doses. For children with suspected RMSF, up to five courses of doxycycline may be administered with minimal risk of dental staining. Other regimens include oral tetracycline (25–50 mg/kg per day) in four divided doses. Treatment with chloramphenicol, a less effective drug, is advised only for patients who are pregnant or allergic to doxycycline. The antirickettsial drug should be administered until the patient has been afebrile and improving clinically for 2–3 days. β-Lactam antibiotics, erythromycin, and

aminoglycosides have no role in the treatment of RMSF, and sulfa-containing drugs are likely to exacerbate this infection. There is little clinical experience with fluoroquinolones, clarithromycin, and azithromycin, which are not recommended. The most seriously ill patients are managed in intensive care units, with careful administration of fluids to achieve optimal tissue perfusion without precipitating noncardiogenic pulmonary edema. In some severely ill patients, hypoxemia requires intubation and mechanical ventilation; oliguric or anuric acute renal failure requires hemodialysis; seizures necessitate the use of antiseizure medication; anemia or severe hemorrhage necessitates transfusions of packed red blood cells; or bleeding with severe thrombocytopenia requires platelet transfusions. Heparin is not a useful component of treatment, and there is no evidence that glucocorticoids affect outcome.

Prevention

Avoidance of tick bites is the only available preventive approach. Use of protective clothing and tick repellents, inspection of the body once or twice a day, and removal of ticks before they inoculate rickettsiae reduce the risk of infection.

MEDITERRANEAN SPOTTED FEVER (BOUTONNEUSE FEVER), AFRICAN TICK-BITE FEVER, AND OTHER TICK-BORNE SPOTTED FEVERS

R. conorii is prevalent in southern Europe, Africa, and southwestern and south-central Asia. Regional names for the disease caused by this organism include Mediterranean spotted fever, Kenya tick typhus, Indian tick typhus, Israeli spotted fever, and Astrakhan spotted fever. The disease is characterized by high fever, rash, and—in most geographic locales—an inoculation eschar (*tâche noire*) at the site of the tick bite. A severe form of the disease (mortality rate, 50%) occurs in patients with diabetes, alcoholism, or heart failure.

African tick-bite fever, caused by *R. africae,* occurs in rural areas of sub-Saharan Africa and in the Caribbean islands and is transmitted by *Amblyomma hebraeum* and *A. variegatum* ticks. The average incubation period is 4–10 days. The mild illness consists of headache, fever, eschar, and regional lymphadenopathy. *Amblyomma* ticks often feed in groups, with the consequent development of multiple eschars. Rash may be vesicular, sparse, or absent altogether. Because of tourism in sub-Saharan Africa, African tick-bite fever is the most frequently imported rickettsiosis in Europe and North America. A similar disease caused by the very closely related *R. parkeri* is transmitted by *A. maculatum* in the United States and *A. triste* in South America.

R. japonica causes Japanese spotted fever, which also occurs in Korea. Similar diseases in northern Asia are caused by *R. sibirica* and *R. heilongjiangensis*. Queensland tick typhus due to *R. australis* is transmitted by *Ixodes holocyclus*. Flinders Island spotted fever, found on the island for which it is named as well as in Tasmania, mainland Australia, and southeastern Asia, is caused by *R. honei*. In Europe, patients infected with *R. slovaca* after a wintertime *Dermacentor* tick bite manifest an afebrile illness with an eschar (usually on the scalp) and painful regional lymphadenopathy.

Diagnosis

Diagnosis of these tick-borne spotted fevers is based on clinical and epidemiologic findings and is confirmed by serology, immunohistochemical demonstration of rickettsiae in skin biopsy specimens, cell-culture isolation of rickettsiae, or PCR of skin biopsy or blood samples. The serologic identification of the etiologic species requires knowledge of all the potential agents as well as expensive, laborious cross-adsorption of the patient's serum. In an endemic area, a possible diagnosis of one of these rickettsial spotted fevers should be considered when patients present with fever, rash, and/or a skin lesion consisting of a black necrotic area or a crust surrounded by erythema.

TREATMENT Tick-Borne Spotted Fevers

Successful therapeutic agents include doxycycline (100 mg bid orally for 1–5 days), ciprofloxacin (750 mg bid orally for 5 days), and chloramphenicol (500 mg qid orally for 7–10 days). Pregnant patients may be treated with josamycin (3 g/d orally for 5 days). Data on the efficacy of treatment of mildly ill children with clarithromycin or azithromycin should not be extrapolated to adults or to patients with moderate or severe illness.

RICKETTSIALPOX

R. akari infects mice and their mites (*Liponyssoides sanguineus*), which maintain the organisms by transovarian transmission.

Epidemiology

Rickettsialpox is recognized principally in New York City, but cases have also been reported in other urban and rural locations in the United States and in Ukraine, Croatia, Mexico, and Turkey. Investigation of eschars suspected of representing bioterrorism-associated cutaneous anthrax revealed that rickettsialpox occurs more frequently than previously realized.

Clinical manifestations

A papule forms at the site of the mite's feeding, develops a central vesicle, and becomes a 1- to 2.5-cm painless black crusted eschar surrounded by an erythematous halo **(Fig. 79-2)**. Enlargement of the regional lymph nodes draining the eschar suggests initial lymphogenous spread.

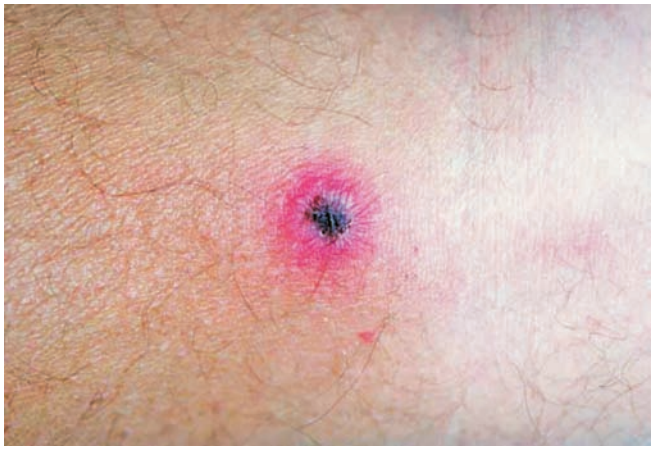


FIGURE 79-2
Eschar at the site of the mite bite in a patient with rickettsialpox. (*Reprinted from A Krusell et al: Emerg Infect Dis 8:727, 2002. Photo obtained by Dr. Kenneth Kaye.*)

After an incubation period of 10–17 days, during which the eschar and regional lymphadenopathy frequently go unnoticed, onset is marked by malaise, chills, fever, headache, and myalgia. A macular rash appears 2–6 days after onset and evolves sequentially into papules, vesicles, and crusts that heal without scarring **(Fig. 79-3)**. The rash may remain macular or maculopapular. Some patients develop nausea, vomiting, abdominal pain, cough, conjunctivitis, or photophobia. If untreated, fever lasts 6–10 days.

Diagnosis and treatment

Clinical, epidemiologic, and convalescent serologic data establish the diagnosis of a spotted fever–group rickettsiosis that is seldom pursued further. Doxycycline is the drug of choice for treatment.

FLEA-BORNE SPOTTED FEVER

An emerging rickettsiosis caused by *R. felis* occurs worldwide. Maintained transovarially in the geographically widespread cat flea *Ctenocephalides felis*, the infection has been described as moderately severe, with fever, rash, headache, and CNS, gastrointestinal, and pulmonary symptoms.

ENDEMIC MURINE TYPHUS

Epidemiology

R. typhi is maintained in mammalian host/flea cycles, with rats (*Rattus rattus* and *R. norvegicus*) and the Oriental rat flea (*Xenopsylla cheopis*) as the classic zoonotic niche. Fleas acquire *R. typhi* from rickettsemic rats and carry the organism throughout their life span. Nonimmune rats and humans are infected when rickettsia-laden flea feces contaminates pruritic bite lesions; less frequently, the flea bite transmits the organisms. Transmission also may occur via inhalation of aerosolized rickettsiae from flea feces. Infected rats appear healthy, although they are rickettsemic for ~2 weeks.

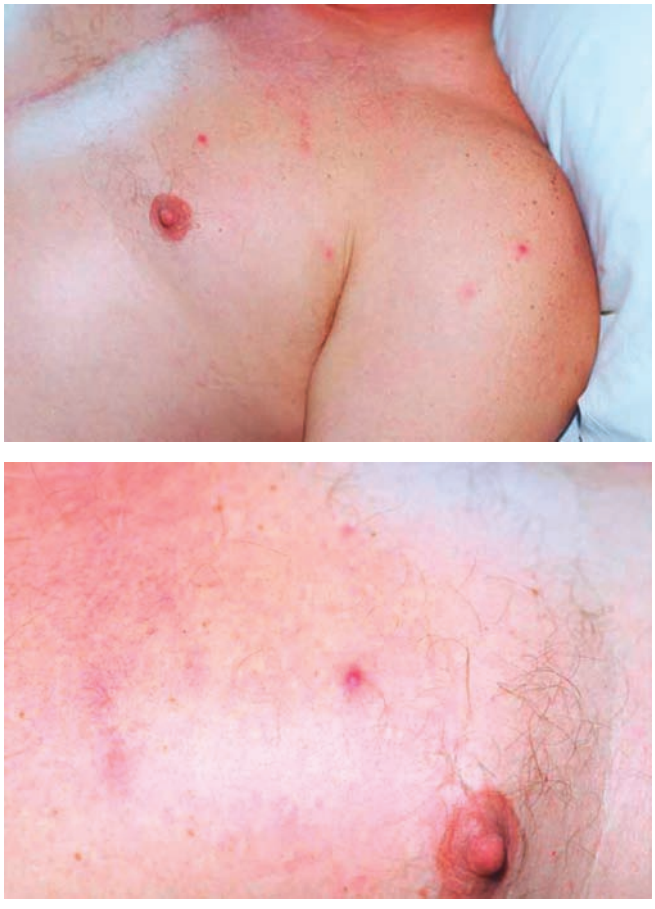


FIGURE 79-3
***Top:* Papulovesicular lesions on the trunk of the patient with rickettsialpox** shown in Fig. 79-2. ***Bottom:* Close-up of lesions** from the same patient. (*Reprinted from A Krusell et al: Emerg Infect Dis 8:727, 2002. Photos obtained by Dr. Kenneth Kaye.*)

Murine typhus occurs mainly in southern Texas and southern California, where the classic rat/flea cycle is absent and an opossum/cat flea (*C. felis*) cycle is prominent. Globally, endemic typhus occurs mainly in warm (often coastal) areas throughout the tropics and subtropics, where it is highly prevalent though often unrecognized. The incidence peaks from April through June in southern Texas and during the warm months of summer and early fall in other geographic locations. Patients seldom recall exposure to fleas, although exposure to animals such as cats, opossums, and rats is reported in nearly 40% of cases.

Clinical manifestations

The incubation period of experimental murine typhus averages 11 days (range, 8–16 days). Headache, myalgia, arthralgia, nausea, and malaise develop 1–3 days before onset of chills and fever. Nearly all patients experience nausea and vomiting early in the illness.

The duration of untreated illness averages 12 days (range, 9–18 days). Rash is present in only 13% of patients

at presentation for medical care (usually ~4 days after onset of fever), appearing an average of 2 days later in half of the remaining patients and never appearing in the others. The initial macular rash is often detected by careful inspection of the axilla or the inner surface of the arm. Subsequently, the rash becomes maculopapular, involving the trunk more often than the extremities; it is seldom petechial and rarely involves the face, palms, or soles. A rash is detected in only 20% of patients with darkly pigmented skin.

Pulmonary involvement is frequently prominent; 35% of patients have a hacking, nonproductive cough, and 23% of patients who undergo chest radiography have pulmonary densities due to interstitial pneumonia, pulmonary edema, and pleural effusions. Bibasilar rales are the most common pulmonary sign. Less common clinical manifestations include abdominal pain, confusion, stupor, seizures, ataxia, coma, and jaundice. Clinical laboratory studies frequently reveal anemia and leukopenia early in the course, leukocytosis late in the course, thrombocytopenia, hyponatremia, hypoalbuminemia, mildly increased serum hepatic aminotransferases, and prerenal azotemia. Complications may include respiratory failure, hematemesis, cerebral hemorrhage, and hemolysis. Severe illness necessitates the admission of 10% of hospitalized patients to an intensive care unit. Greater severity is generally associated with old age, underlying disease, and treatment with a sulfonamide; the case-fatality rate is 1%. In a study of children with murine typhus, 50% suffered only nocturnal fevers, feeling well enough for active daytime play.

Diagnosis and treatment

Cultivation, PCR, or cross-adsorption serologic studies of acute- and convalescent-phase sera can provide a specific diagnosis, and an immunohistochemical method for identification of typhus group-specific antigens has been developed. Nevertheless, most patients are treated empirically with doxycycline (100 mg bid orally for 7–15 days) on the basis of clinical suspicion. Ciprofloxacin provides an alternative if doxycycline is contraindicated. Serologic methods are usually used when laboratory confirmation of the diagnosis is sought.

EPIDEMIC (LOUSE-BORNE) TYPHUS

The human body louse (*Pediculus humanus corporis*) lives in clothing under poor hygienic conditions and usually in impoverished cold areas. Lice acquire *R. prowazekii* when they ingest blood from a rickettsemic patient. The rickettsiae multiply in the midgut epithelial cells of the louse and are shed in the louse's feces. The infected louse leaves a febrile person and deposits infected feces on its subsequent host during its blood meal; the patient autoinoculates the organisms by scratching. The louse is killed by the rickettsiae and does not pass *R. prowazekii* to its offspring.

Epidemic typhus haunts regions afflicted by wars and disasters. An outbreak involved 100,000 people in refugee camps in Burundi in 1997. A small focus occurred in Russia in 1998; sporadic cases have been reported from Algeria, and frequent outbreaks have occurred in Peru. Eastern flying squirrels (*Glaucomys volans*) and their lice and fleas maintain *R. prowazekii* in a zoonotic cycle. The fleas transmit the infection sporadically to humans.

Brill-Zinsser disease is a recrudescent illness occurring years after acute epidemic typhus, probably as a result of waning immunity. *R. prowazekii* remains latent for years; its reactivation results in sporadic cases of disease in louse-free populations or in epidemics in louse-infested populations.

Rickettsiae are potential agents of bioterrorism (Chap. 7). Infections with *R. prowazekii* and *R. rickettsii* have high case-fatality ratios. These organisms cause difficult-to-diagnose diseases, are highly infectious when inhaled as aerosols, and have been selected for resistance to tetracycline or chloramphenicol in the laboratory.

Clinical manifestations

After an incubation period of ~1–2 weeks, the onset of illness is abrupt, with prostration, severe headache, and fever rising rapidly to 38.8°–40.0°C (102°–104°F). Cough is prominent, occurring in 70% of patients. Myalgias are usually severe. In the outbreak in Burundi, the disease was referred to as sutama ("crouching"), a designation reflecting the posture of patients attempting to alleviate the pain. A rash begins on the upper trunk, usually on the fifth day, and then becomes generalized, involving the entire body except the face, palms, and soles. Initially, this rash is macular; without treatment, it becomes maculopapular, petechial, and confluent. The rash often is not detected in black skin; 60% of African patients have spotless epidemic typhus. Photophobia, with considerable conjunctival injection and eye pain, is common. The tongue may be dry, brown, and furred. Confusion and coma are common. Skin necrosis and gangrene of the digits as well as interstitial pneumonia may occur in severe cases. Untreated disease is fatal in 7–40% of cases, with outcome depending primarily on the condition of the host. Patients with untreated infections develop renal insufficiency and multiorgan involvement in which neurologic manifestations are frequently prominent. Overall, 12% of patients with epidemic typhus have neurologic involvement. Infection associated with North American flying squirrels is a milder illness; whether this milder disease is due to host factors (e.g., better health status) or attenuated virulence is unknown.

Diagnosis and treatment

Epidemic typhus is sometimes misdiagnosed as typhoid fever in tropical countries (Chap. 58). The means even for serologic studies are often unavailable in settings of louse-borne typhus. Epidemics may be recognized by the serologic or immunohistochemical diagnosis of a single case or by detection of *R. prowazekii* in a louse found on a patient. Cross-adsorption indirect fluorescent antibody (IFA) studies can distinguish *R. prowazekii* and *R. typhi* infections. Doxycycline (200 mg/d, given in two divided doses) is administered orally or—if the patient is comatose or vomiting—intravenously.

Although under epidemic conditions a single 200-mg dose has proved effective, treatment is generally continued until 2–3 days after defervescence. Pregnant patients should be evaluated individually and treated with either chloramphenicol early in pregnancy or, if necessary, doxycycline late in pregnancy.

Prevention

Prevention of epidemic typhus involves control of body lice. Clothes should be changed regularly, and insecticides should be used every 6 weeks to control the louse population.

SCRUB TYPHUS

O. tsutsugamushi differs substantially from *Rickettsia* species both genetically and in terms of cell wall composition (i.e., it lacks lipopolysaccharide). *O. tsutsugamushi* is maintained by transovarian transmission in trombiculid mites. After hatching, infected larval mites (chiggers, the only stage that feeds on a host) inoculate organisms into the skin. Infected chiggers are found particularly in areas of heavy scrub vegetation during the wet season, when mites lay eggs.

Scrub typhus is endemic and reemerging in eastern and southern Asia, northern Australia, and islands of the western Pacific and Indian Oceans. Infections are prevalent in these regions; in some areas, >3% of the population is infected or reinfected each month. Immunity wanes over 1–3 years, and the organism exhibits remarkable antigenic diversity.

Clinical manifestations

Illness varies from mild and self-limiting to fatal. After an incubation period of 6–21 days, onset is characterized by fever, headache, myalgia, cough, and gastrointestinal symptoms. Some patients recover spontaneously after a few days. The classic case description includes an eschar where the chigger has fed, regional lymphadenopathy, and a maculopapular rash—signs that are seldom seen in indigenous patients. Fewer than 50% of Westerners develop an eschar, and fewer than 40% develop a rash (on day 4–6 of illness). Severe cases typically include encephalitis and interstitial pneumonia due to vascular injury. The case-fatality rate for untreated classic cases is 7%, but would probably be lower if all mild cases were diagnosed.

Diagnosis and treatment

Serologic assays (IFA, indirect immunoperoxidase, and enzyme immunoassays) are the mainstays of laboratory diagnosis, and PCR amplification of *Orientia* genes from eschars and blood is also effective. Patients are treated with doxycycline (100 mg bid orally for 7–15 days), azithromycin (500 mg orally for 3 days), or chloramphenicol (500 mg qid orally for 7–15 days). Some cases of scrub typhus in Thailand are caused by doxycycline- or chloramphenicol-resistant strains that are susceptible to azithromycin and rifampin.

EHRLICHIOSES AND ANAPLASMOSIS

Ehrlichioses are acute febrile infections caused by members of the family Anaplasmataceae, which is made up of obligately intracellular organisms comprised by four genera: *Ehrlichia*, *Anaplasma*, *Wolbachia*, and *Neorickettsia*. The bacteria reside in vertebrate reservoirs and target vacuoles of hematopoietic cells **(Fig. 79-4)**. Two *Ehrlichia* species and one *Anaplasma* species are transmitted by ticks to humans and cause infection that can be severe and prevalent. *E. chaffeensis*, the agent of HME, infects predominantly mononuclear phagocytes; *E. ewingii* and *A. phagocytophilum* infect neutrophils.

Ehrlichia and *Anaplasma* are maintained by horizontal tick-mammal-tick transmission, and humans are only inadvertently infected. Wolbachiae are associated with human filariasis, since they are important for filarial viability and pathogenicity; antibiotic treatment targeting wolbachiae is a strategy for filariasis control. Neorickettsiae parasitize flukes that in turn parasitize aquatic snails, fish, and insects. Only a single human neorickettsiosis has been described: sennetsu fever, an infectious mononucleosis–like illness that was first identified in 1953 and is probably due to the ingestion of raw fish containing *N. sennetsu*–infected flukes.

HUMAN MONOCYTOTROPIC EHRLICHIOSIS

Epidemiology

More than 5496 cases of *E. chaffeensis* infection had been reported to the Centers for Disease Control and Prevention (CDC) as of November 2009. However, active prospective surveillance has demonstrated an

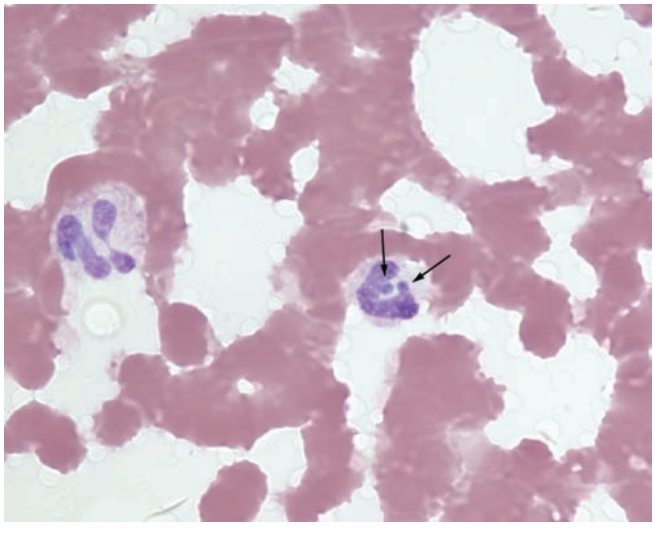


FIGURE 79-4
Peripheral blood smear from a patient with human granulocytotropic anaplasmosis. A neutrophil contains two morulae (vacuoles filled with *A. phagocytophilum*). (*Photo courtesy of Dr. J. Stephen Dumler.*)

incidence as high as 414 cases per 100,000 population in some U.S. regions. Most *E. chaffeensis* infections are identified in the south-central, southeastern, and mid-Atlantic states, but cases have also been recognized in California, New York, and Minnesota. All stages of the Lone Star tick (*A. americanum*) feed on white-tailed deer—a major reservoir. Dogs and coyotes also serve as reservoirs and often lack clinical signs. Tick bites and exposures are frequently reported by patients in rural areas especially in May through July. The median age of HME patients is 53 years; however, severe and fatal infections in children are also well recognized. Of patients with HME, 61% are male.

Clinical manifestations

E. chaffeensis disseminates hematogenously from the dermal blood pool created by the feeding tick. After a median incubation period of 8 days, illness develops. Clinical manifestations are undifferentiated and include fever (96% of cases), headache (72%), myalgia (68%), and malaise (77%). Less frequently observed are nausea, vomiting, and diarrhea (25–57%); cough (28%); rash (26% overall, 6% at presentation); and confusion (20%). HME can be severe: 62% of patients with documented cases are hospitalized, and ~3% die. Severe manifestations include toxic shock–like or septic shock–like syndrome, adult respiratory distress syndrome, cardiac failure, hepatitis, meningoencephalitis, hemorrhage, and—in immunocompromised patients—overwhelming ehrlichial infection. Laboratory findings are valuable in the differential diagnosis of HME; 61% of patients have leukopenia (initially lymphopenia, later neutropenia), 73% have thrombocytopenia, and 84% have elevated serum levels of hepatic aminotransferases. Despite low blood cell counts, the bone marrow is hypercellular, and noncaseating granulomas may be present. Vasculitis is not a component of HME.

Diagnosis

Because HME can be fatal, empirical antibiotic therapy based on clinical diagnosis is required. This diagnosis is suggested by fever with a known tick exposure during the preceding 3 weeks, thrombocytopenia and/or leukopenia, and increased serum aminotransferase levels. Morulae are demonstrated on <10% of peripheral-blood smears. Acute HME can be confirmed by PCR amplification of *E. chaffeensis* nucleic acids in blood obtained before the start of doxycycline therapy. Retrospective serodiagnosis requires a consistent clinical picture and a fourfold increase in *E. chaffeensis* antibody titer to ≥1:64 in paired sera obtained ~3 weeks apart. Separate specific diagnostic tests are necessary for HME and HGA.

EWINGII EHRLICHIOSIS

Ehrlichia ewingii, originally a neutrophil pathogen causing fever and lameness in dogs, resembles *E. chaffeensis* in its tick vector (*A. americanum*) and vertebrate reservoirs (white-tailed deer and dogs). *E. ewingii* illness is similar to but less severe than HME. The majority of cases have occurred in immunocompromised patients. No specific diagnostic test for ewingii ehrlichiosis is readily available.

TREATMENT **Ehrlichioses**

Doxycycline is effective for HME and ewingii ehrlichiosis. Therapy with doxycycline (100 mg given orally or intravenously twice daily) or tetracycline (250–500 mg given orally every 6 h) lowers hospitalization rates and shortens fever duration. *E. chaffeensis* is not susceptible to chloramphenicol in vitro, and the use of this drug is controversial. While a few reports document *E. chaffeensis* persistence in humans, this finding is rare; most infections are cured by short courses of doxycycline (continuing for 3–5 days after defervescence). Although poorly studied, rifampin may be suitable when doxycycline is contraindicated.

Prevention

HME and ewingii ehrlichiosis are prevented by the avoidance of ticks in endemic areas. The use of protective clothing and tick repellents, careful postexposure tick searches, and prompt removal of attached ticks probably diminish infection risk.

HUMAN GRANULOCYTOTROPIC ANAPLASMOSIS

Epidemiology

As of November 2009, 6218 cases of HGA had been reported to the CDC, most in the upper midwestern and northeastern United States; the geographic distribution is similar to that for Lyme disease because of the shared *I. scapularis* tick vector. White-footed mice, squirrels, and white-tailed deer in the United States and red deer in Europe are natural reservoirs for *A. phagocytophilum*. HGA incidence peaks in May through July, but the disease can occur throughout the year with exposure to *Ixodes* ticks. HGA often affects males (57%) and older persons (median age, 51 years).

Clinical manifestations

Seroprevalence rates are high in endemic regions; thus it seems likely that most individuals develop subclinical infections. The incubation period for HGA is 4–8 days, after which the disease manifests as fever (91% of cases), myalgia (77%), headache (77%), and malaise (94%). A minority of patients develop nausea, vomiting, or diarrhea (16–38%); cough (21%); or confusion (17%). Rash (6%) is almost invariably concurrent erythema migrans attributable to Lyme disease. Most patients develop thrombocytopenia (69%) and/or leukopenia (48%) with increased serum hepatic aminotransferase levels (71%).

Severe complications occur most often in the elderly and include adult respiratory distress syndrome, toxic shock–like syndrome, and life-threatening opportunistic infections. Meningoencephalitis has not been conclusively documented with HGA, but brachial plexopathy and demyelinating polyneuropathy are reported. For HGA, 7% of patients require intensive care, and the case-fatality rate is 0.5%. Neither vasculitis nor granulomas are components of HGA. While co-infections with *Borrelia burgdorferi* and *Babesia microti* (transmitted by the same tick vector[s]) occur, there is little evidence of comorbidity or persistence.

Diagnosis

HGA should be included in the differential diagnosis of influenza-like illnesses during seasons with *Ixodes* tick activity (May through December), especially with tick bite or exposure. Concurrent thrombocytopenia, leukopenia, or elevation in serum alanine or aspartate aminotransferase further increases the likelihood of HGA. Many HGA patients develop Lyme disease antibodies in the absence of clinical findings consistent with that diagnosis. Thus, HGA should be considered in the differential diagnosis of atypical severe Lyme disease presentations. Peripheral-blood film examination for neutrophil morulae can yield a diagnosis in 20–75% of infections. PCR testing of blood from patients with active disease before doxycycline therapy is sensitive and specific. Serodiagnosis is retrospective, requiring a fourfold increase in *A. phagocytophilum* antibody titer (to ≥1:80) in paired serum samples obtained 1 month apart. Since seroprevalence is high in some regions, a single acute-phase titer should not be used for diagnosis.

TREATMENT **Human Granulocytotropic Anaplasmosis**

No prospective studies of therapy for HGA have been conducted. However, doxycycline (100 mg by mouth twice daily) is effective. Rifampin therapy is associated with improvement of HGA in pregnant women and children. Most treated patients defervesce within 24–48 h.

Prevention

HGA prevention requires tick avoidance. Transmission can be documented as few as 4 h after a tick bite.

Q FEVER

The agent of Q fever is *C. burnetii*, a small intracellular microorganism that only recently was grown in cell-free medium. *C. burnetii*, a pleomorphic coccobacillus with a gram-negative cell wall, survives in harsh environments; it escapes intracellular killing in macrophages by inhibiting the final phagosome maturation step (cathepsin fusion) and has adapted to the acidic phagolysosome by producing superoxide dismutase. Infection with *C. burnetii* induces a range of immunomodulatory responses, from immunosuppression in chronic Q fever to the production of autoantibodies, particularly those to smooth muscle and cardiac muscle.

Q fever encompasses two broad clinical syndromes: acute and chronic infection. The host's immune response (rather than the particular strain) most likely determines whether chronic Q fever develops. *C. burnetii* survives in monocytes from patients with chronic Q fever, but not in monocytes from patients with acute Q fever or from uninfected subjects. Impairment of the bactericidal activity of the *C. burnetii*–infected monocyte is associated with overproduction of interleukin 10. The CD4+/CD8+ ratio is decreased in Q fever endocarditis. Very few organisms and a strong cellular response are observed in patients with acute Q fever, while many organisms and a moderate cellular response occur in chronic Q fever. Immune control of *C. burnetii* is T cell–dependent, but 80–90% of bone marrow aspirates obtained years after recovery from Q fever contain *C. burnetii* DNA.

Epidemiology

Q fever is a zoonosis. The primary sources of human infection are infected cattle, sheep, and goats. However, cats, rabbits, pigeons, and dogs have also served as sources for transmission of *C. burnetii* to humans. The wildlife reservoir is extensive and includes ticks, coyotes, gray foxes, skunks, raccoons, rabbits, deer, mice, bears, birds, and opossums. In female animals *C. burnetii* localizes to the uterus and mammary glands. Infection is reactivated during pregnancy and following radiotherapy in mouse models. High concentrations of *C. burnetii* are found in the placenta. At the time of parturition, the bacteria are released into the air, and infection follows inhalation of aerosolized organisms by a susceptible host. Windstorms can generate *C. burnetii* aerosols months after soil contamination during parturition. Individuals up to 18 km from the source have been infected. Because it is easily dispersed as an aerosol, *C. burnetii* is a potential agent of bioterrorism (Chap. 7), with a high infectivity rate and pneumonia as the major manifestation.

Determining the source of an outbreak of Q fever can be challenging. An outbreak of Q fever at a horse-boarding ranch in Colorado in 2005 was due to spread of infection from two herds of goats that had been acquired by the owners. PCR testing confirmed the presence of *C. burnetii* in the soil and among the goats. Of 138 persons who lived within 1 mile of the ranch and who were also tested, 11 (8%) had evidence of *C. burnetii* infection, and 8 of these 11 individuals had had no direct contact with the ranch.

Persons at risk for Q fever include abattoir workers, veterinarians, farmers, and other individuals who have contact with infected animals, particularly newborn animals, or products of conception. The organism is shed in milk for weeks to months after parturition. The ingestion of contaminated milk in some geographic areas probably represents a major route of transmission to humans,

although experimental evidence on this point is contradictory. In rare instances, human-to-human transmission has followed labor and childbirth in an infected woman, autopsy of an infected individual, or blood transfusion. Some evidence suggests that *C. burnetii* can be sexually transmitted among humans. Crushing an infected tick between the fingers has resulted in Q fever; the implication is that percutaneous transmission can occur.

Infections due to *C. burnetii* occur in most geographic locations except New Zealand and Antarctica. Thus, Q fever can be associated with travel. The number of reported cases of Q fever in the United States ranges from 28 to 54 per year. More than 70% of these cases occur in males, and April through June is the most common time for acquisition. Q fever continues to be common in Australia, with 30 cases per 1 million population per year. Cases among abattoir workers in Australia declined dramatically due to a vaccination program. An outbreak of Q fever began in the Netherlands in 2007, and by August 2009 more than 2000 cases had been reported. Pneumonia was a common manifestation in this outbreak, which appeared to be primarily due to transmission from infected goats.

The primary manifestations of acute Q fever differ geographically (e.g., pneumonia in Nova Scotia and granulomatous hepatitis in Marseille). These differences may reflect the route of infection (i.e., ingestion of contaminated milk for hepatitis and inhalation of contaminated aerosols for pneumonia).

Young age seems to be protective against infection with *C. burnetii*. In a large outbreak in Switzerland, symptomatic infection occurred five times more often among persons >15 years of age than among younger individuals. In many outbreaks, men are affected more commonly than women; the proposed explanation is that female hormones are partially protective.

Clinical manifestations

Acute Q fever

After an incubation period of 3–30 days, 1070 patients with acute Q fever in southern France presented with hepatitis (40%), both pneumonia and hepatitis (20%), pneumonia (17%), isolated fever (14%), CNS involvement (2%), and pericarditis or myocarditis (1%). Acalculous cholecystitis, pancreatitis, lymphadenopathy, spontaneous rupture of the spleen, transient hypoplastic anemia, bone marrow necrosis, hemolytic anemia, histiocytic hemophagocytosis, optic neuritis, and erythema nodosum are less common manifestations.

The symptoms of acute Q fever are nonspecific; common among them are fever, extreme fatigue, photophobia, and severe headache that is frequently retro-orbital. Other symptoms include chills, sweats, nausea, vomiting, and diarrhea, each occurring in 5–20% of cases. Cough develops in about half of patients with Q fever pneumonia. Neurologic manifestations of acute Q fever are uncommon; however, in one outbreak in the United Kingdom, 23% of 102 patients had neurologic signs and symptoms as the major manifestation. A nonspecific rash may be evident in 4–18% of patients. The WBC count is usually normal. Thrombocytopenia occurs in ~25% of patients, and reactive thrombocytosis (with platelet counts exceeding $10^6/\mu L$) frequently develops during recovery. Chest radiography may show opacities similar to those seen in pneumonia caused by other pathogens, but multiple rounded opacities in patients in endemic areas suggest a diagnosis of Q fever pneumonia.

Acute Q fever occasionally complicates pregnancy. In one series, it resulted in premature birth in 35% of cases and in abortion or neonatal death in 43%. Neonatal death (previous or current) and lower infant birth weight are three times more likely among women seropositive for *C. burnetii*.

Post–Q fever fatigue syndrome

Prolonged fatigue can follow Q fever and can be accompanied by a constellation of symptoms including headaches, sweats, arthralgia, myalgias, blurred vision, muscle fasciculations, and enlarged and painful lymph nodes. Long-term persistence of a noninfective, nonbiodegraded complex of *Coxiella* cell components with its antigens and specific lipopolysaccharide has been detected in the affected persons. Patients who develop this syndrome have a higher frequency of carriage of HLA-DRB1*11 and of the 2/2 genotype of the interferon γ intron 1 microsatellite.

Chronic Q fever

Chronic Q fever almost always implies endocarditis and usually occurs in patients with previous valvular heart disease, immunosuppression, or chronic renal insufficiency. Fever is usually absent or low grade. Valvular vegetations are detected in only 12% of patients by transthoracic echocardiography, but the rate of detection is higher with transesophageal echocardiography. The vegetations in chronic Q fever endocarditis differ from those in bacterial endocarditis, manifesting as endothelium-covered nodules on the valves. A high index of suspicion is necessary for timely diagnosis. Patients with chronic Q fever are often ill for >1 year before the diagnosis is made. The disease should be suspected in all patients with culture-negative endocarditis. In addition, all patients with valvular heart disease and an unexplained purpuric eruption, renal insufficiency, stroke, and/or progressive heart failure should be tested for *C. burnetii* infection. Patients with chronic Q fever have hepatomegaly and/or splenomegaly, which, in combination with rheumatoid factor, elevated erythrocyte sedimentation rate, high C-reactive protein level, and/or increased γ-globulin concentrations (up to 60–70 g/L), suggests this diagnosis. Other manifestations of chronic Q fever include infection of vascular prostheses, aneurysms, and bone as well as chronic sternal wound infection. Unusual manifestations include chronic thrombocytopenia, mixed cryoglobulinemia, and livedo reticularis.

Diagnosis

Isolation of *C. burnetii* from buffy-coat blood samples or tissue specimens by a shell-vial technique is easy but

requires a biosafety level 3 laboratory. PCR detects *C. burnetii* DNA in tissue specimens, including paraffin-embedded samples. Serology is the most commonly used diagnostic tool. Indirect immunofluorescence is sensitive and specific and is the method of choice. Rheumatoid factor should be adsorbed from the specimen before testing. An IgG antibody titer of ≥1:800 to phase I antigen (i.e., naturally occurring *C. burnetii* with intact lipopolysaccharide) is suggestive of chronic Q fever; in chronic infection, the titer to phase I antigen is usually much higher than that to phase II antigen (i.e., *C. burnetii* that has truncated lipopolysaccharide associated with gene deletions during laboratory passages). The reverse is true in acute Q fever, in which a fourfold rise in titer may be demonstrated between acute- and convalescent-phase serum samples.

TREATMENT **Q Fever**

Treatment of acute Q fever with doxycycline (100 mg twice daily for 14 days) is usually successful. Quinolones are also effective. When Q fever is diagnosed during pregnancy, treatment with trimethoprim-sulfamethoxazole (TMP-SMX) is recommended for the duration of the pregnancy. One study showed no intrauterine fetal deaths and substantial reduction of obstetric complications in a group of Q fever patients treated with TMP-SMX.

The treatment of chronic Q fever is difficult and requires careful follow-up. Addition of hydroxychloroquine (to alkalinize the phagolysosome) renders doxycycline bactericidal against *C. burnetii,* and this combination is currently the favored regimen. Treatment with doxycycline (100 mg bid) and hydroxychloroquine (200 mg tid; plasma concentration maintained at 0.8–1.2 μg/mL) for 8 months is superior to a regimen of doxycycline and ofloxacin. Among 21 patients who received doxycycline and hydroxychloroquine, 1 died of a surgical complication, 2 were still being treated at the end of the study, 1 was still being evaluated, and 17 were cured. The mean duration of treatment was 31 months. In the ofloxacin and doxycycline group of 14 patients, 1 had died, 1 was still being treated, 7 had relapsed, and 5 had been cured by the end of the study. Optimal management of Q fever endocarditis entails determining the minimal inhibitory concentration (MIC) of doxycycline for the patient's isolate and measuring serum doxycycline levels. A serum level–to–doxycycline MIC ratio of ≥1 is associated with a rapid decline in phase I antibodies with the doxycycline-hydroxychloroquine regimen. Patients treated with this regimen must be advised about photosensitivity and retinal toxicity risks. The doxycycline-hydroxychloroquine regimen was successful in one patient with HIV infection and Q fever endocarditis. The Jarisch-Herxheimer reaction occasionally complicates the treatment of chronic Q fever. Treatment of *C. burnetii*–infected aortic aneurysms is the same as that for Q fever endocarditis. Surgical intervention is often required.

If doxycycline-hydroxychloroquine cannot be used, the regimen chosen should include at least two antibiotics active against *C. burnetii*. Rifampin (300 mg once daily) combined with doxycycline (100 mg twicedaily) or ciprofloxacin (750 mg twice daily) has been used successfully. The optimal duration of antibiotic therapy for chronic Q fever remains undetermined. At least 3 years of treatment, with discontinuation only if the phase I IgA antibody titer is ≤1:50 and the phase I IgG titer is ≤1:200, is recommended.

Patients with acute Q fever and lesions of native heart valves (e.g., bicuspid aortic valve), prosthetic valves, or prosthetic intravascular material should undergo serologic monitoring every 4 months for 2 years. If the phase I IgG titer is >1:800, further investigation is warranted. Some authorities recommend that patients with valvulopathy and acute Q fever receive doxycycline and hydroxychloroquine to prevent chronic Q fever. For women who exhibit a serologic profile of chronic Q fever after childbirth, hydroxychloroquine and doxycycline should be given for 1 year.

THERAPY WITH BIOLOGIC MODIFYING AGENTS Interferon γ was successful in the treatment of a 3-year-old boy with prolonged fever, abdominal pain, and thrombocytopenia due to *C. burnetii* that had not been eradicated with conventional antibiotic therapy. Many patients with granulomatous hepatitis due to Q fever have a prolonged febrile illness that is unresponsive to antibiotics. For these individuals, treatment with prednisone (0.5 mg/kg) has resulted in defervescence within 2–15 days. After defervescence, the glucocorticoid dose is tapered over the next month.

Prevention

A whole-cell vaccine (Q-Vax) licensed in Australia effectively prevents Q fever in abattoir workers. Before administration of the vaccine, skin testing with intradermal diluted *C. burnetii* vaccine is performed, serologic testing is undertaken, and a history of possible Q fever is sought. Vaccine is given only to patients with no history of Q fever and negative results in serologic and skin testing.

Good animal-husbandry practices are important in preventing widespread contamination of the environment by *C. burnetii*. These practices include isolating aborting animals for up to 14 days, raising feed bunks to prevent contamination of feed by excreta, destroying aborted materials (by burning and burying fetal membranes and stillborn animals), and wearing masks and gloves when handling aborted materials. Only seronegative pregnant animals should be used in research settings, and only seronegative animals should be permitted in petting zoos.

During an outbreak of Q fever and for 4 weeks after it ceases, blood donations should not be accepted from individuals who live in the affected area.

ACKNOWLEDGMENT

The contributions of Didier Raoult, MD, to this chapter in previous editions of Harrison's Principles of Internal Medicine are gratefully acknowledged.

CHAPTER 80

INFECTIONS DUE TO MYCOPLASMAS

R. Doug Hardy

Mycoplasmas are prokaryotes of the class Mollicutes. Their size (150–350 nm) is closer to that of viruses than to that of bacteria. Unlike viruses, however, mycoplasmas grow in cell-free culture media; in fact, they are the smallest organisms capable of independent replication.

The entire genomes of many *Mycoplasma* species have been sequenced and have been found to be among the smallest of all prokaryotic genomes. Sequencing information for these genomes has helped define the minimal set of genes necessary for cellular life. The absence of genes related to the synthesis of amino acids, fatty acid metabolism, and cholesterol dictates the mycoplasmas' parasitic or saprophytic dependence on a host for exogenous nutrients and necessitates the use of complex fastidious media to culture these organisms. Mycoplasmas lack a cell wall and are bound only by a cell membrane. The absence of a cell wall explains the inactivity of β-lactam antibiotics (penicillins and cephalosporins) against infections caused by these organisms.

At least 13 *Mycoplasma* species, two *Acholeplasma* species, and two *Ureaplasma* species have been isolated from humans. Most of these species are thought to be normal inhabitants of oral and urogenital mucous membranes. Only four species—*M. pneumoniae*, *M. hominis*, *U. urealyticum*, and *U. parvum*—have been shown conclusively to be pathogenic in immunocompetent humans. *M. pneumoniae* primarily infects the respiratory tract, while *M. hominis*, *U. urealyticum*, and *U. parvum* are associated with a variety of genitourinary tract disorders and neonatal infections. Some data indicate that *M. genitalium* may be a cause of disease in humans. Other mycoplasmas may cause disease in immunocompromised persons.

MYCOPLASMA PNEUMONIAE

PATHOGENICITY

M. pneumoniae is generally thought to act as an extracellular pathogen. Although the organism has been shown to exist and replicate within human cells, it is not known whether these intracellular events contribute to the pathogenesis of disease. *M. pneumoniae* attaches to ciliated respiratory epithelial cells by means of a complex terminal organelle at the tip of one end of the organism. Cytoadherence is mediated by interactive adhesins and accessory proteins clustered on this organelle. After extracellular attachment, *M. pneumoniae* causes injury to host respiratory tissue. The mechanism of injury is thought to be mediated by the production of hydrogen peroxide and of a recently identified ADP-ribosylating and vacuolating cytotoxin of *M. pneumoniae* that has many similarities to pertussis toxin. Because mycoplasmas lack a cell wall, they also lack cell wall–derived stimulators of the innate immune system, such as lipopolysaccharide, lipoteichoic acid, and murein (peptidoglycan) fragments. However, lipoproteins from the mycoplasmal cell membrane appear to have inflammatory properties, probably acting through Toll-like receptors (primarily TLR2) on macrophages and other cells. Lung biopsy specimens from patients with *M. pneumoniae* respiratory tract infection reveal an inflammatory process involving the trachea, bronchioles, and peribronchial tissue, with a monocytic infiltrate coinciding with a luminal exudate of polymorphonuclear leukocytes.

Experimental evidence indicates that innate immunity provides most of the host's defense against mycoplasmal infection in the lungs, whereas cellular immunity may actually play an immuno pathogenic role, exacerbating mycoplasmal lung disease. Humoral immunity appears to provide protection against dissemination of *M. pneumoniae* infection; patients with humoral immunodeficiencies do not have more severe lung disease than do immunocompetent patients in the early stages of infection but more often develop disseminated infection resulting in syndromes such as arthritis, meningitis, and osteomyelitis. The immunity that follows severe *M. pneumoniae* infections is more protective and longer-lasting than that following mild infections. Genuine second attacks of *M. pneumoniae* pneumonia have been reported infrequently.

EPIDEMIOLOGY

M. pneumoniae infection occurs worldwide. It is likely that the incidence of upper respiratory illness due to *M. pneumoniae* is up to 20 times

that of pneumonia caused by this organism. Infection is spread from one person to another by respiratory droplets expectorated during coughing and results in clinically apparent disease in an estimated 80% of cases. The incubation period for *M. pneumoniae* is 2–4 weeks; therefore, the time-course of infection in a specific population may be several weeks long. Intrafamilial attack rates are as high as 84% among children and 41% among adults. Outbreaks of *M. pneumoniae* illness often occur in institutional settings such as military bases, boarding schools, and summer camps. Infections tend to be endemic, with sporadic epidemics every 4–7 years. There is no seasonal pattern.

Most significantly, *M. pneumoniae* is a major cause of community-acquired respiratory illness in both children and adults and is often grouped with *Chlamydia pneumoniae* and *Legionella* species as being among the most important bacterial causes of "atypical" community-acquired pneumonia. For community-acquired pneumonia in adults, *M. pneumoniae* is the most frequently detected "atypical" organism. Analysis of 13 studies of community-acquired pneumonia published since 1995 (which included 6207 ambulatory and hospitalized adults) showed that the overall prevalence of *M. pneumoniae* was 22.7%; by comparison, the prevalence of *C. pneumoniae* was 11.7%, and that of *Legionella* species was 4.6%. *M. pneumoniae* pneumonia is also referred to as Eaton agent pneumonia (the organism having first been isolated in the early 1940s by Monroe Eaton), primary atypical pneumonia, and "walking" pneumonia.

CLINICAL MANIFESTATIONS

Upper respiratory tract infections and pneumonia

Acute *M. pneumoniae* infections generally manifest as pharyngitis, tracheobronchitis, reactive airway disease/wheezing, or a nonspecific upper respiratory syndrome. Little evidence supports the commonly held belief that this organism is an important cause of otitis media, with or without bullous myringitis. Pneumonia develops in 3–13% of infected individuals; its onset is usually gradual, occurring over several days, but may be more abrupt. Although *Mycoplasma* pneumonia may begin with a sore throat, the most common presenting symptom is cough. The cough is typically nonproductive, but some patients produce sputum. Headache, malaise, chills, and fever are noted in the majority of patients.

On physical examination, wheezes or rales are detected in ~80% of patients with *M. pneumoniae* pneumonia. In many patients, however, pneumonia can be diagnosed only by chest radiography. The most common radiographic pattern is that of peribronchial pneumonia with thickened bronchial markings, streaks of interstitial infiltration, and areas of subsegmental atelectasis. Segmental or lobar consolidation is not uncommon. While clinically evident pleural effusions are uncommon, lateral decubitus views reveal that up to 20% of patients have pleural effusions.

Overall, the clinical presentation of pneumonia in an individual patient is not useful for differentiating *M. pneumoniae* pneumonia from other types of community-acquired pneumonia. The possibility of *M. pneumoniae* infection deserves particular consideration when community-acquired pneumonia fails to respond to treatment with a penicillin or a cephalosporin—antibiotics that are ineffective against mycoplasmas. Symptoms usually resolve within 2–3 weeks after the onset of illness. Although *M. pneumoniae* pneumonia is generally self-limited, appropriate antimicrobial therapy significantly shortens the duration of clinical illness. Infection uncommonly results in critical illness and only rarely in death. In some patients, long-term recurrent wheezing may follow the resolution of acute pneumonia. The significance of chronic infection, especially as it relates to asthma, is an area of active investigation.

Extrapulmonary manifestations

An array of extrapulmonary manifestations may develop during *M. pneumoniae* infection. The most significant are neurologic, dermatologic, cardiac, rheumatologic, and hematologic in nature. Extrapulmonary manifestations can be a result of active infection (e.g., septic arthritis) or postinfectious autoimmune phenomena (e.g., Guillain-Barré syndrome). Overall, these manifestations are uncommon, given the frequency of *M. pneumoniae* infection. Notably, many patients with extrapulmonary *M. pneumoniae* disease do not have respiratory disease.

Skin eruptions described with *M. pneumoniae* infection include erythematous (macular or maculopapular), vesicular, bullous, petechial, and urticarial rashes. In some reports, 17% of patients with *M. pneumoniae* pneumonia have had an exanthem. Erythema multiforme major (Stevens-Johnson syndrome) is the most clinically significant skin eruption associated with *M. pneumoniae* infection; it appears to occur more commonly with *M. pneumoniae* than with other infectious agents.

A wide spectrum of neurologic manifestations has been reported with *M. pneumoniae* infection. The most common are meningoencephalitis, encephalitis, Guillain-Barré syndrome, and aseptic meningitis. *M. pneumoniae* has been implicated as a likely etiologic agent in 5–7% of cases of encephalitis. Other neurologic manifestations may include cranial neuropathy, acute psychosis, cerebellar ataxia, acute demyelinating encephalomyelitis, cerebrovascular thromboembolic events, and transverse myelitis. The roles of antimicrobial drugs, glucocorticoids, and IV immunoglobulin in the treatment of neurologic disease due to *M. pneumoniae* remain unknown.

Hematologic manifestations of *M. pneumoniae* infection include hemolytic anemia, aplastic anemia, cold agglutinins, disseminated intravascular coagulation, and hypercoagulopathy. When anemia does occur, it generally develops in the second or third week of illness.

In addition, hepatitis, glomerulonephritis, pancreatitis, myocarditis, pericarditis, rhabdomyolysis, and arthritis (septic and reactive) have been convincingly ascribed to *M. pneumoniae* infection. Septic arthritis has been described most commonly in hypogammaglobulinemic patients.

DIAGNOSIS (TABLE 80-1)

Clinical findings, nonmicrobiologic laboratory tests, and chest radiography are not useful for differentiating *M. pneumoniae* pneumonia from other types of community-acquired pneumonia. In addition, since *M. pneumoniae* lacks a cell wall, it is not visible on Gram's stain. Although of historical interest, the measurement of cold agglutinin titers is no longer recommended for the diagnosis of *M. pneumoniae* infection because the findings are nonspecific and assays specific for *M. pneumoniae* are now available.

Acute *M. pneumoniae* infection can be diagnosed by polymerase chain reaction (PCR) detection of the organism in respiratory tract secretions or by isolation of the organism in culture. Oropharyngeal, nasopharyngeal, and pulmonary specimens are all acceptable for diagnosing *M. pneumoniae* pneumonia. Other bodily fluids, such cerebrospinal fluid, are acceptable for extrapulmonary infection. *M. pneumoniae* culture (which requires special media) is not recommended for routine diagnosis because the organism may take weeks to grow and is often difficult to isolate from clinical specimens. In contrast, PCR allows rapid, specific diagnosis earlier in the course of clinical illness.

The diagnosis can also be established by serologic tests for IgM and IgG antibodies to *M. pneumoniae* in paired (acute- and convalescent-phase) serum samples; enzyme-linked immunoassay is the recommended serologic method. An acute-phase sample alone is not adequate for diagnosis, as antibodies to *M. pneumoniae* may not develop until 2 weeks into the illness; therefore, it is important to test paired samples. In addition, IgM antibody to *M. pneumoniae* can persist for up to 1 year after acute infection. Thus, its presence may indicate recent rather than acute infection.

The combination of PCR of respiratory tract secretions and serologic testing constitutes the most sensitive and rapid approach to the diagnosis of *M. pneumoniae* infection.

TABLE 80-1

DIAGNOSTIC TESTS FOR RESPIRATORY *MYCOPLASMA PNEUMONIAE* INFECTION[a]

TEST	SENSITIVITY, %	SPECIFICITY, %	COMMENT
Respiratory culture	≤60	100	—
Respiratory PCR	65–90	90–100	—
Serologic studies	55–100	55–100	Acute- and convalescent-phase serum samples are recommended.

[a]A combination of PCR and serology is suggested for routine diagnosis. If macrolide resistance is suspected, *M. pneumoniae* culture may prove useful, providing an isolate for susceptibility testing.
Abbreviation: PCR, polymerase chain reaction.

TREATMENT *Mycoplasma pneumoniae* Infections (Table 80-2)

Although in the majority of untreated cases symptoms resolve within 2–3 weeks without significant associated morbidity, *M. pneumoniae* pneumonia can be a serious illness that responds to appropriate antimicrobial therapy. Randomized, double-blind, placebo-controlled trials have demonstrated that antimicrobial treatment significantly decreases the duration of fever, cough, malaise, hospitalization, and radiologic abnormalities in *M. pneumoniae* pneumonia. Treatment options for acute *M. pneumoniae* infection include macrolides (e.g., oral azithromycin, 500 mg on day 1, then 250 mg/d on days 2–5), tetracyclines (e.g., oral doxycycline, 100 mg twice daily for 10–14 days), and respiratory fluoroquinolones. However, ciprofloxacin and ofloxacin are *not* recommended because of their high minimal inhibitory concentrations against *M. pneumoniae* isolates and their poor performance in experimental studies. A 10- to 14-day course of therapy appears adequate.

In Japan and China, high levels of *M. pneumoniae* resistance to macrolides have been reported. In Europe and to a lesser degree in the United States, macrolide-resistant *M. pneumoniae* is emerging. If macrolide resistance is prominent in a geographic locale or is suspected, then a nonmacrolide antibiotic should be considered for treatment; in addition, culture of *M. pneumoniae* may prove useful in these instances, providing an isolate for susceptibility testing.

Clinical observations and experimental data suggest that the addition of glucocorticoids to an antibiotic regimen may be of value for the treatment of severe or refractory *M. pneumoniae* pneumonia. However, relevant clinical experience is still limited. Even though appropriate antibiotic therapy significantly reduces the duration of respiratory illness, it does not appear to shorten the duration of detection of *M. pneumoniae* by culture or PCR; therefore, a test of cure or eradication is not suggested.

TABLE 80-2

ANTIMICROBIAL AGENTS OF CHOICE FOR MYCOPLASMA INFECTIONS[a]

ORGANISM	DRUG(S)
M. pneumoniae	Azithromycin, clarithromycin, erythromycin, doxycycline, levofloxacin, moxifloxacin, gemifloxacin (*not* ciprofloxacin)
U. urealyticum, *U. parvum*	Azithromycin, clarithromycin, erythromycin, doxycycline
M. hominis	Doxycycline, clindamycin
M. genitalium	Azithromycin

[a]Antimicrobial resistance has been reported for mycoplasmas, as described in the text.

UROGENITAL MYCOPLASMAS (SEE ALSO CHAP. 30)

EPIDEMIOLOGY

M. hominis, *M. genitalium*, *U. urealyticum*, and *U. parvum* can cause urogenital tract disease. The significance of isolation of these organisms in a variety of other syndromes is unknown and in some cases is being investigated. *M. fermentans* has not been shown convincingly to cause human disease.

While urogenital mycoplasmas may be transmitted to a fetus during passage through a colonized birth canal, sexual contact is the major mode of transmission, and the risk of colonization increases dramatically with increasing numbers of sexual partners. In asymptomatic women, these mycoplasmas may be found throughout the lower urogenital tract. The vagina yields the largest number of organisms; next most densely colonized are the periurethral area and the cervix. Ureaplasmas are isolated less often from urine than from the cervix, but *M. hominis* is found with approximately the same frequency at these two sites. Ureaplasmas are isolated from the vagina of 40–80% of sexually active, asymptomatic women and *M. hominis* from 21–70%. The two microorganisms are found concurrently in 31–60% of women. In men, colonization with each organism is less prevalent. Mycoplasmas have been isolated from urine, semen, and the distal urethra of asymptomatic men.

CLINICAL MANIFESTATIONS

Urethritis, pyelonephritis, and urinary calculi

In many episodes of *Chlamydia*-negative nongonococcal urethritis, ureaplasmas may be the causative agent. These organisms may also cause chronic voiding symptoms in women. The common presence of ureaplasmas in the urethra of asymptomatic men suggests either that only certain serovars are pathogenic or that predisposing factors, such as lack of immunity, must exist in persons who develop symptomatic infection. Alternatively, disease may develop only upon initial exposure to ureaplasmas. Ureaplasmas have been implicated in epididymitis. *M. genitalium* also appears to cause urethritis. *M. genitalium* and ureaplasmas do not have a known role in prostatitis. *M. hominis* does not appear to have a primary etiologic role in urethritis, epididymitis, or prostatitis.

Evidence suggests that *M. hominis* causes up to 5% of cases of acute pyelonephritis. Ureaplasmas have not been associated with this disease.

Ureaplasmas play a limited role in the production of urinary calculi. The frequency with which ureaplasmas reach the kidney, the predisposing factors that allow them to do so, and the relative frequency of urinary tract calculi induced by this organism (as compared with other organisms) are not known.

Pelvic inflammatory disease

M. hominis can cause pelvic inflammatory disease. In most episodes, *M. hominis* occurs as part of a polymicrobial infection, but the organism may play an independent role in a limited number of cases. Some data also support an association of *M. genitalium* with pelvic inflammatory disease. Ureaplasmas are not thought to cause pelvic inflammatory disease.

Postpartum and postabortal infection

Studies implicate *M. hominis* as the primary pathogen in ~5–10% of women who have postpartum or postabortal fever; ureaplasmas have been implicated to a lesser degree. These infections are generally self-limited; however, if symptoms persist, specific antimicrobial therapy should be given. Ureaplasmas also appear to play a role in occasional postcesarean wound infections.

Nonurogenital infection

M. hominis rarely causes nonurogenital infections, such as brain abscess, wound infection, poststernotomy mediastinitis, endocarditis, and neonatal meningitis. These infections are most common among immunocompromised and hypogammaglobulinemic patients. Ureaplasmas and *M. hominis* can cause septic arthritis in immunodeficient patients. Ureaplasmas probably cause neonatal pneumonitis; their significant role in the development of bronchopulmonary dysplasia, the chronic lung disease of premature infants, has been documented in a number of studies. It is unclear whether ureaplasmas and *M. hominis* cause infertility, spontaneous abortion, premature labor, low birth weight, or chorioamnionitis.

DIAGNOSIS

Culture and PCR are both appropriate methods for the isolation of urogenital mycoplasmas. Culture of these organisms, however, requires special techniques and media that generally are available only at larger medical centers and reference laboratories. Serologic testing is not recommended for the clinical diagnosis of urogenital *Mycoplasma* infections.

TREATMENT **Urogenital Mycoplasma Infections (Table 80-2)**

Because colonization with urogenital mycoplasmas is common, it appears at present that their isolation from the urogenital tract in the absence of disease generally does not warrant treatment. Macrolides and doxycycline are considered the antimicrobial agents of choice for *Ureaplasma* infections. *Ureaplasma* resistance to macrolides, doxycycline, quinolones, and chloramphenicol has been reported. *M. hominis* is resistant to macrolides. Doxycycline is generally the drug of choice for *M. hominis* infections, although resistance has been reported. Clindamycin is also generally active against *M. hominis*. Quinolones are active in vitro against *M. hominis*. For *M. genitalium,* the agent of choice appears to be azithromycin; treatment failures have been reported with other macrolides as well as with quinolones.

CHAPTER 81

CHLAMYDIAL INFECTIONS

Charlotte A. Gaydos ■ Thomas C. Quinn

Chlamydiae are obligate intracellular bacteria that cause a wide variety of diseases in humans and animals.

ETIOLOGIC AGENTS

The chlamydiae were originally classified as four species in the genus *Chlamydia*: *C. trachomatis*, *C. pneumoniae*, *C. psittaci*, and *C. pecorum* (the last species being found in ruminants). The *C. psittaci* group has been separated into three species: *C. psittaci*, *C. felis*, and *C. abortus*. The mouse pneumonitis strain (MoPn) is now classified as *C. muridarum*, and the guinea pig inclusion conjunctivitis strain (GPIC) is now designated *C. caviae*.

C. trachomatis is divided into two biovars: trachoma and LGV (lymphogranuloma venereum). The trachoma biovar causes two major types of disease in humans: ocular trachoma, the leading infectious cause of preventable blindness in the developing world; and urogenital infections, which are sexually or neonatally transmitted. The 18 serovars of *C. trachomatis* fall into three groups: the trachoma serovars A, B, Ba, and C; the oculogenital serovars D–K; and the LGV serovars L_1–L_3. Serovars can be distinguished by serologic typing with monoclonal antibodies or by molecular gene typing. However, serovar identification usually is not important clinically, since the antibiotic susceptibility pattern is the same for all three groups. The one exception applies when LGV is suspected on clinical grounds; in this situation, serovar determination is important because a longer treatment duration is required for LGV strains.

BIOLOGY, GROWTH CYCLE, AND PATHOGENESIS

BIOLOGY

During their intracellular growth, chlamydiae produce characteristic intracytoplasmic inclusions that can be visualized by direct fluorescent antibody (DFA) or Giemsa staining of infected clinical material, such as conjunctival scrapings or cervical or urethral epithelial cells. Chlamydiae are nonmotile, gram-negative, obligate intracellular bacteria that replicate within the cytoplasm of host cells, forming the characteristic membrane-bound inclusions that are the basis for some diagnostic tests. Originally considered to be large viruses, chlamydiae differ from viruses in possessing RNA and DNA as well as a cell wall that is quite similar in structure to the cell wall of typical gram-negative bacteria. However, chlamydiae lack peptidoglycan; their structural integrity depends on disulfide binding of outer-membrane proteins.

GROWTH CYCLE

Among the defining characteristics of chlamydiae is a unique growth cycle that involves alternation between two highly specialized morphologic forms **(Figs. 81-1 and 81-2)**: the elementary body (EB), which is the infectious form and is specifically adapted for extracellular survival, and the metabolically active and replicating reticulate body (RB), which is not infectious, is adapted for an intracellular environment, and does not survive well outside the host cell. The biphasic growth cycle begins with attachment of the EB (diameter, 0.25–0.35 μm) at specific sites on the surface of the host cell. The EB enters the cell through a process similar to receptor-mediated endocytosis and resides in an inclusion, where the entire growth cycle is completed. The chlamydiae prevent phagosome-lysosome fusion. The inclusion membrane is modified by insertion of chlamydial antigens. Once the EB has entered the cell, it reorganizes into an RB, which is larger (0.5–1 μm) and contains more RNA. After ~8 h, the RB starts to divide by binary fission. The intracytoplasmic, membrane-bound inclusion body containing the RBs increases in size as the RBs multiply. Approximately 18–24 h after infection of the cell, these RBs begin to become EBs by a reorganization or condensation process that is poorly understood. After rupture of the inclusion body, the EBs are released to initiate another cycle of infection.

Chlamydiae are susceptible to many broad-spectrum antibiotics and possess a number of enzymes, but they have a very restricted metabolic capacity. None of these

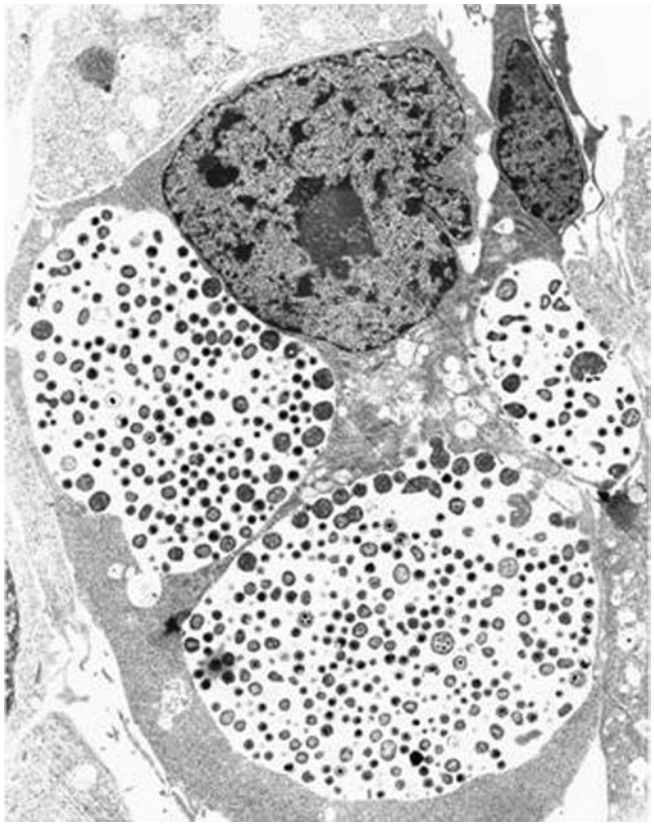


FIGURE 81-1
Chlamydial intracellular inclusions filled with smaller dense elementary bodies and larger reticulate bodies. (*Reprinted with permission from WE Stamm: Chlamydial infections, in Harrison's Principles of Internal Medicine, 17th ed, AS Fauci et al [eds]. New York, McGraw-Hill, 2008, p 1070.*)

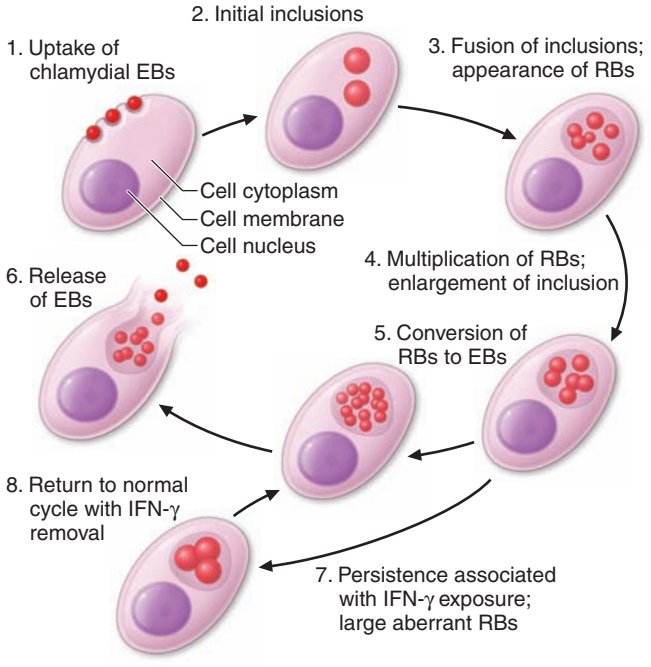


FIGURE 81-2
Chlamydial life cycle. EBs, elementary bodies; RBs, reticulate bodies; IFN-γ, interferon γ. (*Reprinted with permission from WE Stamm: Chlamydial infections, in Harrison's Principles of Internal Medicine, 17th ed, AS Fauci et al [eds]. New York, McGraw-Hill, 2008, p 1071.*)

metabolic reactions results in the production of energy. Chlamydiae have thus been considered to be energy parasites that use the ATP produced by the host cell for their own metabolic functions. Many aspects of chlamydial molecular biology are not well understood, but the sequencing of several chlamydial genomes and new proteomics research have provided researchers with many relevant tools for elucidating the biology of the life cycle.

PATHOGENESIS

Genital infections are mostly caused by *C. trachomatis* serovars D–K, with serovars D, E, and F involved most often. Molecular typing of the major outer-membrane protein gene (*omp1*) from which serovar differences arise has been used to demonstrate that polymorphisms can occur in isolates from patients who are exposed frequently to multiple infections, while less variation is observed in isolates from less sexually active populations. Polymorphisms in the major outer-membrane protein may provide antigenic variation, and the different forms allow persistence in the community because immunity to one is not protective against the others.

The trachoma biovar is essentially a parasite of squamocolumnar epithelial cells; the LGV biovar is more invasive and involves lymphoid cells. As is typical of chlamydiae, *C. trachomatis* strains are capable of causing chronic, clinically inapparent, asymptomatic infections. Because the duration of the chlamydial growth cycle is ~48–72 h, the incubation period of sexually transmitted chlamydial infections is relatively long—generally 1–3 weeks. *C. trachomatis* causes cell death as a result of its replicative cycle and can induce cell damage whenever it persists. However, few toxic effects are demonstrated, and cell death because of chlamydial replication is not sufficient to account for disease manifestations, the majority of which are due to immunopathologic mechanisms or nonspecific host responses to the organism or its byproducts.

In recent years, the entire genomes of various chlamydial species have been sequenced, the field of proteomics has become established, host innate immunity has been more precisely delineated, and innovative host cell–chlamydial interaction studies have been conducted. As a result, many insights have been gained into how chlamydiae adapt and replicate in their intracellular environment and produce disease. These insights into pathogenesis include information on the regulation of gene expression, protein localization, the type III secretion system, the roles of CD4+ and CD8+ T lymphocytes in the host response, and T lymphocyte trafficking.

The chlamydial heat-shock protein, which shares antigenic epitopes with similar proteins of other bacteria

and with human heat-shock protein, may sensitize the host, and repeated infections may cause host cell damage. Persistent or recurrent chlamydial infections are associated with fibrosis, scarring, and complications following simple epithelial infections. A common endpoint of these late consequences is scarring of mucous membranes. Genital complications can lead to pelvic inflammatory disease (PID) and its late consequences of infertility, ectopic pregnancy, and chronic pelvic pain, while ocular infections may lead to blinding trachoma. High levels of antibody to human heat-shock protein have been associated with tubal factor infertility and ectopic pregnancy. Without adequate therapy, chlamydial infections may persist for several years, although symptoms—if present—usually abate.

Pathogenic mechanisms of *C. pneumoniae* have yet to be completely elucidated. The same is true for *C. psittaci,* except that this agent infects cells very efficiently and causes disease that may reflect direct cytopathic effects.

CHLAMYDIA TRACHOMATIS INFECTIONS

GENITAL INFECTIONS

Spectrum

Although chlamydiae cause a number of human diseases, localized lower genital tract infections caused by *C. trachomatis* and the sequelae of such infections are the most important in terms of medical and economic impact. Oculogenital infections due to *C. trachomatis* serovars D–K are transmitted during sexual contact or from mother to baby during childbirth and are associated with many syndromes, including cervicitis, salpingitis, acute urethral syndrome, endometritis, ectopic pregnancy, infertility, and PID in female patients; urethritis, proctitis, and epididymitis in male patients; and conjunctivitis and pneumonia in infants. Women bear the greatest burden of morbidity because of the serious sequelae of these infections. Untreated infections lead to PID, and multiple episodes of PID can lead to tubal factor infertility and chronic pelvic pain. Studies estimate that up to 80–90% of women and >50% of men with *C. trachomatis* genital infections lack symptoms; other patients have very mild symptoms. Thus, a large reservoir of infected persons continues to transmit infection to sexual partners.

As their designations reflect, the LGV serovars (L_1, L_2, and L_3) cause LGV, an invasive sexually transmitted disease (STD) characterized by acute lymphadenitis with bubo formation and/or acute hemorrhagic proctitis (see "Lymphogranuloma Venereum," later in the chapter).

Epidemiology

C. trachomatis genital infections are global in distribution. The World Health Organization (WHO) estimates that >89 million cases occur annually worldwide. In the United States, these infections are the most commonly reported of all infectious diseases. In 2009, 1.24 million cases were reported to the U.S. Centers for Disease Control and Prevention (CDC); however, the CDC estimates that 2–3 million new cases occur per year, with substantial underreporting due to lack of screening in some populations. Rates of infection increase every year; higher rates among women than among men reflect the focus on expansion of screening programs in women during the past 20 years, the use of increasingly sensitive diagnostic tests, an increased emphasis on case reporting, and improvements in the information systems used for reporting. The CDC and other professional organizations recommend annual screening of all sexually active women ≥25 years of age as well as rescreening of previously infected individuals at 3 months. Young women have the highest infection rates; in 2008, the figures were 3275.8 and 3179.9 cases per 100,000 population at 15–19 and 20–24 years of age, respectively. Age-specific rates among men, while much lower than those among women, were highest in the 20- to 24-year-old age group, at 1056.1 cases per 100,000. In 2008, rates increased for all racial and ethnic groups; however, the rate among blacks was more than eight times higher than that among whites, with 1519.3 and 173.6 cases per 100,000, respectively. The rates among American Indian/Alaska Natives (808.8) and Latinos (510.4) were 4.7 and 2.9 times higher, respectively, than that among whites. These disparities are important reflections of health inequities in the United States.

The earlier statistics are based on case reporting. Studies based on screening surveys estimate that the U.S. prevalence of *C. trachomatis* cervical infection is 5% among asymptomatic female college students and prenatal patients, >10% for women seen in family planning clinics, and >20% for women seen in STD clinics. The prevalence of genital *C. trachomatis* infections varies substantially by geographic locale, with the highest rates in the southeastern United States. However, asymptomatic infections have been detected in >8–10% of young female military recruits from all parts of the country. The prevalence of *C. trachomatis* in the cervix of pregnant women is 5–10 times higher than that of *Neisseria gonorrhoeae*. The prevalence of genital infection with either agent is highest among women who are between the ages of 18 and 24, single, and non-Caucasian (e.g., African-American, Latina, Asian, Pacific Islander). Recurrent infections occur frequently in these same risk groups and are often acquired from untreated sexual partners. The use of oral contraception and the presence of cervical ectopy also confer an increased risk. The proportion of infections that are asymptomatic appears to be higher for *C. trachomatis* than for *N. gonorrhoeae*, and symptomatic *C. trachomatis* infections are clinically less severe. Mild or asymptomatic *C. trachomatis* infections of the fallopian tubes nonetheless cause ongoing tubal damage and infertility. The costs of *C. trachomatis* infections and their complications to the U.S. health care system are projected to be >$2.4 billion annually.

Clinical manifestations

Nongonococcal and postgonococcal urethritis

C. trachomatis is the most common cause of nongonococcal urethritis (NGU) and postgonococcal urethritis (PGU). The designation *PGU* refers to NGU developing in men 2–3 weeks after treatment of gonococcal urethritis with single doses of agents such as penicillin or cephalosporins, which lack antimicrobial activity against chlamydiae. Since current treatment regimens for gonorrhea have evolved and now include combination therapy with tetracycline, doxycycline, or azithromycin—all of which are effective against concomitant chlamydial infection—both the incidence of PGU and the causative role of *C. trachomatis* in this syndrome have declined.

In the United States, most of the estimated 2 million cases of acute urethritis are NGU, and *C. trachomatis* is implicated in 30–50% of these cases. The cause of most of the remaining cases of NGU is uncertain, but recent evidence suggests that *Ureaplasma urealyticum*, *Mycoplasma genitalium*, *Trichomonas vaginalis*, and herpes simplex virus (HSV) cause some cases. The rate of involvement of *C. trachomatis* in urethral infection ranges from 3–7% among asymptomatic men to 15–20% among symptomatic men attending STD clinics. One recent multisite study of men in Baltimore, Seattle, Denver, and San Francisco reported an overall chlamydial prevalence of 7% in urine samples assessed by nucleic acid amplification tests (NAATs). As in women, infection in men is age related, with young age as the greatest risk factor for chlamydial urethritis. The prevalence among men is highest at 20–24 years of age. In STD clinics, urethritis is usually less prevalent among men who have sex with men (MSM) than among heterosexual men and is almost always much more common among black men than among white men. One study reported prevalences of 19% and 9% among nonwhite and white heterosexual men, respectively.

NGU is diagnosed by documentation of a leukocytic urethral exudate and by exclusion of gonorrhea by Gram's staining or culture. *C. trachomatis* urethritis is generally less severe than gonococcal urethritis, although in any individual patient these two forms of urethritis cannot reliably be differentiated solely on clinical grounds. Symptoms include urethral discharge (often whitish and mucoid rather than frankly purulent), dysuria, and urethral itching. Physical examination may reveal meatal erythema and tenderness as well as a urethral exudate that is often demonstrable only by stripping of the urethra.

At least one-third of male patients with *C. trachomatis* urethral infection have no evident signs or symptoms of urethritis. The availability of NAATs for first-void urine specimens has facilitated broader-based testing for asymptomatic infection in male patients. As a result, asymptomatic chlamydial urethritis has been demonstrated in 5–10% of sexually active male adolescents screened at school-based clinics or community centers. Such patients generally have pyuria (≥15 leukocytes per 400× microscopic field in the sediment of first-void urine), a positive leukocyte esterase test, or an increased number of leukocytes on a Gram-stained smear prepared from a urogenital swab inserted 1–2 cm into the anterior urethra. To differentiate between true urethritis and functional symptoms in symptomatic patients or to make a presumptive diagnosis of *C. trachomatis* infection in high-risk but asymptomatic men (e.g., male patients in STD clinics, sex partners of women with nongonococcal salpingitis or mucopurulent cervicitis, fathers of children with inclusion conjunctivitis), the examination of an endourethral specimen for increased leukocytes is useful if specific diagnostic tests for chlamydiae are not available. Alternatively, urethritis can be assayed noninvasively by examination of a first-void urine sample for pyuria, either by microscopy or by the leukocyte esterase test. Urine (or a urethral swab) can also be tested directly for chlamydiae by DNA amplification methods, as described later (see "Detection Methods").

Epididymitis

Chlamydial urethritis may be followed by acute epididymitis, but this condition is rare, generally occurring in sexually active patients <35 years of age; in older men, epididymitis is usually associated with gram-negative bacterial infection and/or instrumentation procedures. It is estimated that 50–70% of cases of acute epididymitis are caused by *C. trachomatis*. The condition usually presents as unilateral scrotal pain with tenderness, swelling, and fever in a young man, often occurring in association with chlamydial urethritis. The illness may be mild enough to treat with oral antibiotics on an outpatient basis or severe enough to require hospitalization and parenteral therapy. Testicular torsion should be excluded promptly by radionuclide scan, Doppler flow study, or surgical exploration in a teenager or young adult who presents with acute unilateral testicular pain without urethritis. The possibility of testicular tumor or chronic infection (e.g., tuberculosis) should be excluded when a patient with unilateral intrascrotal pain and swelling does not respond to appropriate antimicrobial therapy.

Reactive arthritis

Reactive arthritis consists of conjunctivitis, urethritis (or, in female patients, cervicitis), arthritis, and characteristic mucocutaneous lesions. It may develop in 1–2% of cases of NGU and is thought to be the most common type of peripheral inflammatory arthritis in young men. *C. trachomatis* has been recovered from the urethra of 16–44% of patients with reactive arthritis and from 69% of men who have signs of urogenital inflammation at the time of examination. Antibodies to *C. trachomatis* have also been detected in 46–67% of patients with reactive arthritis, and *Chlamydia*-specific cell-mediated immunity has been documented in 72%. In addition, *C. trachomatis* has been isolated from synovial biopsy samples from 15 of 29 patients in a number of small series and from a smaller proportion of synovial fluid specimens. Chlamydial nucleic acids have been identified in synovial membranes and chlamydial EBs in

joint fluid. The pathogenesis of reactive arthritis is unclear, but this condition probably represents an abnormal host response to a number of infectious agents, including those associated with bacterial gastroenteritis (e.g., *Salmonella*, *Shigella*, *Yersinia*, or *Campylobacter*) or to infection with *C. trachomatis* or *N. gonorrhoeae*. Since >80% of affected patients have the HLA-B27 phenotype and since other mucosal infections produce an identical syndrome, chlamydial infection is thought to initiate an aberrant hyperactive immune response that produces inflammation of the involved target organs in these genetically predisposed individuals. Evidence of exaggerated cell-mediated and humoral immune responses to chlamydial antigens in reactive arthritis supports this hypothesis. The finding of chlamydial EBs and DNA in joint fluid and synovial tissue from patients with reactive arthritis suggests that chlamydiae may actually spread from genital to joint tissues in these patients—perhaps in macrophages.

NGU is the initial manifestation of reactive arthritis in 80% of patients, typically occurring within 14 days after sexual exposure. The urethritis may be mild and may even go unnoticed by the patient. Similarly, gonococcal urethritis may precede reactive arthritis, but co-infection with an agent of NGU is difficult to rule out. The urethral discharge may be purulent or mucopurulent, and patients may or may not report dysuria. Accompanying prostatitis, usually asymptomatic, has been described. Arthritis usually begins ~4 weeks after the onset of urethritis but may develop sooner or, in a small percentage of cases, may actually precede urethritis. The knees are most frequently involved; next most commonly affected are the ankles and small joints of the feet. Sacroiliitis, either symmetrical or asymmetrical, is documented in two-thirds of patients. Mild bilateral conjunctivitis, iritis, keratitis, or uveitis is sometimes present but lasts for only a few days. Finally, dermatologic manifestations occur in up to 50% of patients. The initial lesions—usually papules with a central yellow spot—most often involve the soles and palms and, in ~25% of patients, eventually epithelialize and thicken to produce keratoderma blenorrhagicum. Circinate balanitis is usually painless and occurs in fewer than half of patients. The initial episode of reactive arthritis usually lasts 2–6 months.

Proctitis

Primary anal or rectal infections with *C. trachomatis* have been described in women and MSM who practice anal intercourse. In these infections, rectal involvement is initially characterized by severe anorectal pain, a bloody mucopurulent discharge, and tenesmus. Oculogenital serovars D–K and LGV serovars L_1, L_2, and L_3 have been found to cause proctitis. The LGV serovars are far more invasive and cause much more severely symptomatic disease, including severe ulcerative proctocolitis that can be clinically confused with HSV proctitis. Histologically, LGV proctitis may resemble Crohn's disease in that giant cell formation and granulomas are detected. In the United States and Europe, cases of LGV proctitis occur almost exclusively in MSM, many of whom are positive for HIV infection.

The less invasive non-LGV serovars of *C. trachomatis* cause mild proctitis. Many infected individuals are asymptomatic, and in these cases infection is diagnosed only by routine culture or NAAT of rectal swabs. The number of fecal leukocytes is usually abnormal in both asymptomatic and symptomatic cases. Sigmoidoscopy may yield normal findings or may reveal mild inflammatory changes or small erosions or follicles in the lower 10 cm of the rectum. Histologic examination of rectal biopsies generally shows anal crypts and prominent follicles as well as neutrophilic infiltration of the lamina propria. Chlamydial proctitis is best diagnosed by isolation of *C. trachomatis* from the rectum and documentation of a response to appropriate therapy. NAATs are reportedly more sensitive than culture for diagnosis and are also specific.

Mucopurulent cervicitis

Although many women with chlamydial infections of the cervix have no symptoms, almost half generally have local signs of infection on examination. Cervicitis is usually characterized by the presence of a mucopurulent discharge, with >20 neutrophils per microscopic field visible in strands of cervical mucus in a thinly smeared, gram-stained preparation of endocervical exudate. Hypertrophic ectopy of the cervix may also be evident as an edematous area near the cervical os that is congested and bleeds easily on minor trauma (e.g., when a specimen is collected with a swab). A Papanicolaou smear shows increased numbers of neutrophils as well as a characteristic pattern of mononuclear inflammatory cells including plasma cells, transformed lymphocytes, and histiocytes. Cervical biopsy shows a predominantly mononuclear cell infiltrate of the subepithelial stroma. Clinical experience and collaborative studies indicate that a cutoff of >30 polymorphonuclear leukocytes (PMNs)/1000× field in a gram-stained smear of cervical mucus correlates best with chlamydial or gonococcal cervicitis.

Clinical recognition of chlamydial cervicitis depends on a high index of suspicion and careful cervical examination. No genital symptoms are specifically correlated with chlamydial cervical infection. The differential diagnosis of a mucopurulent discharge from the endocervical canal in a young, sexually active woman includes gonococcal endocervicitis, salpingitis, endometritis, and intrauterine contraceptive device–induced inflammation. Diagnosis of cervicitis is based on the presence of PMNs on a cervical swab as noted earlier; the presence of chlamydiae is confirmed by either culture or NAAT.

Pelvic inflammatory disease

Inflammation of sections of the fallopian tube is often referred to as salpingitis or PID. The proportion of acute salpingitis cases caused by *C. trachomatis* varies geographically and with the population studied. It has been estimated that *C. trachomatis* causes up to 50% of PID cases in the United States. PID occurs via ascending intraluminal spread of *C. trachomatis* or *N. gonorrhoeae* from the lower genital tract. Mucopurulent cervicitis is often followed by endometritis, endosalpingitis, and

finally pelvic peritonitis. Evidence of mucopurulent cervicitis is often found in women with laparoscopically verified salpingitis. Similarly, endometritis, demonstrated by an endometrial biopsy showing plasma cell infiltration of the endometrial epithelium, is documented in most women with laparoscopy-verified chlamydial (or gonococcal) salpingitis. Chlamydial endometritis can also occur in the absence of clinical evidence of salpingitis. Histologic evidence of endometritis has been correlated with a syndrome consisting of vaginal bleeding, lower abdominal pain, and uterine tenderness in the absence of adnexal tenderness. Chlamydial salpingitis produces milder symptoms than gonococcal salpingitis and may be associated with less marked adnexal tenderness. Thus, mild adnexal or uterine tenderness in a sexually active woman with cervicitis suggests chlamydial PID.

Chronic untreated endometrial and tubal inflammation can result in tubal scarring, impaired tubal function, tubal occlusion, and infertility even among women who report no prior treatment for PID. *C. trachomatis* has been particularly implicated in "subclinical" PID on the basis of a lack of history of PID among *Chlamydia*-seropositive women with tubal damage and detection of chlamydial DNA or antigen among asymptomatic women with tubal infertility. These data suggest that the best method to prevent PID and its sequelae is surveillance and control of lower genital tract infections along with diagnosis and treatment of sex partners and prevention of reinfections. Promotion of early symptom recognition and health care presentation may reduce the frequency and severity of sequelae of PID.

Perihepatitis

The Fitz-Hugh–Curtis syndrome was originally described as a complication of gonococcal PID. However, studies over the past several decades have suggested that chlamydial infection is more commonly associated with perihepatitis than is *N. gonorrhoeae*. Perihepatitis should be suspected in young, sexually active women who develop right-upper-quadrant pain, fever, or nausea. Evidence of salpingitis may or may not be found on examination. Frequently, perihepatitis is strongly associated with extensive tubal scarring, adhesions, and inflammation observed at laparoscopy, and high titers of antibody to the 57-kDa chlamydial heat-shock protein have been documented. Culture and/or serologic evidence of *C. trachomatis* is found in three-fourths of women with this syndrome.

Urethral syndrome in women

In the absence of infection with uropathogens such as coliforms or *Staphylococcus saprophyticus*, *C. trachomatis* is the pathogen most commonly isolated from college women with dysuria, frequency, and pyuria. Screening studies can recover *C. trachomatis* at both the cervix and the urethra; in up to 25% of infected women, the organism is isolated only from the urethra. The urethral syndrome in women consists of dysuria and frequency in conjunction with chlamydial urethritis, pyuria, and no bacteriuria or urinary pathogens. Although symptoms of the urethral syndrome may develop in some women with chlamydial infection, the majority of women attending STD clinics for urethral chlamydial infection do not have dysuria or frequency. Even in women with chlamydial urethritis causing the acute urethral syndrome, signs of urethritis such as urethral discharge, meatal redness, and swelling are uncommon. However, mucopurulent cervicitis in a woman presenting with dysuria and frequency strongly suggests *C. trachomatis* urethritis. Other correlates of chlamydial urethral syndrome include a duration of dysuria of >7–10 days, lack of hematuria, and lack of suprapubic tenderness. Abnormal urethral Gram's stains showing >10 PMNs/1000x field in women with dysuria but without coliform bacteriuria support the diagnosis of chlamydial urethritis. Other possible diagnoses include gonococcal or trichomonal infection of the urethra.

Infection in pregnancy and the neonatal period

Infections during pregnancy can be transmitted to infants during delivery. Approximately 20–30% of infants exposed to *C. trachomatis* in the birth canal develop conjunctivitis, and 10–15% subsequently develop pneumonia. Consequently, all newborn infants receive ocular prophylaxis at birth to prevent ophthalmia neonatorum. Without treatment, conjunctivitis usually develops at 5–19 days of life and often results in a profuse mucopurulent discharge. Roughly half of infected infants develop clinical evidence of inclusion conjunctivitis. However, it is impossible to differentiate chlamydial conjunctivitis from other forms of neonatal conjunctivitis (e.g., that due to *N. gonorrhoeae*, *Haemophilus influenzae*, *Streptococcus pneumoniae*, or HSV) on clinical grounds; thus laboratory diagnosis is required. Inclusions within epithelial cells are often detected in Giemsa-stained conjunctival smears, but these smears are considerably less sensitive than cultures or NAATs for chlamydiae. Gram-stained smears may show gonococci or occasional small gram-negative coccobacilli in *Haemophilus* conjunctivitis, but smears should be accompanied by cultures or NAATs for these agents.

C. trachomatis has also been isolated frequently and persistently from the nasopharynx, rectum, and vagina of infected infants—occasionally for >1 year in the absence of treatment. In some cases, otitis media results from perinatally acquired chlamydial infection. Pneumonia may develop in infants from 2 weeks to 4 months of age. *C. trachomatis* is estimated to cause 20–30% of pneumonia cases in infants <6 months of age. Epidemiologic studies have linked chlamydial pulmonary infection in infants with increased occurrence of subacute lung disease (bronchitis, asthma, wheezing) in later childhood.

Lymphogranuloma venereum

C. trachomatis serovars L_1, L_2, and L_3 cause LGV, an invasive systemic STD. The peak incidence of LGV corresponds with the age of greatest sexual activity: the second and third decades of life. The worldwide incidence of LGV is falling, but the disease is still endemic and a major cause of morbidity in parts of Asia, Africa, South America, and the Caribbean. LGV is rare in industrialized countries; for more than a decade,

the reported incidence in the United States has been only 0.1 case per 100,000 population. In the Bahamas, an apparent outbreak of LGV was described in association with a concurrent increase in heterosexual infection with HIV. Reports of outbreaks with the newly identified variant L_{2b} in Europe, Australia, and the United States indicate that LGV is becoming more prevalent among MSM. These cases have usually presented as hemorrhagic proctocolitis in HIV-positive men. More widespread use of NAATs for identification of rectal infections may have enhanced case recognition.

The frequency of infection following exposure is believed to be much lower for LGV than for gonorrhea and syphilis. Early manifestations are recognized more often in men than in women, who usually present with late complications. In the United States, where the reported male-to-female ratio of cases is 3.4:1, most cases involve MSM and persons returning from abroad (travelers, sailors, and military personnel).

LGV begins as a small painless papule that tends to ulcerate at the site of inoculation, often escaping attention. This primary lesion heals in a few days without scarring and, even when noticed, is usually recognized as LGV only in retrospect. LGV strains of *C. trachomatis* have occasionally been recovered from genital ulcers and from the urethra of men and the endocervix of women who present with inguinal adenopathy; these areas may be the primary sites of infection in some cases. Proctitis is more common among people who practice receptive anal intercourse, and an elevated white blood cell count in anorectal smears may predict LGV in these patients. Ulcer formation may facilitate transmission of HIV infection and other sexually transmitted and blood-borne diseases.

As NAATs for *C. trachomatis* are being used more often, increasing numbers of cases of LGV proctitis are being recognized in MSM. Such patients present with anorectal pain and mucopurulent, bloody rectal discharge. Although these patients may report diarrhea, they are often referring not to diarrhea but rather to frequent, painful, unsuccessful attempts at defecation (tenesmus). Sigmoidoscopy reveals ulcerative proctitis or proctocolitis, with purulent exudate and mucosal bleeding. Histopathologic findings in the rectal mucosa include granulomas with giant cells, crypt abscesses, and extensive inflammation. These clinical, sigmoidoscopic, and histopathologic findings may closely resemble those of Crohn's disease of the rectum.

The most common presenting picture in heterosexual men and women is the *inguinal syndrome*, which is characterized by painful inguinal lymphadenopathy beginning 2–6 weeks after presumed exposure; in rare instances, the onset comes after a few months. The inguinal adenopathy is unilateral in two-thirds of cases, and palpable enlargement of the iliac and femoral nodes is often evident on the same side as the enlarged inguinal nodes. The nodes are initially discrete, but progressive periadenitis results in a matted mass of nodes that becomes fluctuant and suppurative. The overlying skin becomes fixed, inflamed, and thin, and multiple draining fistulas finally develop. Extensive enlargement of chains of inguinal nodes above and below the inguinal ligament ("the sign of the groove") is not specific and, although not uncommon, is documented in only a minority of cases. On histologic examination, infected nodes are initially found to have characteristic small stellate abscesses surrounded by histiocytes. These abscesses coalesce to form large, necrotic, suppurative foci. Spontaneous healing usually takes place after several months; inguinal scars or granulomatous masses of various sizes persist for life. Massive pelvic lymphadenopathy may lead to exploratory laparotomy.

Constitutional symptoms are common during the stage of regional lymphadenopathy and, in cases of proctitis, may include fever, chills, headache, meningismus, anorexia, myalgias, and arthralgias. These findings in the presence of lymphadenopathy are sometimes mistakenly interpreted as malignant lymphoma. Other systemic complications are infrequent but include arthritis with sterile effusion, aseptic meningitis, meningoencephalitis, conjunctivitis, hepatitis, and erythema nodosum (Fig. 11-40). *C. trachomatis* has been recovered from the cerebrospinal fluid and in one case was isolated from the blood of a patient with severe constitutional symptoms—a result indicating dissemination of infection. Laboratory-acquired infections suspected of being due to the inhalation of aerosols have been associated with mediastinal lymphadenitis, pneumonitis, and pleural effusion.

Complications of untreated anorectal infection include perirectal abscess; anal fistulas; and rectovaginal, rectovesical, and ischiorectal fistulas. Secondary bacterial infection probably contributes to these complications. Rectal stricture is a late complication of anorectal infection and usually develops 2–6 cm from the anal orifice—i.e., at a site within reach on digital rectal examination. Proximal extension of the stricture for several centimeters may lead to a mistaken clinical and radiographic diagnosis of carcinoma. A small percentage of cases of LGV in men present as chronic progressive infiltrative, ulcerative, or fistular lesions of the penis, urethra, or scrotum. Associated lymphatic obstruction may produce elephantiasis. When urethral stricture occurs, it usually involves the posterior urethra and causes incontinence or difficulty with urination.

Diagnosis

Detection methods

Historically, chlamydiae were cultivated in the yolk sac of embryonated eggs. The organisms can be grown more easily in tissue culture, but cell culture—once considered the diagnostic gold standard—has been replaced by nonculture assays **(Table 81-1)**. In general, culture for chlamydiae in clinical specimens is now performed only in specialized laboratories. The first nonculture assays, such as DFA staining of clinical material and enzyme immunoassay (EIA), have been replaced by molecular tests that amplify the nucleic acids in clinical specimens. These NAATS are currently recommended by the CDC as the diagnostic assays of choice.

TABLE 81-1

DIAGNOSTIC TESTS FOR SEXUALLY TRANSMITTED AND PERINATAL *CHLAMYDIA TRACHOMATIS* INFECTION

INFECTION	SUGGESTIVE SIGNS/SYMPTOMS	PRESUMPTIVE DIAGNOSIS[a]	CONFIRMATORY TEST OF CHOICE
Men			
NGU, PGU	Discharge, dysuria	Gram's stain with >4 neutrophils per oil-immersion field; no gonococci	Urine or urethral NAAT for *C. trachomatis*
Epididymitis	Unilateral intrascrotal swelling, pain, tenderness; fever; NGU	Gram's stain with >4 neutrophils per oil-immersion field; no gonococci; urinalysis with pyuria	Urine or urethral NAAT for *C. trachomatis*
Women			
Cervicitis	Mucopurulent cervical discharge, bleeding and edema of the zone of cervical ectopy	Cervical Gram's stain with ≥20 neutrophils per oil-immersion field in cervical mucus	Urine, cervical, or vaginal NAAT for *C. trachomatis*
Salpingitis	Lower abdominal pain, cervical motion tenderness, adnexal tenderness or masses	*C. trachomatis* always potentially present in salpingitis	Urine, cervical, or vaginal NAAT for *C. trachomatis*
Urethritis	Dysuria and frequency without hematuria	MPC; sterile pyuria; negative routine urine culture	Urine or urethral NAAT for *C. trachomatis*
Adults of Either Sex			
Proctitis	Rectal pain, discharge, tenesmus, bleeding; history of receptive anorectal intercourse	Negative gonococcal culture and Gram's stain; at least 1 neutrophil per oil-immersion field in rectal Gram's stain	Rectal NAAT for *C. trachomatis* or culture
Reactive arthritis	NGU, arthritis, conjunctivitis, typical skin lesions	Gram's stain with >4 neutrophils per oil-immersion field; lack of gonococci indicative of NGU	Urine or urethral NAAT for *C. trachomatis*
LGV	Regional adenopathy, primary lesion, proctitis, systemic symptoms	None	Culture of LGV strain from node or rectum, occasionally from urethra or cervix; NAAT for *C. trachomatis* from these sites; LGV CF titer, ≥1:64; micro-IF titer, ≥1:512
Neonates			
Conjunctivitis	Purulent conjunctival discharge 6–18 days after delivery	Negative culture and Gram's stain for gonococci, *Haemophilus* spp., pneumococci, staphylococci	Conjunctival NAAT for *C. trachomatis*; FA-stained scraping of conjunctival material
Infant pneumonia	Afebrile, staccato cough, diffuse rales, bilateral hyperinflation, interstitial infiltrates	None	Chlamydial culture or NAAT of sputum, pharynx, eye, rectum; micro-IF antibody to *C. trachomatis*—fourfold change in IgG or IgM antibody titer

[a]A presumptive diagnosis of chlamydial infection is often made in the syndromes listed when gonococci are not found. A positive test for *Neisseria gonorrhoeae* does not exclude the involvement of *C. trachomatis*, which often is present in patients with gonorrhea.

Abbreviations: CF, complement-fixing; FA, fluorescent antibody; LGV, lymphogranuloma venereum; micro-IF, microimmunofluorescence; MPC, mucopurulent cervicitis; NAAT, nucleic acid amplification test; NGU, nongonococcal urethritis; PGU, postgonococcal urethritis.

Source: Reprinted with permission from WE Stamm: Chlamydial infections, in *Harrison's Principles of Internal Medicine*, 17th ed, AS Fauci et al (eds). New York, McGraw-Hill, 2008, p 1075.

Choice of specimen

Cervical and urethral swabs have traditionally been used for the diagnosis of STDs in female and male patients, respectively. However, given the greatly increased sensitivity and specificity of NAATs, less invasive samples (e.g., urine for both sexes and vaginal swabs for women) can be used. For screening of asymptomatic women, the CDC now recommends that self-collected vaginal swabs, which are slightly more sensitive than urine, be used. Urine screening tests are often used in outreach

screening programs, however. For symptomatic women undergoing a pelvic examination, cervical swab samples are desirable because they have slightly higher chlamydial counts. For male patients, a urine specimen is the sample of choice.

Alternative specimen types

Ocular samples from babies and adults can be assessed by NAATs. However, since commercial NAATs for this purpose have not yet been approved by the U.S. Food and Drug Administration (FDA), laboratories must perform their own verification studies. Samples from rectal and pharyngeal sites have been used successfully to detect chlamydiae, but again, laboratories must verify test performance.

Other diagnostic issues

Because NAATs measure nucleic acids instead of live organisms, they should be used with caution as test-of-cure assays. Residual nucleic acid from cells rendered noninfective by antibiotics may continue to yield a positive result in NAATs until as long as 3 weeks after therapy, when viable organisms have actually been eradicated. Therefore, clinicians should not use NAATs for test of cure until after 3 weeks. The CDC currently does not recommend a test of cure after treatment for infection with *C. trachomatis*. However, because incidence studies have demonstrated that previous chlamydial infection increases the probability of becoming reinfected, the CDC does recommend that previously infected individuals be rescreened 3 months after treatment.

Serology

Serologic testing may be helpful in the diagnosis of LGV and neonatal pneumonia caused by *C. trachomatis*. The serologic test of choice is the microimmunofluorescence (MIF) test, in which high-titer purified EBs mixed with embryonated chicken yolk sac material are affixed to a glass microscope slide to which dilutions of sera are applied. After incubation and washing, fluorescein-conjugated IgG or IgM antibody is applied. The test is read with an epifluorescence microscope, with the highest dilution of serum producing visible fluorescence designated as the titer. The MIF test is not widely available and is highly labor intensive. Although the complement fixation (CF) test can also be used, it employs only lipopolysaccharide (LPS) as the antigen and therefore identifies the pathogen only to the genus level. Single-point titers of >1:64 support a diagnosis of LGV, in which it is difficult to demonstrate rising antibody titers—i.e., paired serum samples are difficult to obtain since, by its very nature, the disease results in the patient's being seen by the physician after the acute stage. Any antibody titer of >1:16 is considered significant evidence of exposure to chlamydiae. However, serologic testing is not recommended for diagnosis of uncomplicated genital infections of the cervix, urethra, and lower genital tract or for *C. trachomatis* screening of asymptomatic individuals.

TREATMENT *C. trachomatis* Genital Infections

A 7-day course of tetracycline (500 mg four times daily), doxycycline (100 mg twice daily), erythromycin (500 mg four times daily), or a fluoroquinolone (ofloxacin, 300 mg twice daily; or levofloxacin, 500 mg/d) can be used for treatment of uncomplicated chlamydial infections. A single 1-g oral dose of azithromycin is as effective as a 7-day course of doxycycline for the treatment of uncomplicated genital *C. trachomatis* infections in adults. Azithromycin causes fewer adverse gastrointestinal reactions than do older macrolides such as erythromycin. The single-dose regimen of azithromycin has great appeal for the treatment of patients with uncomplicated chlamydial infection (especially those without symptoms and those with a likelihood of poor compliance) and of the sexual partners of infected patients. These advantages must be weighed against the considerably greater cost of azithromycin. Whenever possible, the single 1-g dose should be given as directly observed therapy. Although not approved by the FDA for use in pregnancy, this regimen appears to be safe and effective for this purpose. However, amoxicillin (500 mg three times daily for 7 days) can also be given to pregnant women. The fluoroquinolones are contraindicated in pregnancy. A 2-week course of treatment is recommended for complicated chlamydial infections (e.g., PID, epididymitis) and at least a 3-week course of doxycycline (100 mg orally twice daily) or erythromycin base (500 mg orally four times daily) for LGV. Failure of treatment with a tetracycline in genital infections usually indicates poor compliance or reinfection rather than involvement of a drug-resistant strain. To date, clinically significant drug resistance has not been observed in *C. trachomatis*.

Treatment or testing for chlamydiae should be considered among *N. gonorrhoeae*–infected patients because of the frequency of co-infection. Systemic treatment with erythromycin has been recommended for ophthalmia neonatorum and for *C. trachomatis* pneumonia in infants. For the treatment of adult inclusion onjunctivitis, a single 1-g dose of azithromycin was as effective as standard 10-day treatment with doxycycline. Recommended treatment regimens for both bubonic and anogenital LGV include tetracycline, doxycycline, or erythromycin for 21 days.

SEX PARTNERS The continued high prevalence of chlamydial infections in most parts of the United States is due primarily to the failure to diagnose—and therefore treat—patients with symptomatic or asymptomatic infection and their sex partners. Urethral or cervical infection with *C. trachomatis* has been well documented in a high proportion of the sex partners of patients with NGU, epididymitis, reactive arthritis, salpingitis, and endocervicitis. If possible, confirmatory laboratory tests for chlamydiae should be undertaken in these individuals, but even those without positive tests or evidence of clinical disease who have recently been exposed to proven or possible chlamydial infection (e.g., NGU)

should be offered therapy. A novel approach is partner-delivered therapy, in which infected patients receive treatment and are also provided with single-dose azithromycin to give to their sex partner(s).

NEONATES AND INFANTS In neonates with conjunctivitis or infants with pneumonia, erythromycin ethylsuccinate or estolate can be given orally at a dosage of 50 mg/kg per day, preferably in four divided doses, for 2 weeks. Careful attention must be given to compliance with therapy—a frequent problem. Relapses of eye infection are common after topical treatment with erythromycin or tetracycline ophthalmic ointment and may also follow oral erythromycin therapy. Thus follow-up cultures should be performed after treatment. Both parents should be examined for *C. trachomatis* infection and, if diagnostic testing is not readily available, should be treated with doxycycline or azithromycin.

Prevention

Since many chlamydial infections are asymptomatic, effective control and prevention must involve periodic screening of individuals at risk. Selective cost-effective screening criteria have been developed. Among women, young age (generally <25 years) is a critical risk factor for chlamydial infections in nearly all studies. Other risk factors include mucopurulent cervicitis; multiple, new, or symptomatic male sex partners; and lack of barrier contraceptive use. In some settings, screening based on young age may be as sensitive as criteria that incorporate behavioral and clinical measures. Another strategy is universal testing of all patients in high-prevalence clinic populations (e.g., STD clinics, juvenile detention facilities, and family planning clinics).

The effectiveness of selective screening in reducing the prevalence of chlamydial infection among women has been demonstrated in several studies. In the Pacific Northwest, where extensive screening began in family planning clinics in 1998 and in STD clinics in 1993, the prevalence declined from 10% in the 1980s to <5% in 2000. Similar trends have occurred in association with screening programs elsewhere. In addition, screening can effect a reduction in upper genital tract disease. In Seattle, women at a large health maintenance organization who were screened for chlamydial infection on a routine basis had a lower incidence of symptomatic PID than did women who received standard care and underwent more selective screening.

In settings with low to moderate prevalence, the prevalence at which selective screening becomes more cost-effective than universal screening must be defined. Most studies have concluded that universal screening is preferable in settings with a chlamydial prevalence of >3–7%. Depending on the criteria used, selective screening is likely to be more cost-effective when prevalence falls below 3%. Nearly all regions of the United States have now initiated screening programs, particularly in family planning and STD clinics. Along with single-dose therapy, the availability of highly sensitive and specific diagnostic NAATs using urine specimens and self-obtained vaginal swabs makes it feasible to mount an effective nationwide *Chlamydia* control program, with screening of high-risk individuals in traditional health-care settings and in novel outreach and community-based settings.

TRACHOMA

Epidemiology

Trachoma—a sequela of ocular disease in developing countries—continues to be a leading cause of preventable infectious blindness worldwide. The WHO estimates that ~6 million people have been blinded by trachoma and that ~1.3 million people in developing countries still suffer from preventable blindness due to trachoma; certainly hundreds of millions live in trachoma-endemic areas. Foci of trachoma persist in Australia, the South Pacific, and Latin America. Serovars A, B, Ba, and C are isolated from patients with clinical trachoma in areas of endemicity in developing countries in Africa, the Middle East, Asia, and South America.

The trachoma-hyperendemic areas of the world are in northern and sub-Saharan Africa, the Middle East, drier regions of the Indian subcontinent, and Southeast Asia. In hyperendemic areas, the prevalence of trachoma is essentially 100% by the second or third year of life. Active disease is most common among young children, who are the reservoir for trachoma. By adulthood, active infection is infrequent but sequelae result in blindness. In such areas, trachoma constitutes the major cause of blindness.

Trachoma is transmitted through contact with discharges from the eyes of infected patients. Transmission is most common under poor hygienic conditions and most often takes place between family members or between families with shared facilities. Flies can also transfer the mucopurulent ocular discharges, carrying the organisms on their legs from one person to another. The International Trachoma Initiative founded by the WHO in 1998 aims to eliminate blinding trachoma globally by 2020.

Clinical manifestations

Both endemic trachoma and adult inclusion conjunctivitis present initially as conjunctivitis characterized by small lymphoid follicles in the conjunctiva. In regions with hyperendemic classic blinding trachoma, the disease usually starts insidiously before the age of 2 years. Reinfection is common and probably contributes to the pathogenesis of trachoma. Studies using polymerase chain reaction (PCR) or other NAATs indicate that chlamydial DNA is often present in the ocular secretions of patients with trachoma, even in the absence of positive cultures. Thus persistent infection may be more common than was previously thought.

The cornea becomes involved, with inflammatory leukocytic infiltrations and superficial vascularization (pannus formation). As the inflammation continues,

conjunctival scarring eventually distorts the eyelids, causing them to turn inward so that the lashes constantly abrade the eyeball (trichiasis and entropion); eventually the corneal epithelium is abraded and may ulcerate, with subsequent corneal scarring and blindness. Destruction of the conjunctival goblet cells, lacrimal ducts, and lacrimal gland may produce a "dry-eye" syndrome, with resultant corneal opacity due to drying (xerosis) or secondary bacterial corneal ulcers.

Communities with blinding trachoma often experience seasonal epidemics of conjunctivitis due to *H. influenzae* that contribute to the intensity of the inflammatory process. In such areas, the active infectious process usually resolves spontaneously in affected persons at 10–15 years of age, but conjunctival scars continue to shrink, producing trichiasis and entropion with subsequent corneal scarring in adults. In areas with milder and less prevalent disease, the process may be much slower, with active disease continuing into adulthood; blindness is rare in these cases.

Eye infection with oculogenital *C. trachomatis* strains in sexually active young adults presents as an acute onset of unilateral follicular conjunctivitis and preauricular lymphadenopathy similar to that seen in acute conjunctivitis caused by adenovirus or HSV. If untreated, the disease may persist for 6 weeks to 2 years. It is frequently associated with corneal inflammation in the form of discrete opacities ("infiltrates"), punctate epithelial erosions, and minor degrees of superficial corneal vascularization. Very rarely, conjunctival scarring and eyelid distortion occur, particularly in patients treated for many months with topical glucocorticoids. Recurrent eye infections develop most often in patients whose sexual partners are not treated with antimicrobial agents.

Diagnosis

The clinical diagnosis of classic trachoma can be made if two of the following signs are present: (1) lymphoid follicles on the upper tarsal conjunctiva; (2) typical conjunctival scarring; (3) vascular pannus; or (4) limbal follicles or their sequelae, Herbert's pits. The clinical diagnosis of endemic trachoma should be confirmed by laboratory tests in children with relatively marked degrees of inflammation. Intracytoplasmic chlamydial inclusions are found in 10–60% of Giemsa-stained conjunctival smears in such populations, but chlamydial NAATs are more sensitive and are often positive when smears or cultures are negative. Follicular conjunctivitis in European or American adults living in trachomatous regions is rarely due to trachoma.

TREATMENT Trachoma

Adult inclusion conjunctivitis responds well to treatment with the same regimens used in uncomplicated genital infections—namely, azithromycin (a 1-g single oral dose) or doxycycline (100 mg twice daily for 7 days).

Simultaneous treatment of all sexual partners is necessary to prevent ocular reinfection and chlamydial genital disease. Topical antibiotic treatment is not required for patients who receive systemic antibiotics.

PSITTACOSIS

Psittacine birds and many other avian species act as natural reservoirs for *C. psittaci*–type organisms, common pathogens in domestic mammals and birds. The species *C. psittaci,* which now includes only avian strains, affects humans only as a zoonosis. (The other strains previously included in this species have been placed into different species that reflect the animals they infect: *C. abortus*, *C. muridarum*, *C. suis, C. felis*, and *C. caviae*.) Although all birds are susceptible, pet birds (parrots, parakeets, macaws, and cockatiels) and poultry (turkeys and ducks) are most frequently involved in transmission of *C. psittaci* to humans. Exposure is greatest in poultry-processing workers and in owners of pet birds. Infectious forms of the organisms are shed from both symptomatic and apparently healthy birds and may remain viable for several months. *C. psittaci* can be transmitted to humans by direct contact with infected birds or by inhalation of aerosols from avian nasal discharges and from infectious avian fecal or feather dust. Transmission from person to person has never been demonstrated.

The diagnosis is usually established serologically. Psittacosis in humans may present as acute primary atypical pneumonia (which can be fatal in up to 10% of untreated cases); as severe chronic pneumonia; or as a mild illness or asymptomatic infection in persons exposed to infected birds.

EPIDEMIOLOGY

Fewer than 50 confirmed cases of psittacosis are reported in the United States each year, although many more cases probably occur than are reported. Control of psittacosis depends on control of avian sources of infection. A pandemic of psittacosis was once stopped by banning shipment or importation of psittacine birds. Birds can receive prophylaxis in the form of a tetracycline-containing feed. Imported birds are currently quarantined for 30 days of treatment.

CLINICAL MANIFESTATIONS

Typical symptoms include fever, chills, muscular aches and pains, severe headache, hepato- and/or splenomegaly, and gastrointestinal symptoms. Cardiac complications may involve endocarditis and myocarditis. Fatal cases were common in the preantibiotic era. As a result of quarantine of imported birds and improved veterinary-hygienic measures, outbreaks and sporadic cases of psittacosis are now rare. Severe pneumonia requiring management in an intensive care unit may develop.

Endocarditis, hepatitis, and neurologic complications may occur, and fatal cases have been reported. The incubation period is usually 5–19 days, but can last as long as 28 days.

DIAGNOSIS

Previously, the most widely used serologic test for diagnosing chlamydial infections was the genus-specific CF test, in which assay of paired serum specimens often shows fourfold or greater increases in antibody titer. The CF test remains useful, but the gold standard of serologic tests is now the MIF test, which is not widely available (see section on diagnosis of *C. trachomatis* genital infection, earlier). Any antibody titer above 1:16 is considered significant evidence of exposure to chlamydiae, and a fourfold titer rise in paired sera in combination with a clinically compatible syndrome can be used to diagnose psittacosis. Some commercially available serologic tests based on measurement of antibodies to LPS can be useful when the clinical diagnosis is consistent with bird exposure; however, since these tests are reactive for all chlamydiae (i.e., all chlamydiae contain LPS), caution must be used in their interpretation.

TREATMENT **Psittacosis**

The antibiotic of choice is tetracycline; the dosage for adults is 250 mg four times a day, continued for at least 3 weeks to avoid relapse. Severely ill patients may need cardiovascular and respiratory support. Erythromycin (500 mg four times a day by mouth) is an alternative therapy.

CHLAMYDIA PNEUMONIAE INFECTIONS

C. pneumoniae is a common cause of human respiratory diseases, such as pneumonia and bronchitis. This organism has been reported to account for as many as 10% of cases of community-acquired pneumonia, most of which are diagnosed by serology. Serologic studies have linked *C. pneumoniae* to atherosclerosis; isolation and PCR detection in cardiovascular tissues have also been reported. These findings suggest an expanded range of diseases and syndromes for *C. pneumoniae*. The role of *C. pneumoniae* in the etiology of atherosclerosis has been discussed since 1988, when Finnish researchers presented serologic evidence of an association of this organism with coronary heart disease and acute myocardial infarction. Subsequently, the organism was identified in atherosclerotic lesions by culture, PCR, immunohistochemistry, and transmission electron microscopy; however, discrepant study results (including those of animal studies) and failure of large-scale treatment studies have raised doubts as to the etiologic role of *C. pneumoniae* in atherosclerosis. Large-scale case-cohort studies have recently demonstrated some association of *C. pneumoniae* with lung cancer, as evaluated by serology.

EPIDEMIOLOGY

Primary infection occurs mainly in school-aged children and reinfection in adults. Seroprevalence rates of 40–70% show that *C. pneumoniae* is widespread in both industrialized and developing countries. Seropositivity usually is first detected at school age, and rates generally increase by ~10% per decade. About 50% of individuals have detectable antibody at 30 years of age, and most have detectable antibody by the eighth decade of life. Although serologic evidence suggests that *C. pneumoniae* may be associated with up to 10% of cases of community-acquired pneumonia, most of this evidence is based not on paired serum samples but rather on a single high IgG titer. Some doubt exists about the true prevalence and etiologic role of *C. pneumoniae* in atypical pneumonia, especially since reports of cross-reactivity have raised questions about the specificity of serology when only a single serum sample is used for diagnosis.

PATHOGENESIS

Little is known about the pathogenesis of *C. pneumoniae* infection. It begins in the upper respiratory tract and, in many persons, persists as a prolonged asymptomatic condition of the upper respiratory mucosal surfaces. However, evidence of replication within vascular endothelium and synovial membranes of joints shows that, in at least some individuals, the organism is transported to distant sites, perhaps within macrophages. A *C. pneumoniae* outer-membrane protein may induce host immune responses whose cross-reactivity with human proteins results in an autoimmune reaction.

As mentioned earlier, epidemiologic studies have demonstrated an association between serologic evidence of *C. pneumoniae* infection and atherosclerotic disease of the coronary and other arteries. In addition, *C. pneumoniae* has been identified in atherosclerotic plaques by electron microscopy, DNA hybridization, and immunocytochemistry. The organism has been recovered in culture from atheromatous plaque—a result indicating the presence of viable replicating bacteria in vessels. Evidence from animal models supports the hypothesis that *C. pneumoniae* infection of the upper respiratory tract is followed by recovery of the organism from atheromatous lesions in the aorta and that the infection accelerates the process of atherosclerosis, especially in hypercholesterolemic animals. Antimicrobial treatment of the infected animals reverses the increased risk of atherosclerosis. In humans, two small trials in patients with unstable angina or recent myocardial infarction suggested that antibiotics reduce the likelihood of subsequent untoward cardiac events. However, larger-scale trials have not documented an effect of various antichlamydial regimens on the risk of these events.

CLINICAL MANIFESTATIONS

C. pneumoniae was first reported as the etiologic agent of mild atypical pneumonia in military recruits and college students. The clinical spectrum of *C. pneumoniae* infection includes acute pharyngitis, sinusitis, bronchitis, and pneumonitis, primarily in young adults. The clinical manifestations of primary infection appear to be more severe and prolonged than those of reinfection. The pneumonitis of *C. pneumoniae* pneumonia resembles that of *Mycoplasma* pneumonia in that leukocytosis is frequently lacking and patients often have prominent antecedent upper respiratory tract symptoms, fever, nonproductive cough, mild to moderate illness, minimal findings on chest auscultation, and small segmental infiltrates on chest x-ray. In elderly patients, pneumonia due to *C. pneumoniae* can be especially severe and may necessitate hospitalization and respiratory support.

Chronic infection with *C. pneumoniae* has been reported among patients with chronic obstructive pulmonary disease and may also play a role in the natural history of asthma, including exacerbations. The clinical symptoms of respiratory infections caused by *C. pneumoniae* are nonspecific and do not differ from those caused by other agents of atypical pneumonia, such as *Mycoplasma pneumoniae*.

DIAGNOSIS

Serology, PCR amplification, and culture can be used to diagnose *C. pneumoniae* infection. Serology has been the traditional method of diagnosing infection by *C. pneumoniae*. The gold standard serologic test is the MIF test (see section on diagnosis of *C. trachomatis* genital infection, earlier in chapter). Any antibody titer above 1:16 is considered significant evidence of exposure to chlamydiae. According to a CDC-sponsored expert working group, the diagnosis of acute *C. pneumoniae* infection requires demonstration of a fourfold rise in titer in paired serum samples. There are no official recommendations for diagnosis of chronic infections, although many research studies have used high titers of IgA as an indicator. The older CF tests and EIAs for LPS are not recommended, as they are not specific for *C. pneumoniae* but identify the chlamydiae only to the genus level. The organism is very difficult to grow in tissue culture but has been cultivated in HeLa cells, HEp-2 cells, and HL cells. Although NAATs are commercially available for *C. trachomatis,* only research-based PCR assays are available for *C. pneumoniae*.

TREATMENT ***C. pneumoniae* Infections**

Although few controlled trials of treatment have been reported, *C. pneumoniae* is inhibited in vitro by erythromycin, tetracycline, azithromycin, clarithromycin, gatifloxacin, and gemifloxacin. Recommended therapy consists of 2 g/d of either tetracycline or erythromycin for 10–14 days. Other macrolides (e.g., azithromycin) and some fluoroquinolones (e.g., levofloxacin and gatifloxacin) also appear to be effective.

Acknowledgment

The authors wish to acknowledge the late Walter E. Stamm, MD, for his significant contributions to the field of Chlamydia research. Dr. Stamm wrote the chapters on chlamydiae for previous editions of Harrison's Principles of Internal Medicine, and we thank the editors for permission to reproduce Figs. 81-1 and 81-2 as well as Table 81-1 from his chapter in the 17th edition. Dr. Stamm died on December 14, 2009, and this chapter is dedicated to him.

SECTION V

VIRAL INFECTIONS

CHAPTER 82

MEDICAL VIROLOGY

Fred Wang ■ Elliott Kieff

DEFINING A VIRUS

Viruses consist of a nucleic acid surrounded by one or more proteins. Some viruses also have an outer-membrane envelope. Viruses are obligate intracellular parasites: they can replicate only within cells since their nucleic acids do not encode the many enzymes necessary for protein, carbohydrate, or lipid metabolism and for the generation of high-energy phosphates. Typically, viral nucleic acids encode proteins necessary for replicating and packaging the nucleic acids within the biochemical milieu of host cells.

Viruses differ from virusoids, viroids, and prions. *Virusoids* are nucleic acids that depend on helper viruses to package their nucleic acids into virus-like particles. *Viroids* are naked, cyclical, mostly double-strand, small RNAs that appear to be restricted to plants, spread from cell to cell, and are replicated by cellular RNA polymerase II. *Prions* (Chap. 104) are abnormal protein molecules that can spread, reproducing by changing the structure of their normal cellular protein counterparts. Prions have been implicated in neurodegenerative conditions such as Creutzfeldt-Jakob disease, Gerstmann-Straüssler disease, kuru, and human bovine spongiform encephalopathy ("mad cow disease").

VIRAL STRUCTURE

Viral genomes consist of (1) a single-strand or double-strand DNA, (2) a single-strand sense RNA, (3) a single-strand or segmented antisense RNA, or (4) a double-strand segmented RNA genome. The viral nucleic acid may encode only a few genes or more than 100. Sense-strand RNA genomes can be translated directly into protein, whereas antisense RNAs must be copied into translatable RNA. Sense and antisense genomes are also referred to as *positive-strand* and *negative-strand genomes*, respectively. Viral nucleic acid is usually associated with one or more virus-encoded nucleoproteins in the core of the viral particle. The viral nucleic acid and nucleoproteins are almost always enclosed in a protein shell called a *capsid*. Because of the limited genetic complexity of viruses, their capsids are usually composed of multimers of identical capsomeres. Capsomeres are in turn composed of one or a few proteins. Capsids have icosahedral or helical symmetry. Icosahedral structures approximate spheres but have two-, three-, and fivefold axes of symmetry, while helical structures have only a twofold axis of symmetry. The entire structural unit of nucleic acid, nucleoprotein(s), and capsid is called a *nucleocapsid*.

Many human viruses are composed simply of a core and a capsid. For these viruses, the outer surface of the capsid mediates contact with uninfected cells. Other viruses are more complex and have an outer lipid-containing envelope derived from virus-modified membranes of the infected cell. The piece of infected-cell membrane that becomes the viral envelope has usually been modified during infection by the insertion of virus-encoded glycoproteins, which mediate contact of enveloped viruses with uninfected cells. Matrix or tegument proteins fill the space between the nucleocapsid and the envelope in many enveloped viruses. In general, enveloped viruses are sensitive to lipid solvents and nonionic detergents that can dissolve the envelope, while viruses that consist only of nucleocapsids are somewhat resistant. A schematic diagram for large and complex herpesviruses is shown in **Fig. 82-1**. Prototypical pathogenic human viruses are listed in **Table 82-1**. The relative sizes and structures of typical pathogenic human viruses are shown in **Fig. 82-2**.

TAXONOMY OF PATHOGENIC HUMAN VIRUSES

As is apparent from Table 82-1 and Fig. 82-2, the classification of viruses into orders and families is based on nucleic acid composition, nucleocapsid size and symmetry, and presence or absence of an envelope. Viruses of a single family have similar types of genomes and are often morphologically indistinguishable in electron micrographs. Further subclassification into genera depends on similarities in epidemiology, biologic effects, and nucleic acid sequence.

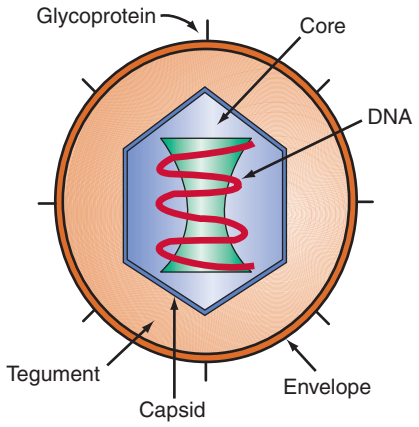


FIGURE 82-1
Schematic diagram of an enveloped herpesvirus with an icosahedral nucleocapsid. The approximate respective dimensions of the nucleocapsid and the enveloped particles are 110 and 180 nm. The capsid is composed of 162 capsomeres: 150 with sixfold and 12 with fivefold axes of symmetry.

Most human viruses have a common name related to their pathologic effects or the circumstances of their discovery. Formal species names have been assigned by the International Committee on Taxonomy of Viruses. The formal designation consists of the name of the host followed by the family or genus of the virus and a number. This dual terminology can cause confusion when viruses are referred to and referenced by either name—e.g., varicella-zoster virus (VZV) or human herpesvirus (HHV) 3.

VIRAL INFECTION IN VITRO

STAGES OF VIRAL INFECTION AT THE CELLULAR LEVEL

Viral interactions with the cell surface and cell entry

All viruses must overcome the barrier posed by the cell's plasma membrane in order to deliver their payload of nucleic acid into the cell. Infection is initiated by attachment of the virus to the cell surface. Various cellular proteins, carbohydrates, and lipids (e.g., heparan sulfate proteoglycans, sialic acids, and lectins) can act as attachment factors that concentrate viruses at the cell surface through relatively weak or nonspecific interactions with viral surface proteins. Higher-affinity binding of viral surface proteins to specific cell-surface proteins, or receptors (see Table 2-1), is more critical for viral infection. Receptor binding is often augmented by interaction of viral surface proteins with other cell- surface proteins, or co-receptors, important for various aspects of virus entry. Receptors and co-receptors are important determinants of the cell types and species that a virus can infect. For example, the HIV envelope glycoprotein binds to the T cell surface protein CD4 and then engages one of several chemokine receptors that are co-receptors for the virus. Epstein-Barr virus (EBV) glycoprotein gp350 binds to the B lymphocyte complement receptor CD21 and then uses major histocompatibility complex (MHC) class II molecules as a co-receptor.

Viruses use different strategies to penetrate the cell membrane. Some enveloped viruses use membrane fusion to deliver their contents into the cytoplasm. In general, a trigger (e.g., receptor binding) induces a conformational change that allows the viral surface protein to extend into the cell membrane, bringing the virus and cell membrane into close proximity and thereby enabling fusion and formation of a pore through which the viral nucleocapsid can be delivered into the cytoplasm. Nonenveloped viruses and some enveloped viruses cannot use direct membrane fusion at the plasma membrane and are internalized by endocytosis. The low pH in endosomes can trigger viral membrane or capsid fusion with the endocytic membrane. Conformational changes in nonenveloped capsids can lead to endosomal membrane penetration and release of viral nucleic acid into the cytoplasm.

Influenza virus provides a well-studied example of the effect of low pH on viral penetration. Influenza hemagglutinin mediates adsorption, receptor aggregation, and endocytosis. In low-pH endosomes, changes in conformation of the hemagglutinin expose amphipathic domains that interact chemically with the cell membrane and initiate fusion of the virus and cell membranes. For influenza virus, the M2 membrane protein plays a key role in the uncoating of the viral envelope by providing an ion channel in the envelope.

The fusion of viral proteins with cell membranes is a crucial step in viral infection. The hydrophobic interactions required for fusion can be susceptible to chemical inhibition or blockade. The HIV envelope glycoprotein gp120 is associated with gp41 on the viral surface. Binding of HIV gp120 to CD4 and chemokine receptors results in a conformational change, allowing gp41 to initiate cell membrane fusion. Enfuvirtide is a small-peptide drug derived from gp41 that binds to gp41 and prevents the conformational change required for fusion. Maraviroc prevents virus entry by binding to CCR5, blocking interaction with gp120, and preventing fusion triggering.

Viral gene expression and replication

After uncoating and release of viral nucleoprotein into the cytoplasm, the viral genome is transported to a site for expression and replication. In order to produce infectious progeny, viruses must (1) produce proteins necessary to replicate their nucleic acid, (2) produce structural proteins, and (3) assemble the nucleic acid and proteins into progeny virions. Different viruses use different strategies and gene repertoires to accomplish these goals. DNA viruses, except for poxviruses, replicate their nucleic acid and assemble into nucleocapsid complexes in the cell nucleus. RNA viruses, except for influenza viruses, transcribe and replicate their nucleic acid and assemble entirely in the cytoplasm. Thus, the replication strategies of DNA and RNA viruses are presented separately next. Positive-strand and negative-strand RNA viruses are discussed separately. Medically important viruses of each group are used for illustrative purposes.

TABLE 82-1

VIRUS FAMILIES PATHOGENIC FOR HUMANS

FAMILY	REPRESENTATIVE VIRUSES	TYPE OF RNA/DNA	LIPID ENVELOPE
RNA Viruses			
Picornaviridae	Poliovirus Coxsackievirus Echovirus Enterovirus Rhinovirus Hepatitis A virus	(+) RNA	No
Caliciviridae	Norwalk agent Hepatitis E virus	(+) RNA	No
Togaviridae	Rubella virus Eastern equine encephalitis virus Western equine encephalitis virus	(+) RNA	Yes
Flaviviridae	Yellow fever virus Dengue virus St. Louis encephalitis virus West Nile virus Hepatitis C virus Hepatitis G virus	(+) RNA	Yes
Coronaviridae	Coronaviruses[a]	(+) RNA	Yes
Rhabdoviridae	Rabies virus Vesicular stomatitis virus	(–) RNA	Yes
Filoviridae	Marburg virus Ebola virus	(–) RNA	Yes
Paramyxoviridae	Parainfluenza virus Respiratory syncytial virus Newcastle disease virus Mumps virus Rubeola (measles) virus	(–) RNA	Yes
Orthomyxoviridae	Influenza A, B, and C viruses	(–) RNA, 8 segments	Yes
Bunyaviridae	Hantavirus California encephalitis virus Sandfly fever virus	(–) RNA, 3 circular segments	Yes
Arenaviridae	Lymphocytic choriomeningitis virus Lassa fever virus South American hemorrhagic fever virus	(–) RNA, 2 circular segments	Yes
Reoviridae	Rotavirus Reovirus Colorado tick fever virus	ds RNA, 10–12 segments	No
Retroviridae	Human T lymphotropic virus types I and II Human immunodeficiency virus types 1 and 2	(+) RNA, 2 identical segments	Yes
DNA Viruses			
Hepadnaviridae	Hepatitis B virus	ds DNA with ss portions	Yes
Parvoviridae	Parvovirus B19	ss DNA	No
Papovaviridae	Human papillomaviruses JC virus BK virus	ds DNA	No
Adenoviridae	Human adenoviruses	ds DNA	No

(*continued*)

TABLE 82-1

VIRUS FAMILIES PATHOGENIC FOR HUMANS (*CONTINUED*)

FAMILY	REPRESENTATIVE VIRUSES	TYPE OF RNA/DNA	LIPID ENVELOPE
DNA Viruses (*continued*)			
Herpesviridae	Herpes simplex virus types 1 and 2[b] Varicella-zoster virus[c] Epstein-Barr virus[d] Cytomegalovirus[e] Human herpesvirus 6 Human herpesvirus 7 Kaposi's sarcoma–associated herpesvirus[f]	ds DNA	Yes
Poxviridae	Variola (smallpox) virus Orf virus Molluscum contagiosum virus	ds DNA	Yes

[a]Including the coronavirus causing severe acute respiratory syndrome (SARS).
[b]Also called human herpesvirus (HHV) 1 and 2, respectively.
[c]Also called HHV-3.
[d]Also called HHV-4.
[e]Also called HHV-5.
[f]Also called HHV-8.
Abbreviations: ds, double-strand; ss, single-strand.

Positive-strand RNA viruses

Medically important positive-strand RNA viruses include picornaviruses, flaviviruses, togaviruses, caliciviruses, and coronaviruses. Genomic RNA from positive-strand RNA viruses is released into the cytoplasm without associated enzymes. Cell ribosomes recognize and associate with an internal ribosome entry sequence in the viral RNA and translate a polyprotein. Protease components of the polyprotein cleave out the viral RNA polymerase and other viral proteins necessary for replication. Antigenomic RNA is then transcribed from the genomic RNA template. Positive-strand genomes and mRNAs are next transcribed from the antigenomic RNA by the viral RNA polymerase and are translated into capsid proteins. Genomic RNA is encapsidated in the cytoplasm as the infected cell undergoes lysis.

Negative-strand RNA viruses

Medically important negative-strand RNA viruses include rhabdoviruses, filoviruses, paramyxoviruses, orthomyxoviruses, and bunyaviruses. The genomes of negative-strand viruses are frequently segmented. Negative-strand RNA virus genomes are released into the cytoplasm with an associated RNA polymerase and one or more polymerase accessory proteins. The viral RNA polymerase transcribes messenger RNAs (mRNAs) as well as full-length antigenomic RNA, which is the template for genomic RNA replication. Viral mRNAs encode the viral RNA polymerase and accessory factors as well as viral structural proteins. Except for influenza virus, which transcribes its mRNAs and antigenomic RNAs in the cell's nucleus, negative-strand RNA viruses replicate entirely in the cytoplasm. All negative-strand RNA viruses, including influenza viruses, assemble in the cytoplasm.

Double-strand segmented RNA viruses

Double-strand RNA viruses are taxonomically grouped in the family Reoviridae. The medically important viruses in this group are rotaviruses and Colorado tick fever virus. Reovirus genomes have 10–12 RNA segments. Reovirus particles contain an RNA polymerase complex. These viruses replicate and assemble in the cytoplasm.

DNA viruses

Medically important DNA viruses include parvoviruses, papovaviruses (e.g., human papillomaviruses [HPVs] and polyomaviruses), adenoviruses, herpesviruses, and poxviruses. Most DNA virus genomes enter the cell's nucleus and are transcribed by cellular RNA polymerase II. For example, after receptor binding and fusion with plasma membranes or endocytic vesicle membranes, herpesvirus nucleocapsids are released into the cytoplasm along with tegument proteins. The nucleocapsid is transported along microtubules to a nuclear pore. Capsids then release DNA into the nucleus.

DNA virus transcription and mRNA processing depend on both viral and cellular proteins. For herpes simplex virus (HSV), a viral tegument protein enters the nucleus and activates immediate-early genes, the first genes expressed after infection. Transcription of immediate-early genes requires the viral tegument protein and cell transcription factors. HSV becomes nonreplicating, or latent, in neurons because essential cell transcription factors for viral immediate-early gene expression are docked in the cytoplasm in neurons. Heat shock or other cell stresses can cause these cell factors to enter the nucleus, activate viral gene expression, and initiate replication. This information explains HSV-1 latency in neurons and activation of lytic infection.

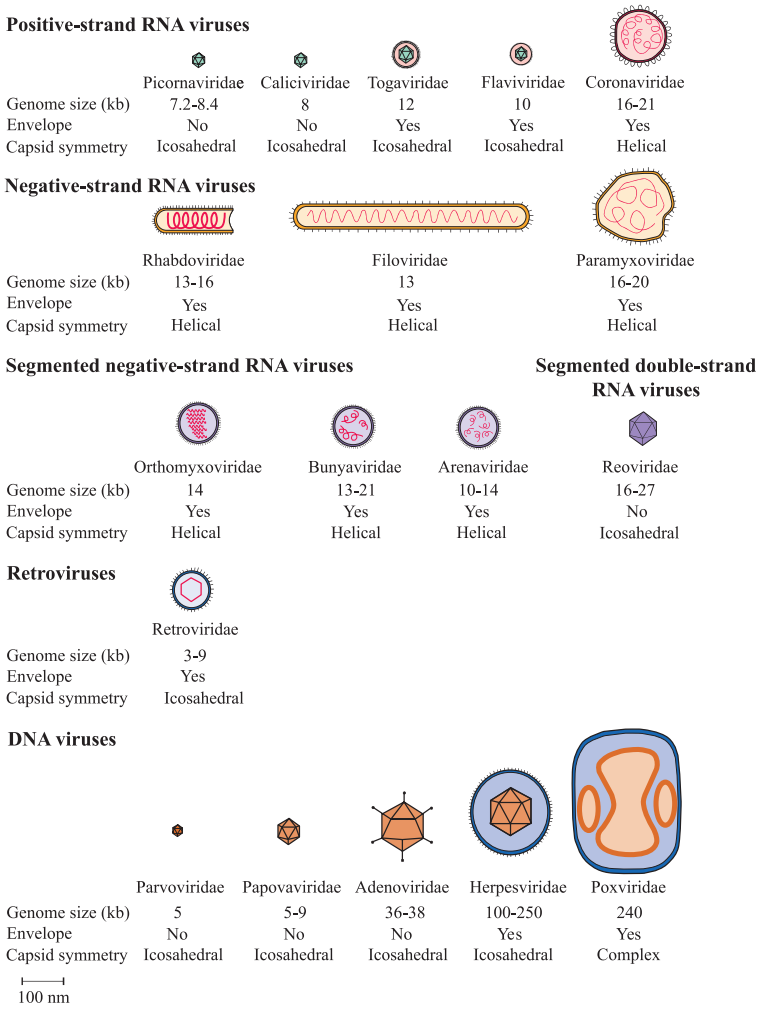


FIGURE 82-2
Schematic diagrams of the major virus families including species that infect humans. The viruses are grouped by genome type and are drawn approximately to scale. Prototype viruses of each family that cause human disease are listed in Table 82-1.

For adenoviruses and herpesviruses, immediate-early gene transcription results in expression of early proteins necessary for viral DNA replication. Viral DNA synthesis is required to turn on late gene expression and production of viral structural components. The HPVs, polyomaviruses, and parvoviruses are not dependent on transactivators encoded from the viral genome for early-gene transcription. Instead, their early genes have upstream enhancing elements that bind cell transcription factors. The early genes encode proteins that are necessary for viral DNA synthesis and late-gene transcription. DNA virus late genes encode structural proteins necessary for viral assembly and for viral egress from the infected cell. Late-gene transcription is continuously dependent on DNA replication. Therefore, inhibitors of DNA replication also stop late-gene transcription.

Each DNA virus family uses unique mechanisms for replicating its DNA. Adenovirus and herpesvirus DNAs are linear in the virion. Adenovirus DNA remains linear in infected cells and replicates as a linear genome, using an initiator protein-DNA complex. In contrast, herpesvirus DNA circularizes in the infected cell, and genomes replicate into linear concatemers through a "rolling-circle"mechanism. Full-length DNA genomes are cleaved and packaged into virus. Herpesviruses encode a DNA polymerase and at least six other viral proteins necessary for viral DNA replication. These viruses also encode enzymes that increase the deoxynucleotide triphosphate pools. HPV and polyomavirus DNAs are circular both within the virus and in infected cells. These genomes are reproduced by cellular DNA replication enzymes and remain circular through replication and packaging. HPV and polyomavirus early proteins are necessary for latent and lytic viral DNA replication. Early viral proteins stimulate cells to remain in cycle, facilitating viral DNA replication.

Parvoviruses have negative single-strand DNA genomes and are the smallest DNA viruses. Their genomes are half the size of the papovavirus genomes and include only two genes. The replication of autonomous parvoviruses, such as B19, depends on cellular DNA replication and requires the virus-encoded Rep protein. Other parvoviruses, such

as adeno-associated virus (AAV), are not autonomous and require helper viruses of the adenovirus or herpesvirus family for their replication. AAV is being used as a potentially safe human gene therapy vector because its replication protein causes integration at a single chromosome site. The small genome size limits the range of proteins that can be expressed from AAV vectors.

Poxviruses are the largest DNA viruses. They are unique among DNA viruses in replicating and assembling in the cytoplasm. To accomplish cytoplasmic replication, poxviruses encode transcription factors, an RNA polymerase II orthologue, enzymes for RNA capping, enzymes for RNA polyadenylation, and enzymes for viral DNA synthesis. Poxvirus DNA also has a unique structure. The double-strand linear DNA is covalently linked at the ends; the packaged genome is therefore a covalently closed single-strand circle. In addition, there are inverted repeats at the ends of the linear DNA. During DNA replication, the genome is cleaved within the terminal inverted repeat, and the inverted repeats self-prime complementary-strand synthesis by the virus-encoded DNA polymerase. Like herpesviruses, poxviruses encode several enzymes that increase deoxynucleotide triphosphate precursor levels and thus facilitate viral DNA synthesis.

Viruses that use both RNA and DNA genomes in their life cycle

Retroviruses, including HIV, are RNA viruses that use a DNA intermediate to replicate their genomes; hepatitis B virus (HBV) is a DNA virus that uses an RNA intermediate to replicate its genome. Thus, these viruses are not purely RNA or DNA viruses. Retroviruses are enveloped RNA viruses with two identical sense-strand genomes and associated reverse transcriptase and integrase enzymes. Retroviruses differ from all other viruses in that they reverse-transcribe themselves into partially duplicated double-strand DNA copies and then routinely integrate into the host genome as part of their replication strategy. The fact that remnants and even complete copies of simple retroviral DNA are integrated into the human genome raises the possibility of replication-competent simple human retroviruses. However, replication has not been documented or associated with any disease. Integrated, replication-competent retroviral DNAs are also present in many animal species, such as pigs. These porcine retroviruses are a potential cause for concern in xenotransplantation because retroviral replication could cause disease in humans.

Cellular RNA polymerase II and transcription factors regulate transcription from the integrated provirus DNA genome. Some retroviruses also encode for regulators of transcription and RNA processing, such as Tax and Rex in human T lymphotropic virus (HTLV) types I and II. HIV-1 and HIV-2 have orthologous Tat and Rev genes as well as the additional accessory proteins Vpr, Vpu, and Vif, which are important for efficient infection and immune escape. Full-length proviral transcripts are made from a promoter in the viral terminal repeat and serve as both genomic RNAs that will be packaged in the nucleocapsids and differentially spliced mRNAs that encode for the viral Gag protein, polymerase/integrase protein, and envelope glycoprotein. The Gag protein includes a protease that cleaves it into several components, including a viral matrix protein that coats the viral RNA. Viral RNA polymerase/integrase, matrix protein, and cellular tRNA are key components of the viral nucleocapsid. The HIV reverse transcriptase, integrase, and Gag protease are important targets for inhibition of HIV replication.

HBV replication is unique in several respects. HBV has a partially double-strand DNA genome that is repaired to a fully double-strand circular DNA by the virion polymerase upon entry into an infected cell. Viral mRNAs are transcribed from the closed circular viral episome by cellular RNA polymerase II and are translated to produce viral proteins including core protein, surface antigen, and polymerase. In addition, a full-genome-length mRNA is packaged into viral core particles in the cytoplasm of infected cells as an intermediate for viral DNA replication. This RNA associates with the viral polymerase, which also has reverse transcriptase activity, to convert the full-length encapsidated RNA genome into partially double-strand DNA. HBV is believed to mature by budding through the cell's plasma membrane, which has been modified by the insertion of viral surface antigen protein.

Viral assembly and egress

For most viruses, nucleic acid and structural protein synthesis is accompanied by the assembly of protein and nucleic acid complexes. The assembly and egress of mature infectious virus mark the end of the eclipse phase of infection, during which infectious virus cannot be recovered from the infected cell. Nucleic acids from RNA viruses and poxviruses assemble into nucleocapsids in the cytoplasm. For all DNA viruses except poxviruses, viral DNA assembles into nucleocapsids in the nucleus. In general, the capsid proteins of viruses with icosahedral nucleocapsids can self-assemble into densely packed and highly ordered capsid structures. Herpesviruses require an assemblin protein as a scaffold for capsid assembly. Viral nucleic acid then spools into the assembled capsid. For herpesviruses, a full unit of the viral DNA genome is packaged into the capsid, and a capsid-associated nuclease cleaves the viral DNA at both ends. In the case of viruses with helical nucleocapsids, the protein component appears to assemble around the nucleic acid, which contributes to capsid organization.

Viruses must egress from the infected cell and not bind back to their receptor(s) on the outer surface of the plasma membrane. Viruses can acquire envelopes from cytoplasmic membranes or by budding through the cell's plasma membrane. Excess viral membrane glycoproteins are synthesized to saturate cell receptors and facilitate separation of the virus from the infected cell. Some viruses encode membrane proteins with enzymatic activity for receptor destruction. Influenza virus, for example, encodes a glycoprotein with

neuraminidase activity. Neuraminidase destroys sialic acid on the infected cell's plasma membrane so that newly released virus does not get stuck to the dying cell. Herpesvirus nucleocapsids acquire an initial envelope by assembling in the nucleus and then budding through the nuclear membrane into the endoplasmic reticular space. The initially enveloped herpesvirus is then de-enveloped and released from the cell either by exocytosis or by re-envelopment at the plasma membrane. Nonenveloped viruses depend on the death and dissolution of the infected cell for their release.

FIDELITY OF VIRAL REPLICATION

Hundreds or thousands of progeny may be produced from a single virus-infected cell. Many particles partially assemble and never mature into virions. Many mature-appearing virions are imperfect and have only incomplete or nonfunctional genomes. Despite the inefficiency of assembly, a typical virus-infected cell releases 10–1000 infectious progeny. Some of these progeny may contain genomes that differ from those of the virus that infected the cell. Smaller, "defective" viral genomes have been noted with the replication of many RNA and DNA viruses. Virions with defective genomes can be produced in large numbers through packaging of incompletely synthesized nucleic acid. Adenovirus packaging is notoriously inefficient, and a high ratio of particle to infectious virus may limit the amount of recombinant adenovirus that can be administered for gene therapy since the immunogenicity of defective particles may contribute to adverse effects.

Changes in viral genomes can lead to mutant viruses of medical significance. In general, viral nucleic acid replication is more error-prone than cellular nucleic acid replication. RNA polymerases and reverse transcriptases are significantly more error-prone than DNA polymerases. Mutations can also be introduced into the HIV genome by APOBEC3G, a cellular protein that is packaged in the virion. APOBEC3G deaminates cytidine in the virion RNA to uridine. When reverse transcriptase subsequently uses the altered virion RNA as a template in the infected cell, a guanosine-to-adenosine mutation is introduced into the proviral DNA. Mutations resulting in less efficient viral growth, or fitness, may be detrimental to the virus. HIV-encoded Vif blocks APOBEC3G activity in the virion, inhibiting the debilitating effects of hypermutation on genetic integrity. Nevertheless, mutations resulting in evasion of the host immune response or resistance to antiviral drugs are preferentially selected in patients, with the consequent perpetuation of infection. Viral genomes can also be altered by recombination or reassortment between two related viruses in a single infected cell. While this occurrence is unusual under most circumstances of natural infection, the genome changes can be substantial and can significantly alter virulence or epidemiology. Reassortment of the avian or mammalian influenza A hemagglutinin gene into a human influenza background can result in the emergence of new epidemic or pandemic influenza A strains.

VIRAL GENES NOT REQUIRED FOR VIRAL REPLICATION

Viruses frequently have genes encoding proteins that are not directly involved in replication or packaging of the viral nucleic acid, in virion assembly, or in regulation of the transcription of viral genes involved in those processes. Most of these proteins fall into five classes: (1) proteins that directly or indirectly alter cell growth; (2) proteins that inhibit cellular RNA or protein synthesis so that viral mRNA can be efficiently transcribed or translated; (3) proteins that promote cell survival or inhibit apoptosis so that progeny virus can mature and escape from the infected cell; (4) proteins that inhibit the host interferon response; and (5) proteins that downregulate host inflammatory or immune responses so that viral infection can proceed in an infected person to the extent consistent with the survival of the virus and its efficient transmission to a new host. More complex viruses of the poxvirus or herpesvirus family encode many proteins that serve these functions. Some of these viral proteins have motifs similar to those of cellular proteins, while others are quite novel. Virology has increasingly focused on these more sophisticated strategies evolved by viruses to permit the establishment of long-term infection in humans and other animals. These strategies often provide unique insights into the control of cell growth, cell survival, macromolecular synthesis, proteolytic processing, immune or inflammatory suppression, immune resistance, cytokine mimicry, or cytokine blockade.

MicroRNAs (miRNAs) are small noncoding RNAs that can regulate gene expression at the posttranscriptional level by targeting—and usually silencing—mRNAs. MiRNAs were initially discovered in plants and plant viruses, where they alter expression of cell defensins. Herpesviruses are especially rich in miRNAs; for example, at least 23 miRNAs have been identified in EBV and 11 in cytomegalovirus (CMV). Adenovirus and polyomavirus miRNAs have also been described. Increasing data indicate that animal viruses encode miRNAs to alter the growth and survival of host cells and the innate and acquired immune responses.

HOST RANGE

The concept of host range was originally based on the cell types in which a virus replicates in tissue culture. For the most part, the host range is limited by specific cell-surface proteins required for viral adsorption or penetration—i.e., to the cell types that express receptors or co-receptors for a specific virus. Another common basis for host-range limitation is the degree of transcriptional activity from viral promoters in different cell types. Most DNA viruses depend not only on cellular RNA polymerase II and the basal components of the cellular transcription complex but also on activated components and transcriptional accessory factors, both of which differ among differentiated tissues, among cells at various phases of the cell cycle, and between resting and cycling cells. APOBEC3G, an important cell

restriction factor for HIV infection, hypermutates viral RNA. The balance between HIV Vif and APOBEC3G is an important determinant of HIV-1 infection.

The importance of host range factors is illustrated by the effects of specific host determinants that limit the replication of influenza virus with avian or porcine hemagglutinins in humans. These viral proteins have adapted to bind avian or porcine sialic acids, and spread of avian or porcine influenza viruses in human populations is limited by their ability to infect human cells.

VIRAL CYTOPATHIC EFFECTS AND INHIBITORS OF APOPTOSIS

The replication of almost all viruses has adverse effects on the infected cell, inhibiting cellular synthesis of DNA, RNA, or proteins through efficient competition for key substrates and enzymatic processes. These general inhibitory effects enable viruses to nonspecifically limit components of innate host resistance, such as interferon (IFN) production. Viruses can specifically inhibit host protein synthesis by attacking a component of the translational initiation complex—frequently, a component that is not required for efficient translation of viral RNAs. Poliovirus protease 2A, for example, cleaves a cellular component of the complex that ordinarily facilitates translation of cellular mRNAs by interacting with their cap structure. Poliovirus RNA is efficiently translated without a cap since it has an internal ribosome entry sequence. Influenza virus inhibits the processing of mRNA by snatching cap structures from nascent cellular RNAs and using them as primers in the synthesis of viral mRNA. HSV has a virion tegument protein that inhibits cellular mRNA translation.

Apoptosis is the expected consequence of virus-induced inhibition of cellular macromolecular synthesis and viral nucleic acid replication. While the induction of apoptosis may be important for the release of some viruses (particularly nonenveloped viruses), many viruses have acquired genes or parts of genes that enable them to forestall infected-cell death. This delay increases the yield from viral replication. Adenoviruses and herpesviruses encode analogues of the cellular Bc12 protein, which blocks mitochondrial enhancement of proapoptotic stimuli. Poxviruses and some herpesviruses also encode caspase inhibitors. Many viruses, including HPVs and adenoviruses, encode proteins that inhibit p53 or its downstream proapoptotic effects.

VIRAL INFECTION IN VIVO

TRANSMISSION

The capsid and envelope of a virus protect the genome and enable efficient transmission of the virus from cell to cell and to new prospective hosts. Most common viral infections are spread by direct contact, by ingestion of contaminated water or food, or by inhalation of aerosolized particles. In all these situations, infection begins on an epithelial or mucosal surface and spreads along the mucosa and into deeper tissues. Infection may spread to cells that can enter blood vessels, lymphatics, or neural circuits. HBV, hepatitis C virus (HCV), HTLV, and HIV are dependent on transmission by parenteral inoculation. Insect vectors can mediate parenteral transfer of viruses that reach high titers in animal or human hosts.

Some viruses are transmitted only between humans. The dependence of smallpox and poliovirus infections on interhuman transmission makes it feasible to eliminate these viruses from human circulation by mass vaccination. Herpesviruses also survive by interhuman transmission but may be more difficult to eliminate because they establish persistent latent infection in humans and continuously reactivate to infect new and naïve generations.

Animals are also important reservoirs and vectors for transmission of viruses causing human disease. Arboviruses are parenterally transmitted from mammalian species to humans by mosquito vectors. Herpes B, monkeypox, rabies, and viral hemorrhagic fevers are other examples of zoonotic infections caused by direct contact with animals, animal tissues, or arthropod vectors.

PRIMARY INFECTION

Initial viral infections usually last for several days or weeks. During this period, the concentration of virus at sites of infection rises and then falls, usually to unmeasurable levels. The rise and fall of viral replication at a given site depend on local innate immune responses and the access of systemic antibody and cell immune effectors to the virus. Typically, primary infections with enteroviruses, mumps virus, measles virus, rubella virus, rotavirus, influenza virus, AAV, adenovirus, HSV, and VZV are cleared from almost all sites within 3–4 weeks. Some viruses are especially proficient in altering or evading innate and acquired immune responses. Primary infection with AAV, EBV, or CMV can last for several months. Characteristically, primary infections due to HBV, HCV, hepatitis D virus (HDV), HIV, HPV, and molluscum contagiosum virus (MCV) extend beyond several weeks. For some of these viruses (e.g., HPV, HBV, HCV, HDV, and MCV), the manifestations of primary infection are almost indistinguishable from the persistent phase.

Disease manifestations usually arise as a consequence of viral replication, infected cell injury or death, and local inflammatory and innate immune responses. Disease severity may not necessarily correlate with the level of viral replication alone. For example, the clinical manifestations of intense primary infection with poliovirus, enterovirus, rabies virus, measles virus, mumps virus, or HSV at mucosal surfaces may be inapparent or relatively mild, whereas limited replication in neural cells can have dramatic consequences. Similarly, rubella virus or CMV infections in utero or neonatal HSV infections may have much more devastating effects than infections in adults.

Primary infections are cleared by nonspecific innate and specific adaptive immune responses. Thereafter, an immunocompetent host is usually immune to the disease manifestations of reinfection by the same virus.

Immunity frequently does not prevent transient surface colonization on re-exposure, persistent colonization, or even limited deeper infection.

PERSISTENT AND LATENT INFECTIONS

Relatively few viruses cause persistent or latent infections. HBV, HCV, rabies virus, measles virus, HIV, HTLV, HPV, HHVs, and MCV are notable exceptions. The mechanisms for persistent infection vary. HCV RNA polymerase and HIV reverse transcriptase are error prone and generate variant genomes. Genome variation can be sufficient to permit evasion of host immune responses, thereby allowing persistent infection. HIV is also directly immunosuppressive, depleting CD4+ T lymphocytes and compromising CD8+ cytotoxic T cell immune responsiveness. Moreover, HIV encodes the Nef protein, which downmodulates MHC class I expression, rendering HIV-infected cells partially resistant to immune CD8+ T cell lysis.

DNA viruses have low mutation rates. Their persistence in human populations usually depends on their ability to establish latent infection in some cells, to reactivate from latency, and then to replicate at epithelial surfaces. *Latency* is defined as a state of infection in which virus is not replicating, viral genes associated with lytic infection are not expressed, and infectious virus is not made. The complete viral genome is present and may be replicated by cellular DNA polymerase in conjunction with replication of the cell's genome. HPVs establish latent infection in basal epithelial cells. The latently infected basal cell replicates, along with the HPV episome, by using cellular DNA polymerase. Some of the progeny cells provide new latently infected basal cells, while others go on to squamous differentiation. Infected cells that differentiate to squamous cells become permissive for lytic viral infection. Herpesviruses establish latent infection in nonreplicating neural cells (HSV and VZV) or in replicating cells of hematopoietic lineages (EBV, CMV, HHV-6, HHV-7, and Kaposi's sarcoma—associated herpesvirus [KSHV, also known as HHV-8]). In their latent stage, HPV and herpesvirus genomes are largely hidden from the normal immune response. Reactivated HPV and herpesvirus infections escape immediate and effective immune responses in highly immune hosts by inhibiting host innate immune and inflammatory responses. In addition, HPV, HSV, and VZV are somewhat protected because they replicate in the middle and upper layers of the squamous epithelium—sites not routinely visited by cells that mediate or amplify immune and inflammatory responses. HSV and CMV are also known to encode proteins that downregulate MHC class I expression and antigenic peptide presentation, enabling infected cells to escape recognition by and cytotoxic effects of CD8+ T lymphocytes.

Like other poxviruses, MCV cannot establish latent infection. This virus causes persistent infection in hypertrophic skin lesions that last for months or years. MCV encodes a chemokine homologue that probably blocks inflammatory responses, an MHC class I analogue that blocks cytotoxic T lymphocyte attack, and inhibitors of cell death that prolong infected cell viability.

PERSISTENT VIRAL INFECTIONS AND CANCER

Persistent viral infection is estimated to be the root cause of as many as 20% of human malignancies. Cancer is an accidental and highly unusual or long-term effect of oncogenic human virus infection. With most "oncogenic viruses," infection is a critical and ultimately determinative early step in carcinogenesis. Latent HPV infection can block cell death and cause cervical cells to proliferate. A virus-infected cell with an integrated HPV genome overexpressing E6 and E7 undergoes subsequent cellular genetic changes that enhance autonomous malignant cell growth.

Most hepatocellular carcinoma is believed to be caused by chronic inflammatory, immune, and regenerative responses to HBV or HCV infection. Epidemiologic data firmly link HBV and HCV infections to hepatocellular carcinoma. These infections elicit repetitive cycles of virus-induced liver injury followed by tissue repair and regeneration. Over decades, chronic virus infection, repetitive tissue regeneration, and acquired chromosomal changes can result in proliferative nodules. Further chromosomal mutations can lead to the degeneration of cells in a proliferating nodule into hepatocellular carcinoma. In rare instances, HBV DNA integrates into cellular DNA, promoting overexpression of a cell gene that can also contribute to oncogenesis.

Most cervical carcinoma is caused by persistent infection with "high-risk" HPV type 16 or 18. In contrast to HBV and HCV infections, which stimulate cell growth as a consequence of virus- induced cell death, HPV type 16 or 18 proteins E6 and E7 destroy p53 and pRB, respectively. Elimination of these key tumor-suppressive cell proteins increases cell growth, cell survival, and cell genome instability. However, like HBV and HCV infections, HPV infection alone is not sufficient for carcinogenesis. Cervical carcinoma is inevitably associated with persistent HPV infection and integration of the HPV genome into chromosomal DNA. Integrations that result in overexpression of E6 and E7 from HPV type 16 or 18 cause more profound changes in cell growth and survival and enable subsequent chromosomal changes that result in cervical carcinoma.

EBV is the most unusual oncogenic virus in that normal B cell infection results in latency with expression of viral proteins that can cause endless B lymphocyte growth. In almost all humans, strong CD4+ and CD8+ T cell immune responses to the antigenic EBV latent-infection nuclear proteins prevent uncontrolled B cell lymphoproliferation. However, when humans are severely immunosuppressed by transplantation-associated medication, HIV infection, or genetic immunodeficiencies, EBV-induced B cell malignancies can emerge.

EBV infection also plays a role in the long-term development of B lymphocyte and epithelial cell malignancies.

Persistent EBV infection with expression of an EBV latency-associated integral membrane protein (LMP1) in latently infected epithelial cells appears to be a critical early step in the evolution of anaplastic nasopharyngeal carcinoma, a common malignancy in populations in southern China and northern Africa. Genomic instability and chromosomal abnormalities also contribute to the development of EBV-associated nasopharyngeal carcinomas. EBV is an important cause of Hodgkin's lymphoma. High-level expression of LMP1 or LMP2 in Reed-Sternberg cells is a hallmark in up to 50% of Hodgkin's lymphoma cases. LMP1-induced nuclear factor κB (NF-κB) activity may prolong the survival of defective B cells that are normally eliminated by apoptosis, thereby allowing the acquisition of other genetic changes leading to malignant Reed-Sternberg cells.

The HTLV-I Tax and Rex proteins are critical to the initiation of cutaneous adult T cell lymphoma/leukemias that occur long after primary HTLV-I infection. Tax-induced NF-κB activation may contribute to cytokine production, infected cell survival, and eventual outgrowth of malignant cells.

Molecular data confirm the presence of KSHV DNA in all Kaposi's tumors, including those associated with HIV infection, transplantation, and familial transmission. KSHV infection is also etiologically implicated in pleural-effusion lymphomas and multicentric Castleman's disease, which are more common among HIV-infected than among HIV-uninfected people. KSHV can express a virus-encoded cyclin, an IFN regulatory factor, and a latency-associated nuclear antigen that are implicated in increased cell proliferation and survival.

Evidence supporting a causal role for virus infection in all of these malignancies includes (1) epidemiologic data, (2) the presence of viral DNA in all tumor cells, (3) the ability of the viruses to transform human cells in culture, (4) the results of in vitro cell culture–based assays that reveal transforming effects of specific viral genes on cell growth or survival, (5) pathologic data indicating the expression of transforming viral genes in premalignant or malignant cells in vivo, (6) the demonstration in animal models that these viral genes can cause malignant cell growth, and (7) the ability of virus-specific vaccines to reduce the incidence of virus-associated malignancy. Virus-related malignancies provide an opportunity to expand our understanding of the biologic mechanisms important in the development of cancer. They also offer unique opportunities to develop diagnostics, vaccines, or therapeutics that could prevent or specifically treat cancers associated with virus infection. Widespread immunization against hepatitis B has resulted in a decreased prevalence of HBV-associated hepatitis and will probably prevent most HBV-related liver cancers. An HPV vaccine can reduce rates of colonization with high-risk HPV strains and thereby decrease the risk of cervical cancer. The successful use of in vitro–expanded EBV-specific T cell populations to treat or prevent EBV-associated post-transplantation lymphoproliferative disease demonstrates the potential of immunoprevention or immunotherapy against virus-associated cancers.

RESISTANCE TO VIRAL INFECTIONS

Resistance to viral infections is initially provided by factors that are not virus-specific. Physical protection is afforded by the cornified layers of the skin and by mucous secretions that continuously sweep over mucosal surfaces. Once the first cell is infected, IFNs are induced and confer resistance to viral replication. Viral infection may also trigger the release of other cytokines from infected cells. These cytokines may be chemotactic to inflammatory and immune cells. Viral protein epitopes expressed on the cell surface in the context of MHC class I and II proteins can stimulate the expansion of T cell populations with receptors that can recognize the virus-encoded peptides. Cytokines and antigens released by virus-induced cell death further attract inflammatory cells, dendritic cells, granulocytes, natural killer (NK) cells, and B lymphocytes to sites of infection and to draining lymph nodes. IFNs and NK cells are particularly important in containing viral infection for the first several days. Granulocytes and macrophages are also important in the phagocytosis and degradation of viruses, especially after an initial antibody response.

By 7–10 days after infection, virus-specific antibody responses, virus-specific HLA class II–restricted CD4+ helper T lymphocyte responses, and virus-specific HLA class I–restricted CD8+ cytotoxic T lymphocyte responses develop. These responses, whose magnitude typically increases over the second and third weeks of infection, are important for rapid recovery. Also between the second and third weeks, the antibody type usually changes from IgM to IgG; IgG or IgA antibody can then be detected at infected mucosal surfaces. Antibody may directly neutralize virus by binding to its surface and preventing cell attachment or penetration. Complement can significantly enhance antibody-mediated virus neutralization. Antibody and complement can also lyse virus-infected cells that express viral membrane proteins on the cell surface. Cells infected with a replicating enveloped virus usually express the virus-envelope glycoproteins on the cell plasma membrane. Specific antibodies can bind to the glycoproteins, fix complement, and lyse the infected cell.

Antibody and CD4+/CD8+ T lymphocyte responses to virus infection can persist at high levels for several months after primary infection. Antibody-producing B lymphocytes and CD4+ or CD8+ T lymphocyte responses can persist in small numbers as memory cells and begin to proliferate rapidly in response to a second infection, providing an early barrier to reinfection with the same virus. Redevelopment of T cell immunity may take longer than secondary antibody responses, particularly when many years have elapsed between primary infection and re-exposure. However, persistent infections or frequent reactivations from latency can result in sustained high-level T cell responses. EBV and CMV typically induce high-level CD4+ and CD8+ T cell responses that are maintained for decades after primary infection.

Some viruses have genes that alter innate and acquired host defenses. Adenoviruses encode small RNAs that

inhibit IFN-induced, protein kinase R (PKR)–mediated shutoff of infected-cell protein synthesis. Adenovirus E1A can also directly inhibit IFN-mediated changes in cell gene transcription. Moreover, adenovirus E3 proteins prevent tumor necrosis factor (TNF)–induced cytolysis and block HLA class I antigen synthesis by the infected cell. HSV ICP47 and CMV US11 also block class I antigen presentation. EBV encodes an interleukin (IL) 10 homologue that inhibits NK and T cell responses. Vaccinia virus encodes a soluble receptor for IFN-α and binding proteins for IFN-γ, IL-1, IL-18, and TNF, which inhibit host innate and adaptive immune responses. Vaccinia virus also encodes a caspase inhibitor that inhibits the ability of CD8+ cytotoxic T cells to kill virus-infected cells. Some poxviruses and herpesviruses encode chemokine-binding proteins that inhibit cell inflammatory responses. The adoption of these strategies by viruses highlights the importance of the corresponding host resistance factors in containing viral infection and the importance of redundancy in host resistance.

The host inflammatory and immune responses to viral infection do not come without a price. These responses contribute to the symptoms, signs, and other pathophysiologic manifestations of viral infection. Inflammation at sites of viral infection can subvert an effective immune response and induce tissue death and dysfunction. Moreover, immune responses to viral infection could, in principle, result in immune attack upon cross-reactive epitopes on normal cells, with consequent autoimmunity.

INTERFERONS

All human cells can synthesize IFN-α or IFN-β in response to viral infection. These IFN responses are usually induced by the presence of double-strand viral RNA, which can be made by both RNA and DNA viruses and sensed by double-strand RNA binding proteins (e.g., PKR and RIG-I) in the cell cytoplasm. IFN-γ is not closely related to IFN-α or IFN-β and is produced mainly by NK cells and by immune T lymphocytes responding to IL-12. IFN-α and -β bind to the IFN-α receptor, while IFN-γ binds to a different but related receptor. Both receptors signal through receptor-associated JAK kinases and other cytoplasmic proteins, including "STAT" proteins, which are tyrosine-phosphorylated by JAK kinases, translocate to the nucleus, and activate promoters for specific cell genes. Three types of antiviral effects are induced by IFN at the transcriptional level. The first effect is attributable to the induction of 2′-5′ oligo(A) synthetases, which require double-strand RNA for their activation. Activated synthetase polymerizes oligo(A) and thereby activates RNAse L, which in turn degrades single-strand RNA. A second effect results from the induction of PKR, a serine and threonine kinase that is also activated by double-strand RNA. PKR phosphorylates and negatively regulates the translational initiation factor eIF2α, shutting down protein synthesis in the infected cell. A third effect is initiated through the induction of Mx proteins, a family of GTPases that is particularly important in inhibiting the replication of influenza virus and vesicular stomatitis virus. These IFN effects are mostly directed against the infected cell, causing virus and cell dysfunction and thereby limiting viral replication.

DIAGNOSTIC VIROLOGY

A wide variety of methods are used to diagnose viral infection. Serology and virus isolation in tissue culture remain important standards. Acute- and convalescent-phase sera with rising titers of antibody to virus-specific antigens and a shift from IgM to IgG antibodies are generally accepted as diagnostic of acute viral infection. Serologic diagnosis is based on a >4-fold rise in IgG antibody concentration when acute- and convalescent-phase serum samples are analyzed at the same time.

Immunofluorescence, hemadsorption, and hemagglutination assays for antiviral antibodies are labor-intensive and have been replaced by enzyme-linked immunosorbent assays (ELISAs), which generally use the specific viral proteins most frequently targeted by the antibody response. The proteins are purified from virus-infected cells or produced by recombinant DNA technology and are attached to a solid phase, where they can be incubated with serum, washed to eliminate nonspecific antibodies, and allowed to react with an enzyme-linked reagent to detect human IgG or IgM antibody specifically adhering to the viral antigen. The amount of antibody can then be quantitated by the intensity of a color reaction mediated by the linked enzyme. ELISAs can be sensitive and automated. Western blots can simultaneously confirm the presence of antibody to multiple specific viral proteins. The proteins are separated by size and transferred to an inert membrane, where they are incubated with serum antibodies. Western blots have an internal specificity control, since the level of reactivity for viral proteins can be compared with that for cellular proteins in the same sample. Western blots require individual evaluation and are inherently difficult to quantitate or automate.

Isolation of virus in tissue culture depends on infection and replication in susceptible cells. Growth of virus in cell cultures can frequently be identified by effects on cell morphology under light microscopy. For example, HSV produces a typical cytopathic effect in rabbit kidney cells within 3 days. Other viral cytopathic effects may not be as diagnostically distinctive. Identification usually requires confirmation by staining with virus-specific monoclonal antibodies. The efficiency and speed of virus identification can be enhanced by combining short-term culture with immune detection. In assays with "shell vials" of tissue culture cells growing on a coverslip, viral infection can be detected by staining with a monoclonal antibody to a specific viral protein expressed early in viral replication. Thus, virus-infected cells can be detected within hours or days of inoculation, whereas several rounds of infection would be required to produce visible cytopathic effects.

Isolation of virus in tissue culture also depends on the collection of specimens from appropriate sites and the rapid transport of these specimens in appropriate medium to the virology laboratory (Chap. 6). Rapid transport maintains viral viability and limits bacterial and fungal overgrowth. Enveloped viruses are generally more sensitive to freezing and thawing than nonenveloped viruses. The most appropriate site for culture depends on the pathogenesis of the virus in question. Nasopharyngeal, tracheal, or endobronchial aspirates are most appropriate for the identification of respiratory viruses. Sputum cultures generally are less appropriate since bacterial contamination and viscosity threaten tissue-culture cell viability. Aspirates of vesicular fluid are useful for isolation of HSV and VZV. Nasopharyngeal aspirates and stool specimens may be useful when the patient has fever and a rash and an enteroviral infection is suspected. Adenoviruses can be cultured from the urine of patients with hemorrhagic cystitis. CMV can frequently be isolated from cultures of urine or buffy coat. Biopsy material can be effectively cultured when viruses infect major organs, as in HSV encephalitis or adenovirus pneumonia.

The isolation of a virus does not necessarily establish disease causality. Viruses can persistently or intermittently colonize normal human mucosal surfaces. Saliva can be positive for herpesviruses, and normal urine samples can be positive for CMV. Isolations from blood, cerebrospinal fluid (CSF), or tissue are more often diagnostic of significant viral infection.

Another method aimed at increasing the speed of viral diagnosis is direct testing for antigen or cytopathic effects. Virus-infected cells from the patient may be detected by staining with virus-specific monoclonal antibodies. For example, epithelial cells obtained by nasopharyngeal aspiration can be stained with a variety of specific monoclonal antibodies to identify the specific infecting respiratory virus.

Nucleic acid amplification techniques bring speed, sensitivity, and specificity to diagnostic virology. The ability to directly amplify minute amounts of viral nucleic acids in specimens means that detection no longer depends on viable virus and its replication. For example, amplification and detection of HSV nucleic acids in the CSF of patients with HSV encephalitis is a more sensitive detection method than culture of virus from CSF. The extreme sensitivity of these tests can be a problem, since subclinical infection or contamination can lead to false-positive results. Detection of viral nucleic acids does not necessarily indicate virus-induced disease.

Measurement of the amount of viral RNA or DNA in peripheral blood is an important means for determining whether a patient is at increased risk for virus-induced disease and for evaluating clinical responses to antiviral chemotherapy. Nucleic acid technologies for RNA quantification are routinely used in AIDS patients to evaluate responses to antiviral agents and to detect viral resistance or noncompliance with therapy. Viral-load measurements are also useful for evaluating the treatment of patients with HBV and HCV infections. Nucleic acid testing or direct staining with CMV-specific monoclonal antibodies to quantitate virus-infected cells in the peripheral blood (CMV antigenemia) is useful for identifying immunosuppressed patients who may be at risk for CMV-induced disease.

DRUG TREATMENT FOR VIRAL INFECTIONS

Multiple steps in the life cycles of viruses can be effectively targeted by antiviral drugs (see also Chaps. 83 and 93). Nucleoside and nonnucleoside reverse transcriptase inhibitors prevent HIV provirus synthesis, while protease inhibitors block maturation of the HIV polyprotein after infection of the cell. Enfuvirtide is a small peptide derived from HIV gp41 that acts before cell infection by preventing a conformational change required for initial fusion of the virus with the cell membrane. Raltegravir is an integrase inhibitor that is approved for use with other anti-HIV drugs. Amantadine and rimantadine inhibit the influenza M2 protein, preventing release of viral RNA early during infection, whereas zanamivir and oseltamivir inhibit the influenza neuraminidase, which is necessary for the efficient release of mature virions from infected cells.

Viral genomes can evolve resistance to drugs by mutation and selection, by recombination with a drug-resistant virus, or (in the case of influenza virus and other segmented RNA viral genomes) by reassortment. The emergence of drug-resistant strains can limit the efficacy of antiviral therapy. As in antibacterial therapy, excessive and inappropriate use of antiviral therapy can select for the emergence of drug-resistant strains. HIV genotyping is a rapid method for identifying drug-resistant viruses. Resistance to reverse transcriptase or protease inhibitors has been associated with specific mutations in the reverse transcriptase or protease genes. Identification of these mutations by polymerase chain reaction amplification and nucleic acid sequencing can be clinically useful for determining which antiviral agents may still be effective. Drug resistance also can arise in herpesviruses but is a less common clinical problem.

IMMUNIZATION FOR THE PREVENTION OF VIRAL INFECTIONS

Viral vaccines are among the outstanding accomplishments of medical science. Smallpox has been eradicated except as a potential weapon of biological warfare or bioterrorism (Chap. 7). Poliovirus eradication may soon follow. Measles can be contained or eliminated. Excess mortality due to influenza virus epidemics can be prevented, and the threat of influenza pandemics can be decreased by contemporary killed or live attenuated influenza vaccines. Mumps, rubella, and chickenpox are well controlled by childhood vaccination in the developed world. Reimmunization of mature adults can be used to control herpes zoster. New rotavirus vaccines can have a major impact on this leading cause of gastroenteritis and prominent cause of childhood death worldwide. Widespread HBV vaccination

has dramatically lowered the frequency of acute and chronic hepatitis and is expected to lead to a dramatic decrease in the incidence of hepatocellular carcinoma. The HPV vaccine was the first vaccine specifically licensed to prevent virus-induced cancer. Use of purified proteins, genetically engineered live-virus vaccines, and recombinant DNA–based strategies will make it possible to immunize against severe infections with other viruses. The development of effective HIV and HCV vaccines is complicated by the high mutation rate of viral RNA polymerase and reverse transcriptase, the population-based and individual divergence of HIV or HCV genomes, and repeated high-level exposure in some populations. Concerns about the use of smallpox and other viruses as weapons necessitate maintenance of immunity to agents that are not encountered naturally.

VIRUSES AS NOVEL THERAPEUTIC TOOLS OR AGENTS

Viruses are being used experimentally to deliver biotherapeutic agents or novel vaccines. Foreign genes can be inserted into viral nucleic acids, and the recombinant virus vectors can be used to infect the patient or the patient's cells ex vivo. Retrovirus integration into the cell genome has been used to functionally replace the abnormal gene in T cells of patients with severe combined immunodeficiency, thereby restoring immune function. Recombinant adenovirus, AAV, and retroviruses are being explored for use in diseases due to single-gene defects, such as cystic fibrosis and hemophilia. Recombinant poxviruses, adenoviruses, and influenza viruses are also being used experimentally as vaccine vectors. Viral vectors are being tested experimentally for the expression of cytokines that can enhance immunity against tumor cells or for the expression of proteins that can increase the sensitivity of tumor cells to chemotherapy. HSV deficient for replication in resting cells is being used to selectively kill proliferating glioblastoma cells after injections into CNS tumors. For improved safety, nonreplicating viruses are frequently employed in clinical trials. Potential adverse events associated with virus-mediated gene transfer include the induction of inflammatory and antiviral immune responses. Instances of retrovirus-induced human malignances have raised concerns about the safety of retroviral gene therapy vectors.

CHAPTER 83

ANTIVIRAL CHEMOTHERAPY, EXCLUDING ANTIRETROVIRAL DRUGS

Lindsey R. Baden ■ Raphael Dolin

The field of antiviral therapy—both the number of antiviral drugs and our understanding of their optimal use—historically has lagged behind that of antibacterial drug treatment, but significant progress has been made in recent years on new drugs for several viral infections. The development of antiviral drugs poses several challenges. Viruses replicate intracellularly and often employ host cell enzymes, macromolecules, and organelles for synthesis of viral particles. Therefore, useful antiviral compounds must discriminate between host and viral functions with a high degree of specificity; agents without such selectivity are likely to be too toxic for clinical use.

Significant progress has also been made in the development of laboratory assays to assist clinicians in the appropriate use of antiviral drugs. Phenotypic and genotypic assays for resistance to antiviral drugs are becoming more widely available, and correlations of laboratory results with clinical outcomes are being better defined. Of particular note has been the development of highly sensitive and specific methods that measure the concentration of virus in blood (*virus load*) and permit direct assessment of the antiviral effect of a given drug regimen in that host site. Virus load measurements have been useful in recognizing the risk of disease progression in patients with certain viral infections and in identifying patients for whom antiviral chemotherapy might be of greatest benefit. As with any in vitro laboratory test, results are highly dependent on (and likely to vary with) the laboratory techniques employed.

Information regarding the pharmacokinetics of some antiviral drugs, particularly in diverse clinical settings, is limited. Assays to measure the concentrations of these drugs, especially of their active moieties within cells, are primarily research procedures and are not widely available to clinicians. Thus, there are relatively few guidelines for adjusting dosages of antiviral agents to maximize antiviral activity and minimize toxicity. Consequently, clinical use of antiviral drugs must be accompanied by particular vigilance with regard to unanticipated adverse effects.

Like that of other infections, the course of viral infections is profoundly affected by an interplay of the pathogen with a complex set of host defenses. The presence or absence of preexisting immunity, the ability to mount humoral and/or cell-mediated immune responses, and the stimulation of innate immunity are important determinants of the outcome of viral infections. The state of the host's defenses needs to be considered when antiviral agents are used or evaluated.

As with any therapy, the optimal use of antiviral compounds requires a specific and timely diagnosis. For some viral infections, such as herpes zoster, the clinical manifestations are so characteristic that a diagnosis can be made on clinical grounds alone. For other viral infections, such as influenza A, epidemiologic information (e.g., the documentation of a community-wide outbreak) can be used to make a presumptive diagnosis with a high degree of accuracy. However, for most of the remaining viral infections, including herpes simplex encephalitis, cytomegaloviral infections other than retinitis, and enteroviral infections, diagnosis on clinical grounds alone cannot be accomplished with certainty. For such infections, rapid viral diagnostic techniques are of great importance. Considerable progress has also been made in recent years in the development of such tests, which are now widely available for a number of viral infections.

Despite these complexities, the efficacy of a number of antiviral compounds has been clearly established in rigorously conducted and controlled studies. As summarized in **Table 83-1**, this chapter reviews the antiviral drugs that are currently approved or are likely to be considered for approval in the near future for use against viral infections other than those caused by HIV. Antiretroviral drugs are reviewed in Chap. 93.

ANTIVIRAL DRUGS ACTIVE AGAINST RESPIRATORY INFECTIONS (ALSO SEE CHAP. 92)

ZANAMIVIR, OSELTAMIVIR, AND PERAMIVIR

Zanamivir and oseltamivir are inhibitors of the influenza viral neuraminidase enzyme, which is essential for release of the virus from infected cells and for its subsequent spread throughout the respiratory tract of the infected host. The enzyme cleaves terminal sialic acid residues and thus destroys the cellular receptors to which the viral hemagglutinin attaches. Zanamivir and oseltamivir are sialic acid transition-state analogues and are highly active and specific inhibitors of the neuraminidases of both influenza A and B viruses. The antineuraminidase activity of the two drugs is similar, although zanamivir has somewhat greater in vitro activity against influenza B. Both zanamivir and oseltamivir act through competitive and reversible inhibition of the active site of influenza A and B viral neuraminidases and have relatively little effect on mammalian cell enzymes.

Oseltamivir phosphate is an ethyl ester prodrug that is converted to oseltamivir carboxylate by esterases in the liver. Orally administered oseltamivir has a bioavailability of >60% and a plasma half-life of 7–9 h. The drug is excreted unmetabolized, primarily by the kidneys. Zanamivir has low oral bioavailability and is administered orally via a hand-held inhaler. By this route, ~15% of the dose is deposited in the lower respiratory tract, and low plasma levels of the drug are detected.

Orally inhaled zanamivir is generally well tolerated, although exacerbations of asthma may occur. The toxicities most frequently encountered with orally administered oseltamivir are nausea, gastrointestinal discomfort, and (less commonly) vomiting. Gastrointestinal discomfort is usually transient and is less likely if the drug is administered with food. Neuropsychiatric events (delirium, self-injury) have been reported in children who have been taking oseltamivir, primarily in Japan. An IV formulation of zanamivir is under development and is available from GlaxoSmith Kline as part of clinical trials.

Inhaled zanamivir and orally administered oseltamivir have been effective in the treatment of naturally occurring, uncomplicated influenza A or B in otherwise healthy adults. In placebo-controlled studies, illness has been shortened by 1.0–1.5 days of therapy with either of these drugs when treatment is administered within 2 days of onset. Pooled analyses of clinical studies of oseltamivir suggest that treatment may reduce the likelihood of hospitalizations and of certain respiratory tract complications associated with influenza (Chap. 92). Once-daily inhaled zanamivir or once-daily orally administered oseltamivir can provide prophylaxis against laboratory-documented influenza A– and influenza B–associated illness.

Resistance to the neuraminidase inhibitors may develop by changes in the viral neuraminidase enzyme, by changes in the hemagglutinin that make it more resistant to the actions of the neuraminidase, or by both mechanisms. Isolates that are resistant to oseltamivir—most commonly through the H275Y mutation, which leads to a change from histidine to tyrosine at that residue in the neuraminidase—remain sensitive to zanamivir. Certain mutations impart resistance to both oseltamivir and zanamivir (e.g., I223R, which leads to a change from isoleucine to arginine). Since the mechanisms of action of the neuraminidase inhibitors differ from those of the adamantanes (see later), zanamivir and oseltamivir are active against strains of influenza A virus that are resistant to amantadine and rimantadine.

Appropriate use of antiviral agents against influenza viruses depends on a knowledge of the resistance patterns

TABLE 83-1

ANTIVIRAL CHEMOTHERAPY AND CHEMOPROPHYLAXIS

INFECTION	DRUG	ROUTE	DOSAGE	COMMENT
Influenza A and B: Treatment	Oseltamivir	Oral	Adults: 75 mg bid × 5 d Children 1–12 years: 30–75 mg bid, depending on weight,[a] × 5 d	When started within 2 days of onset in uncomplicated disease, zanamivir and oseltamivir reduce symptom duration by 1.0–1.5 and 1.3 d, respectively. Their effectiveness in prevention or treatment of complications is unclear, although some analyses suggest that oseltamivir may reduce the frequency of respiratory tract complications and hospitalizations. Oseltamivir's side effects of nausea and vomiting can be reduced in frequency by drug administration with food. Zanamivir may exacerbate bronchospasm in patients with asthma. Amantadine and rimantadine are not recommended for routine use unless antiviral susceptibilities are known because of widespread resistance in A/H3N2 viruses since 2005–2006 and in pandemic A/H1N1 viruses in 2009–2010. Their efficacy in treatment of uncomplicated disease caused by sensitive viruses has been similar to that of neuraminidase inhibitors.
	Zanamivir	Inhaled orally	Adults and children ≥7 years: 10 mg bid × 5 d	
	Amantadine[b]	Oral	Adults: 100 mg qd or bid × 5–7 d Children 1–9 years: 5 mg/kg per day (maximum, 150 mg/d) × 5–7 d	
	Rimantadine[b]	Oral	100 mg qd or bid × 5–7 d in adults	
Influenza A and B: Prophylaxis	Oseltamivir	Oral	Adults: 75 mg/d Children ≥1 year: 30–75 mg/d, depending on weight[a]	Prophylaxis must be continued for the duration of exposure and can be administered simultaneously with inactivated vaccine. Unless the sensitivity of isolates is known, neither amantadine nor rimantadine is currently recommended for prophylaxis or therapy.
	Zanamivir	Inhaled orally	Adults and children ≥5 years: 10 mg/d	
	Amantadine[b] or rimantadine[b]	Oral	Adults: 200 mg/d Children 1–9 years: 5 mg/kg per day (maximum, 150 mg/d)	
RSV infection	Ribavirin	Small-particle aerosol	Administered 12–18 h/d from reservoir containing 20 mg/mL × 3–6 d	Use of ribavirin is to be "considered" for treatment of infants and young children hospitalized with RSV pneumonia and bronchiolitis, according to the American Academy of Pediatrics.
CMV disease	Ganciclovir	IV	5 mg/kg bid × 14–21 d; then 5 mg/kg per day as maintenance dose	Ganciclovir, valganciclovir, foscarnet, and cidofovir are approved for treatment of CMV retinitis in patients with AIDS. They are also used for colitis, pneumonia, or "wasting" syndrome associated with CMV and for prevention of CMV disease in transplant recipients.
	Valganciclovir	Oral	900 mg bid × 21 d; then 900 mg/d as maintenance dose	Valganciclovir has largely supplanted oral ganciclovir and is frequently used in place of IV ganciclovir.
	Foscarnet	IV	60 mg/kg q8h × 14–21 d; then 90–120 mg/kg per day as maintenance dose	Foscarnet is not myelosuppressive and is active against acyclovir- and ganciclovir-resistant herpesviruses.

(*continued*)

TABLE 83-1

ANTIVIRAL CHEMOTHERAPY AND CHEMOPROPHYLAXIS (*CONTINUED*)

INFECTION	DRUG	ROUTE	DOSAGE	COMMENT
	Cidofovir	IV	5 mg/kg once weekly × 2 weeks, then once every other week; given with probenecid and hydration	
	Fomivirsen	Intravitreal	330 mg on days 1 and 15 followed by 330 mg monthly as maintenance	Fomivirsen has reduced the rate of progression of CMV retinitis in patients in whom other regimens have failed or have not been well tolerated. The major form of toxicity is ocular inflammation.
Varicella: Immunocompetent host	Acyclovir Valacyclovir	Oral Oral	20 mg/kg (maximum, 800 mg) 4 or 5 times daily × 5 d Children 2–18 years: 20 mg/kg tid, not to exceed 1 g tid, × 5 d	Treatment confers modest clinical benefit when administered within 24 h of rash onset.
Varicella : Immunocompromised host	Acyclovir	IV	10 mg/kg q8h × 7 d	A change to oral valacyclovir can be considered once fever has subsided if there is no evidence of visceral involvement.
Herpes simplex encephalitis	Acyclovir	IV	10 mg/kg q8h × 14–21 d	Results are optimal when therapy is initiated early. Some authorities recommend treatment for 21 d to prevent relapses.
Neonatal herpes simplex	Acyclovir	IV	20 mg/kg q8h × 14–21 d	Serious morbidity is common despite therapy. Prolonged oral administration after initial IV therapy has been suggested because of long-term sequelae associated with cutaneous recurrences of HSV infection.
Genital herpes simplex: Primary (treatment)	Acyclovir	IV	5 mg/kg q8h × 5–10 d	The IV route is preferred for infections severe enough to warrant hospitalization or with neurologic complications.
		Oral	400 mg tid or 200 mg 5 times daily × 7–10 d or 800 mg tid × 2 d	The oral route is preferred for patients whose condition does not warrant hospitalization. Adequate hydration must be maintained.
		Topical	5% ointment; 4–6 applications daily × 7–10 d	Topical use—largely supplemented by oral therapy—may obviate systemic administration to pregnant women. Systemic symptoms and untreated areas are not affected.
	Valacyclovir	Oral	1 g bid × 7–10 d	Valacyclovir appears to be as effective as acyclovir but can be administered less frequently.
	Famciclovir	Oral	250 mg tid × 7–10 d[c]	Famciclovir appears to be similar in effectiveness to acyclovir.
Genital herpes simplex: Recurrent (treatment)	Acyclovir	Oral	400 mg tid or 800 mg bid × 5 d	The clinical effect is modest and is enhanced if therapy is initiated early. Treatment does not affect recurrence rates.
	Famciclovir	Oral	125 mg bid × 5 d or 1000 mg bid × 1 d	
	Valacyclovir	Oral	500 mg bid × 3 d or 1 g once a day × 5 d	

(*continued*)

TABLE 83-1

ANTIVIRAL CHEMOTHERAPY AND CHEMOPROPHYLAXIS (*CONTINUED*)

INFECTION	DRUG	ROUTE	DOSAGE	COMMENT
Genital herpes simplex: Recurrent (suppression)	Acyclovir	Oral	400 mg bid	Suppressive therapy is recommended only for patients with at least 6–10 recurrences per year. "Breakthrough" occasionally takes place, and asymptomatic shedding of virus occurs. The need for suppressive therapy should be reevaluated after 1 year. Suppression with valacyclovir reduces transmission of genital HSV among discordant couples.
	Valacyclovir	Oral	500–1000 mg/d	
	Famciclovir	Oral	250 mg bid	
Mucocutaneous herpes simplex in immunocompromised host: Treatment	Acyclovir	IV	5 mg/kg q8h × 7–14 d	The choice of the IV or oral route and the duration of therapy depend on the severity of infection and the patient's ability to take oral medication. Oral or IV treatment has supplanted topical therapy except for small, easily accessible lesions. Foscarnet is used for acyclovir-resistant viruses.
		Oral	400 mg 5 times daily × 10–14 d	
		Topical	5% ointment; 4–6 applications daily × 7 d or until healed	
	Valacyclovir	Oral	1 g tid × 7–10 d[c]	
	Famciclovir	Oral	500 mg bid × 7–10 d[d]	
Mucocutaneous herpes simplex in immunocompromised host: Prevention of recurrence during intense immunosuppression	Acyclovir	Oral	400 mg 2–5 times daily or 800 mg bid	Treatment is administered during periods when intense immunosuppression is expected—e.g., during antitumor chemotherapy or after transplantation—and is usually continued for 2–3 months.
		IV	5 mg/kg q12h	
	Valacyclovir	Oral	500 mg to 1 g bid or tid	
	Famciclovir	Oral	500 mg bid[c]	
Herpes simplex orolabialis (recurrent)[e]	Penciclovir	Topical	1.0% cream applied q2h during waking hours × 4 d	Treatment shortens healing time and symptom duration by 0.5–1.0 d (compared with placebo).
	Valacyclovir	Oral	2 g q12h × 1 d	Therapy begun at the earliest symptom reduces disease duration by 1 d.
	Famciclovir[c]	Oral	1500 mg once or 750 bid × 1 d	Therapy begun within 1 h of prodrome decreased time to healing by 1.8–2.2 d.
	Docosanol[f]	Topical	10% cream 5 times daily until healed	Application at initial symptoms reduces healing time by 1 d.
Herpes simplex keratitis	Trifluridine	Topical	1 drop of 1% ophthalmic solution q2h while awake (maximum, 9 drops daily)	Therapy should be undertaken in consultation with an ophthalmologist.
	Vidarabine	Topical	0.5-in. ribbon of 3% ophthalmic ointment 5 times daily	
Herpes zoster: Immunocompetent host	Valacyclovir	Oral	1 g tid × 7 d	Valacyclovir may be more effective than acyclovir for pain relief; otherwise, it has a similar effect on cutaneous lesions and should be given within 72 h of rash onset.
	Famciclovir	Oral	500 mg q8h × 7 d	The duration of postherpetic neuralgia is shorter than with placebo. Famciclovir showed overall efficacy similar to that of acyclovir in a comparative trial. It should be given ≤72 h after rash onset.
	Acyclovir	Oral	800 mg 5 times daily × 7–10 d	Acyclovir causes faster resolution of skin lesions than placebo and provides some relief of acute symptoms if given within 72 h of rash onset. Combined with tapering doses of prednisone, acyclovir improves quality-of-life outcomes.

(*continued*)

TABLE 83-1

ANTIVIRAL CHEMOTHERAPY AND CHEMOPROPHYLAXIS (*CONTINUED*)

INFECTION	DRUG	ROUTE	DOSAGE	COMMENT
Herpes zoster: Immunocompromised host	Acyclovir	IV Oral	10 mg/kg q8h × 7 d 800 mg 5 times daily × 7 d	Effectiveness in localized zoster is most marked when treatment is given early. Foscarnet may be used for acyclovir-resistant VZV infections.
	Famciclovir	Oral	500 mg tid × 10 d[c]	
Herpes zoster ophthalmicus	Acyclovir	Oral	600–800 mg 5 times daily × 10 d	Treatment reduces ocular complications, including ocular keratitis and uveitis.
	Valacyclovir	Oral	1 g tid × 7 d	
	Famciclovir	Oral	500 mg tid × 7 d	
Condyloma acuminatum	IFN-α2b	Intralesional	1 million units per wart (maximum of 5) thrice weekly × 3 weeks	Intralesional treatment frequently results in regression of warts, but lesions often recur. Parenteral administration may be useful if lesions are numerous.
	IFN-αn3	Intralesional	250,000 units per wart (maximum of 10) twice weekly × up to 8 weeks	
Chronic hepatitis B	IFN-α2b	SC	5 million units daily or 10 million units thrice weekly × 16–24 weeks	HBeAg and DNA are eliminated in 33–37% of cases. Histopathologic improvement is also seen.
	Pegylated IFN-α2a	SC	180 μg weekly × 48 weeks	ALT levels return to normal in 39% of patients, and histologic improvement occurs in 38%.
	Lamivudine	Oral	100 mg/d × 12–18 months; 150 mg bid as part of therapy for HIV infection	Lamivudine monotherapy is well tolerated and effective in reduction of HBV DNA levels, normalization of ALT levels, and improvement in histopathology. However, resistance develops in 24% of recipients when lamivudine is used as monotherapy for 1 year.
	Adefovir dipivoxil	Oral	10 mg/d × 48 weeks	A return of ALT levels to normal is documented in 48–72% of recipients and improved liver histopathology in 53–64%. Adefovir is effective in lamivudine-resistant hepatitis B. Renal function should be monitored.
	Entecavir	Oral	0.5 mg/d × 48 weeks (1 mg/d if HBV is resistant to lamivudine)	Normalization of ALT is seen in 68–78% of recipients and loss of HBeAg in 21%. Entecavir is active against lamivudine-resistant HBV.
	Telbivudine	Oral	600 mg/d × 52 weeks	HBV DNA is reduced by >5 $\log_{10}$ copies/mL along with normalization of ALT levels in 74–77% of patients and improved histopathology in 65–67%. Resistance develops in 9–22% of patients after 2 years of therapy. Elevated CPK levels and myopathy may occur.
	Tenofovir	Oral	300 mg/d × 48 weeks	ALT levels return to normal in 68–76% of patients, and liver histopathology improves in 72–74%. Resistance is uncommon with up to 2 years of therapy.
Chronic hepatitis C	IFN-α2a or IFN-α2b	SC	3 million units thrice weekly × 12–24 months	SVRs are noted in 20–30% of patients. Normalization of ALT levels and improvements in liver histopathology are also seen.
	IFN-α2b/ ribavirin	SC (IFN)/ oral (ribavirin)	3 million units thrice weekly (IFN)/ 1000–1200 mg daily (ribavirin) × 6–12 months	Combination therapy results in SVR in up to 40–50% of recipients.

(*continued*)

TABLE 83-1

ANTIVIRAL CHEMOTHERAPY AND CHEMOPROPHYLAXIS (*CONTINUED*)

INFECTION	DRUG	ROUTE	DOSAGE	COMMENT
	Pegylated IFN-α2b	SC	1.5 μg weekly × 48 weeks	The slower clearance of pegylated IFNs than of standard IFNs permits once-weekly administration.
	Pegylated IFN-α2a	SC	180 μg weekly × 48 weeks	Pegylated formulations appear to be superior to standard IFNs in efficacy, both as monotherapy and in combination with ribavirin, and have largely supplanted standard IFNs in treatment of hepatitis C. SVRs were seen in 42–51% of patients infected with genotype 1 and in 76–82% of those infected with genotype 2 or 3.
	Pegylated IFN-α2b/ ribavirin	SC (IFN)/ oral (ribavirin)	1.5 μg/kg weekly (IFN)/800–1400 mg daily (ribavirin) × 24–48 weeks	
	Pegylated IFN-α2a/ ribavirin	SC (IFN)/ oral (ribavirin)	180 μg weekly (IFN)/800–1200 mg daily (ribavirin) × 24–48 weeks	
	IFN-alfacon	SC	9–15 μg thrice weekly × 6–12 months	Doses of 9 and 15 μg are equivalent to IFN-α2a and IFN-α2b doses of 3 million and 5 million units, respectively.
Chronic hepatitis D	IFN-α2a or IFN-α2b	SC	9 million units thrice weekly × 12 months	The overall efficacy and the optimal regimen and duration of therapy have not been established. Response rates have varied among studies.
	Pegylated IFN-α2b	SC	1.5 μg weekly × 48 weeks	
	Pegylated IFN-α2a	SC	180 μg weekly × 48 weeks	

[a]For detailed weight recommendations and for children ≥1 year of age, see *www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm*.
[b]Amantadine and rimantadine are not recommended for routine use because of widespread resistance in A/H3N2 and pandemic A/H1N1 viruses in 2009–2010. Their use may be considered if sensitivities become reestablished.
[c]Not approved for this indication by the U.S. Food and Drug Administration (FDA).
[d]Approved by the FDA for treatment of HIV-infected individuals.
[e]Acyclovir suspension (15 mg/kg PO to a maximum of 200 mg per dose) given for 7 d has been reported to be effective in treatment of primary herpetic gingivostomatitis in children.
[f]Active ingredient: benzyl alcohol. Available without prescription.
Abbreviations: ALT, alanine aminotransferase; CMV, cytomegalovirus; CPK, creatine phosphokinase; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; HSV, herpes simplex virus; IFN, interferon; RSV, respiratory syncytial virus; SVR, sustained virologic response; UV, ultraviolet; VZV, varicella-zoster virus.

of circulating viruses. For example, in the 2008–2009 influenza season, the circulating influenza A/H3N2 viruses were sensitive to both oseltamivir and zanamivir, whereas the seasonal A/H1N1 viruses, although also sensitive to zanamivir, were resistant to oseltamivir. Moreover, the pandemic A/H1N1 viruses that circulated in 2009–2010 remained sensitive to zanamivir and oseltamivir, with a few exceptions in the latter case. Up-to-date information on resistance patterns to antiviral drugs is available from the Centers for Disease Control and Prevention (CDC) at *www.cdc.gov/flu*.

Zanamivir and oseltamivir have been approved by the U.S. Food and Drug Administration (FDA) for treatment of influenza in adults and in children (those ≥7 years old for zanamivir and those ≥1 year old for oseltamivir) who have been symptomatic for ≤2 days. Oseltamivir is approved for prophylaxis of influenza in individuals ≥1 year of age and zanamivir for those ≥5 years of age (Table 83-1). Guidelines for use of oseltamivir in children <1 year of age can be accessed through the CDC website, as noted in the footnote to Table 83-1.

Peramivir, an investigational neuraminidase inhibitor that can be administered intravenously to patients for whom such an intervention is considered necessary, is available as part of clinical trials through BioCryst Pharmaceuticals. Oseltamivir-resistant viruses generally exhibit reduced sensitivity to peramivir.

AMANTADINE AND RIMANTADINE

Amantadine and the closely related compound rimantadine are primary symmetric amines that have antiviral activity limited to influenza A viruses. Amantadine and rimantadine have been shown to be efficacious in the prophylaxis and treatment of influenza A infections in humans for >45 years. High frequencies of resistance to these drugs were noted among influenza A/H3N2 viruses in the 2005–2006 influenza season and continued to be seen in 2008–2009. The pandemic A/H1N1 viruses that circulated in 2009–2010 were also resistant to amantadine and rimantadine. Therefore, these agents are no longer recommended for use unless the sensitivity of the individual influenza A isolate is known, in which case their use may be considered. Amantadine and rimantadine act through inhibition of the ion channel function

of the influenza A M2 matrix protein, on which uncoating of the virus depends. A substitution of a single amino acid at critical sites in the M2 protein can result in a virus that is resistant to amantadine and rimantadine.

Amantadine and rimantadine have been shown to be effective in the prophylaxis of influenza A in large-scale studies of young adults and in less extensive studies of children and elderly persons. In such studies, efficacy rates of 55–80% in the prevention of influenza-like illness were noted, and even higher rates were reported when virus-specific attack rates were calculated. Amantadine and rimantadine have also been found to be effective in the treatment of influenza A infection in studies involving predominantly young adults and, to a lesser extent, children. Administration of these compounds within 24–72 h after the onset of illness has resulted in a reduction of the duration of signs and symptoms by ~50% compared to that in placebo recipients. The effect on signs and symptoms of illness is superior to that of commonly used antipyretic-analgesic agents. Only anecdotal reports are available concerning the efficacy of amantadine or rimantadine in the prevention or treatment of complications of influenza (e.g., pneumonia).

Amantadine and rimantadine are available only in oral formulations and are ordinarily administered to adults once or twice daily, with a dosage of 100–200 mg/d. Despite their structural similarities, the two compounds have different pharmacokinetics. Amantadine is not metabolized and is excreted almost entirely by the kidneys, with a half-life of 12–17 h and peak plasma concentrations of 0.4 μg/mL. In contrast, rimantadine is extensively metabolized to hydroxylated derivatives and has a half-life of 30 h. Only 30–40% of an orally administered dose of rimantadine is recovered in the urine. The peak plasma levels of rimantadine are approximately half those of amantadine, but rimantadine is concentrated in respiratory secretions to a greater extent than amantadine. For prophylaxis, the compounds must be administered daily for the period at risk (i.e., duration of the exposure). For therapy, amantadine or rimantadine is generally administered for 5–7 days.

Although these compounds are generally well tolerated, 5–10% of amantadine recipients experience mild central nervous system side effects consisting primarily of dizziness, anxiety, insomnia, and difficulty in concentrating. These effects are rapidly reversible upon cessation of the drug's administration. At a dose of 200 mg/d, rimantadine is better tolerated than amantadine; in a large-scale study of young adults, adverse effects were no more frequent among rimantadine recipients than among placebo recipients. Seizures and worsening of congestive heart failure have also been reported in patients treated with amantadine, although a causal relationship has not been established. The dosage of amantadine should be reduced to 100 mg/d in patients with renal insufficiency (i.e., a creatinine clearance rate [Cr_{Cl}] of <50 mL/min) and in the elderly. A rimantadine dose of 100 mg/d should be used for patients with a Cr_{Cl} of <10 mL/min and for the elderly.

RIBAVIRIN

Ribavirin is a synthetic nucleoside analogue that inhibits a wide range of RNA and DNA viruses. The mechanism of action of ribavirin is not completely defined and may be different for different groups of viruses. Ribavirin-5′-monophosphate blocks the conversion of inosine-5′-monophosphate to xanthosine–5′-monophosphate and interferes with the synthesis of guanine nucleotides as well as that of both RNA and DNA. Ribavirin-5′-monophosphate also inhibits capping of virus-specific messenger RNA in certain viral systems.

Ribavirin administered as a small-particle aerosol to young children hospitalized with RSV infection has been clinically beneficial and has improved oxygenation in some studies (7 of 11). Although ribavirin has been approved for treatment of infants hospitalized with respiratory syncytial virus (RSV) infection, the American Academy of Pediatrics has recommended that its use be considered on an individual basis rather than routinely in that setting. Aerosolized ribavirin has also been administered to older children and adults (including immunosuppressed patients) with severe RSV and parainfluenza virus infections and to older children and adults with influenza A or B infection, but the benefit of this treatment, if any, is unclear. In RSV infections in immunosuppressed patients, ribavirin is often given in combination with anti-RSV immunoglobulins.

Orally administered ribavirin has not been effective in the treatment of influenza A virus infections. IV or oral ribavirin has reduced mortality rates among patients with Lassa fever; it has been particularly effective in this regard when given within the first 6 days of illness. IV ribavirin has been reported to be of clinical benefit in the treatment of hemorrhagic fever with renal syndrome caused by Hantaan virus and as therapy for Argentinean hemorrhagic fever. Oral ribavirin has also been recommended for the treatment and prophylaxis of Congo-Crimean hemorrhagic fever. An open-label trial suggested that oral ribavirin may be beneficial in the treatment of Nipah virus encephalitis. Use of IV ribavirin in patients with hantavirus pulmonary syndrome in the United States has not been associated with clear-cut benefits. Oral administration of ribavirin reduces serum aminotransferase levels in patients with chronic hepatitis C virus (HCV) infection; since it appears not to reduce serum HCV RNA levels, the mechanism of this effect is unclear. The drug provides added benefit when given by mouth in doses of 800–1200 mg/d in combination with interferon (IFN) α2b or α2a (see later in the chapter), and the ribavirin/IFN combination has been approved for the treatment of patients with chronic HCV infection. Large oral doses of ribavirin (800–1000 mg/d) have been associated with reversible hematopoietic toxicity. This effect has not been observed with aerosolized ribavirin, apparently because little drug is absorbed systemically. Aerosolized administration of ribavirin is generally well tolerated but occasionally is associated with bronchospasm, rash, or conjunctival irritation. It should be administered under close supervision—particularly in the setting of mechanical ventilation, where precipitation of

the drug is possible. Health care workers exposed to the drug have experienced minor toxicity, including eye and respiratory tract irritation. Because ribavirin is mutagenic, teratogenic, and embryotoxic, its use is generally contraindicated in pregnancy. Its administration as an aerosol poses a risk to pregnant health care workers. Because clearance of ribavirin is primarily renal, dose reduction is required in the setting of significant renal dysfunction.

ANTIVIRAL DRUGS ACTIVE AGAINST HERPESVIRUS INFECTIONS

ACYCLOVIR AND VALACYCLOVIR

Acyclovir is a highly potent and selective inhibitor of the replication of certain herpesviruses, including herpes simplex virus (HSV) types 1 and 2, varicella-zoster virus (VZV), and Epstein-Barr virus (EBV). It is relatively ineffective in the treatment of human cytomegalovirus (CMV) infections; however, some studies have indicated effectiveness in the prevention of CMV-associated disease in immunosuppressed patients. Valacyclovir, the L-valyl ester of acyclovir, is converted almost entirely to acyclovir by intestinal and hepatic hydrolysis after oral administration. Valacyclovir has pharmacokinetic advantages over orally administered acyclovir: it exhibits significantly greater oral bioavailability, results in higher blood levels, and can be given less frequently than acyclovir (two or three rather than five times daily).

The high degree of selectivity of acyclovir is related to its mechanism of action, which requires that the compound first be phosphorylated to acyclovir monophosphate. This phosphorylation occurs efficiently in herpesvirus-infected cells by means of a virus-coded thymidine kinase. In uninfected mammalian cells, little phosphorylation of acyclovir occurs, and the drug is therefore concentrated in herpesvirus-infected cells. Acyclovir monophosphate is subsequently converted by host cell kinases to a triphosphate that is a potent inhibitor of virus-induced DNA polymerase but has relatively little effect on host cell DNA polymerase. Acyclovir triphosphate can also be incorporated into viral DNA, with early chain termination.

Acyclovir is available in IV, oral, and topical forms, while valacyclovir is available in an oral formulation. IV acyclovir is effective in the treatment of mucocutaneous HSV infections in immunocompromised hosts, in whom it reduces time to healing, duration of pain, and virus shedding. When administered prophylactically during periods of intense immunosuppression (e.g., related to chemotherapy for leukemia or transplantation) and before the development of lesions, IV acyclovir reduces the frequency of HSV-associated disease. After prophylaxis is discontinued, HSV lesions recur. IV acyclovir is also effective in the treatment of HSV encephalitis.

Because VZV is generally less sensitive to acyclovir than is HSV, higher doses of acyclovir must be used to treat VZV infections. In immunocompromised patients with herpes zoster, IV acyclovir reduces the frequency of cutaneous dissemination and visceral complications and—in one comparative trial—was more effective than vidarabine. Acyclovir, administered at oral doses of 800 mg five times a day, had a modest beneficial effect on localized herpes zoster lesions in both immunocompromised and immunocompetent patients. Combination of acyclovir with a tapering regimen of prednisone appeared to be more effective than acyclovir alone in terms of quality-of-life outcomes in immunocompetent patients over age 50 with herpes zoster. A comparative study of acyclovir (800 mg PO five times daily) and valacyclovir (1 g PO three times daily) in immunocompetent patients with herpes zoster indicated that the latter drug may be more effective in eliciting the resolution of zoster-associated pain. Orally administered acyclovir (600 mg five times a day) reduced complications of herpes zoster ophthalmicus in a placebo-controlled trial.

In chickenpox, a modest overall clinical benefit is attained when oral acyclovir therapy is begun within 24 h of the onset of rash in otherwise healthy children (20 mg/kg, up to a maximum of 800 mg, four times a day) or adults (800 mg five times a day). IV acyclovir has also been reported to be effective in the treatment of immunocompromised children with chickenpox.

The most widespread use of acyclovir is in the treatment of genital HSV infections. IV or oral acyclovir or oral valacyclovir has shortened the duration of symptoms, reduced virus shedding, and accelerated healing when employed for the treatment of primary genital HSV infections. Oral acyclovir and valacyclovir have also had a modest effect in treatment of recurrent genital HSV infections. However, the failure of treatment of either primary or recurrent disease to reduce the frequency of subsequent recurrences has indicated that acyclovir is ineffective in eliminating latent infection. Chronic oral administration of acyclovir for ≥1–6 years or of valacyclovir for ≥1 year has reduced the frequency of recurrences markedly during therapy; once the drug is discontinued, lesions recur. In one study, suppressive therapy with valacyclovir (500 mg once daily for 8 months) reduced transmission of HSV-2 genital infections among discordant couples by 50%. A modest effect on herpes labialis (i.e., a reduction of disease duration by 1 day) was seen when valacyclovir was administered upon detection of the first symptom of a lesion at a dose of 2 g every 12 h for 1 day. In AIDS patients, chronic or intermittent administration of acyclovir has been associated with the development of HSV and VZV strains resistant to the action of the drug and with clinical failures. The most common mechanism of resistance is a deficiency of the virus-induced thymidine kinase. Patients with HSV or VZV infections resistant to acyclovir have frequently responded to foscarnet.

With the availability of the oral and IV forms, there are few indications for topical acyclovir, although treatment with this formulation has been modestly beneficial in primary genital HSV infections and in mucocutaneous HSV infections in immunocompromised hosts.

Overall, acyclovir is remarkably well tolerated and is generally free of toxicity. The most frequently encountered form of toxicity is renal dysfunction because of drug crystallization, particularly after rapid IV administration or with inadequate hydration. Central nervous system changes, including lethargy and tremors, are occasionally reported, primarily in immunosuppressed patients. However, whether these changes are related to acyclovir, to concurrent administration of other therapy, or to underlying infection remains unclear. Acyclovir is excreted primarily unmetabolized by the kidneys via both glomerular filtration and tubular secretion. Approximately 15% of a dose of acyclovir is metabolized to 9-([carboxymethoxy] methyl)guanine or other minor metabolites. Reduction in dosage is indicated in patients with a Cr_{Cl} of <50 mL/min. The half-life of acyclovir is ~3 h in normal adults, and the peak plasma concentration after a 1-h infusion of a dose of 5 mg/kg is 9.8 μg/mL. Approximately 22% of an orally administered acyclovir dose is absorbed, and peak plasma concentrations of 0.3–0.9 μg/mL are attained after administration of a 200-mg dose. Acyclovir penetrates relatively well into the cerebrospinal fluid (CSF), with concentrations approaching half of those found in plasma.

Acyclovir causes chromosomal breakage at high doses, but its administration to pregnant women has not been associated with fetal abnormalities. Nonetheless, the potential risks and benefits of acyclovir should be carefully assessed before the drug is used in pregnancy.

Valacyclovir exhibits three to five times greater bioavailability than acyclovir. The concentration-time curve for valacyclovir, given as 1 g PO three times daily, is similar to that for acyclovir, given as 5 mg/kg IV every 8 h. The safety profiles of valacyclovir and acyclovir are similar, although thrombotic thrombocytopenic purpura/hemolytic-uremic syndrome has been reported in immunocompromised patients who have received high doses of valacyclovir (8 g/d). Valacyclovir is approved for the treatment of herpes zoster, of initial and recurrent episodes of genital HSV infection, and of herpes labialis in immunocompetent adults as well as for suppressive treatment of genital herpes. Although it has not been extensively studied in other clinical settings involving HSV or VZV infections, many consultants use valacyclovir rather than oral acyclovir in settings where only the latter has been approved because of valacyclovir's superior pharmacokinetics and more convenient dosing schedule.

CIDOFOVIR

Cidofovir is a phosphonate nucleotide analogue of cytosine. Its major use is in CMV infections, particularly retinitis, but it is active against a broad range of herpesviruses, including HSV, human herpesvirus (HHV) type 6, HHV-8, and certain other DNA viruses such as polyomaviruses, papillomaviruses, adenoviruses, and poxviruses, including variola (smallpox) and vaccinia. Cidofovir does not require initial phosphorylation by virus-induced kinases; the drug is phosphorylated by host cell enzymes to cidofovir diphosphate, which is a competitive inhibitor of viral DNA polymerases and, to a lesser extent, of host cell DNA polymerases. Incorporation of cidofovir diphosphate slows or terminates nascent DNA chain elongation. Cidofovir is active against HSV isolates that are resistant to acyclovir because of absent or altered thymidine kinase and against CMV isolates that are resistant to ganciclovir because of UL97 phosphotransferase mutations. CMV isolates resistant to ganciclovir on the basis of UL54 mutations are usually resistant to cidofovir as well. Cidofovir is usually active against foscarnet-resistant CMV, although cross-resistance to foscarnet has also been described.

Cidofovir has poor oral availability and is administered intravenously. It is excreted primarily by the kidney and has a plasma half-life of 2.6 h. Cidofovir diphosphate's intracellular half-life of >48 h is the basis for the recommended dosing regimen of 5 mg/kg once a week for the initial 2 weeks and then 5 mg/kg every other week. The major toxic effect of cidofovir is proximal renal tubular injury, as manifested by elevated serum creatinine levels and proteinuria. The risk of nephrotoxicity can be reduced by vigorous saline hydration and by concomitant oral administration of probenecid. Neutropenia, rashes, and gastrointestinal tolerance may also occur.

IV cidofovir has been approved for the treatment of CMV retinitis in AIDS patients who are intolerant of ganciclovir or foscarnet or in whom those drugs have failed. In a controlled study, a maintenance dosage of 5 mg/kg per week administered to AIDS patients reduced the progression of CMV retinitis from that seen at 3 mg/kg. Intravitreal cidofovir has been used to treat CMV retinitis but has been associated with significant toxicity. IV cidofovir has been reported anecdotally to be effective for treatment of acyclovir-resistant mucocutaneous HSV infections. Likewise, topically administered cidofovir is reportedly beneficial against mucocutaneous HSV infections in HIV-infected patients. Anecdotal use of IV cidofovir has been described in disseminated adenoviral infections in immunosuppressed patients and in genitourinary infections with BK virus in renal transplant recipients; however, its efficacy, if any, in these circumstances is not established.

FOMIVIRSEN

Fomivirsen is the first antisense oligonucleotide approved by the FDA for therapy in humans. This phosphorothioate oligonucleotide, 21 nucleotides in length, inhibits CMV replication through interaction with CMV messenger RNA. Fomivirsen is complementary to messenger transcripts of the major immediate early region 2 (IE2) of CMV, which codes for proteins regulating viral gene expression. In addition to its antisense mechanism of action, fomivirsen may exert activity against CMV through inhibition of viral adsorption to cells as well as direct inhibition of viral replication. Because of its different mechanism of action, fomivirsen is active against CMV isolates that are resistant to nucleoside or nucleotide analogues, such as ganciclovir, foscarnet, or cidofovir.

Fomivirsen has been approved for intravitreal administration in the treatment of CMV retinitis in AIDS patients who have failed to respond to other treatments or cannot tolerate them. Injections of 330 mg for two doses 2 weeks apart, followed by maintenance doses of 330 mg monthly, significantly reduce the rate of progression of CMV retinitis. The major toxicity is ocular inflammation, including vitritis and iritis, which usually responds to topically administered glucocorticoids.

GANCICLOVIR AND VALGANCICLOVIR

An analogue of acyclovir, ganciclovir is active against HSV and VZV and is markedly more active than acyclovir against CMV. Ganciclovir triphosphate inhibits CMV DNA polymerase and can be incorporated into CMV DNA, whose elongation it eventually terminates. In HSV- and VZV-infected cells, ganciclovir is phosphorylated by virus-encoded thymidine kinases; in CMV-infected cells, it is phosphorylated by a viral kinase encoded by the UL97 gene. Ganciclovir triphosphate is present in tenfold higher concentrations in CMV-infected cells than in uninfected cells. Ganciclovir is approved for the treatment of CMV retinitis in immunosuppressed patients and for the prevention of CMV disease in transplant recipients. It is widely used for the treatment of other CMV-associated syndromes, including pneumonia, esophagogastrointestinal infections, hepatitis, and "wasting" illness.

Ganciclovir is available for IV or oral administration. Because its oral bioavailability is low (5–9%), relatively large doses (1 g three times daily) must be administered by this route. Oral ganciclovir has largely been supplanted by valganciclovir, which is the L-valyl ester of ganciclovir. Valganciclovir is well absorbed orally, with a bioavailability of 60%, and is rapidly hydrolyzed to ganciclovir in the intestine and liver. The area under the curve for a 900-mg dose of valganciclovir is equivalent to that for 5 mg/kg of IV ganciclovir, although peak serum concentrations are ~40% lower for valganciclovir. The serum half-life is 3.5 h after IV administration of ganciclovir and 4.0 h after PO administration of valganciclovir. Ganciclovir is excreted primarily by the kidneys in an unmetabolized form, and its dosage should be reduced in cases of renal failure. Ganciclovir therapy at the most commonly employed initial IV dosage—i.e., 5 mg/kg every 12 h for 14–21 days—can be changed to valganciclovir (900 mg PO twice daily) when the patient can tolerate oral therapy. The maintenance dose is 5 mg/kg IV daily or five times per week for ganciclovir and 900 mg by mouth once a day for valganciclovir. Dose adjustment in patients with renal dysfunction is required. Intraocular ganciclovir, given by either intravitreal injection or intraocular implantation, has also been used to treat CMV retinitis.

Ganciclovir is effective as prophylaxis against CMV-associated disease in organ and bone marrow transplant recipients. Oral ganciclovir administered prophylactically to AIDS patients with CD4+ T cell counts of $<100/\mu L$ has provided protection against the development of CMV retinitis. However, the long-term benefits of this approach to prophylaxis in AIDS patients have not been established, and most experts do not recommend the use of oral ganciclovir for this purpose. As already mentioned, valganciclovir has supplanted oral ganciclovir in settings where oral prophylaxis or therapy is considered.

The administration of ganciclovir has been associated with profound bone marrow suppression, particularly neutropenia, which significantly limits the drug's use in many patients. Bone marrow toxicity is potentiated in the setting of renal dysfunction and when other bone marrow suppressants, such as zidovudine or mycophenolate mofetil, are used concomitantly.

Resistance has been noted in CMV isolates obtained after therapy with ganciclovir, especially in patients with AIDS. Such resistance may develop through a mutation in either the viral UL97 gene or the viral DNA polymerase. Ganciclovir-resistant isolates are usually sensitive to foscarnet (see later in the chapter) or cidofovir (see earlier in the chapter).

FAMCICLOVIR AND PENCICLOVIR

Famciclovir is the diacetyl 6-deoxyester of the guanosine analogue penciclovir. Famciclovir is well absorbed orally, has a bioavailability of 77%, and is rapidly converted to penciclovir by deacetylation and oxidation in the intestine and liver. Penciclovir's spectrum of activity and mechanism of action are similar to those of acyclovir. Thus, penciclovir usually is not active against acyclovir-resistant viruses. However, some acyclovir-resistant viruses with altered thymidine kinase or DNA polymerase substrate specificity may be sensitive to penciclovir. This drug is phosphorylated initially by a virus-encoded thymidine kinase and subsequently by cellular kinases to penciclovir triphosphate, which inhibits HSV-1, HSV-2, VZV, and EBV as well as hepatitis B virus (HBV). The serum half-life of penciclovir is 2 h, but the intracellular half-life of penciclovir triphosphate is 7–20 h—markedly longer than that of acyclovir triphosphate. The latter is the basis for the less frequent (twice-daily) dosing schedule for famciclovir than for acyclovir. Penciclovir is eliminated primarily in the urine by both glomerular filtration and tubular secretion. The usually recommended dosage interval should be adjusted for renal insufficiency.

Clinical trials involving immunocompetent adults with herpes zoster showed that famciclovir was superior to placebo in eliciting the resolution of skin lesions and virus shedding and in shortening the duration of postherpetic neuralgia; moreover, administered at 500 mg every 8 h, famciclovir was at least as effective as acyclovir administered at an oral dose of 800 mg five times daily. Famciclovir was also effective in the treatment of herpes zoster in immunosuppressed patients. Clinical trials have demonstrated its effectiveness in the suppression of genital HSV infections for up to 1 year and in the treatment of initial and recurrent episodes of genital herpes. Famciclovir is effective as therapy

for mucocutaneous HSV infections in HIV-infected patients. Application of a 1% penciclovir cream reduces the duration of signs and symptoms of herpes labialis in immunocompetent patients (by 0.5–1 day) and has been approved for that purpose by the FDA. Famciclovir is generally well tolerated, with occasional headache, nausea, and diarrhea reported in frequencies similar to those among placebo recipients. The administration of high doses of famciclovir for 2 years was associated with an increased incidence of mammary adenocarcinomas in female rats, but the clinical significance of this effect is unknown.

FOSCARNET

Foscarnet (phosphonoformic acid) is a pyrophosphate-containing compound that potently inhibits herpesviruses, including CMV. This drug inhibits DNA polymerases at the pyrophosphate binding site at concentrations that have relatively little effect on cellular polymerases. Foscarnet does not require phosphorylation to exert its antiviral activity and is therefore active against HSV and VZV isolates that are resistant to acyclovir because of deficiencies in thymidine kinase as well as against most ganciclovir-resistant strains of CMV. Foscarnet also inhibits the reverse transcriptase of HIV and is active against HIV in vivo.

Foscarnet is poorly soluble and must be administered intravenously via an infusion pump in a dilute solution over 1–2 h. The plasma half-life of foscarnet is 3–5 h and increases with decreasing renal function, since the drug is eliminated primarily by the kidneys. It has been estimated that 10–28% of a dose may be deposited in bone, where it can persist for months. The most common initial dosage of foscarnet—60 mg/kg every 8 h for 14–21 days—is followed by a maintenance dose of 90–120 mg/kg once a day.

Foscarnet is approved for the treatment of CMV retinitis in patients with AIDS and of acyclovir-resistant mucocutaneous HSV infections. In a comparative clinical trial, the drug appeared to be about as efficacious as ganciclovir against CMV retinitis but was associated with a longer survival period, possibly because of its activity against HIV. Intraocular foscarnet has been used to treat CMV retinitis. Foscarnet has also been employed to treat acyclovir-resistant HSV and VZV infections as well as ganciclovir-resistant CMV infections, although resistance to foscarnet has been reported in CMV isolates obtained during therapy. Foscarnet has also been used to treat HHV-6 infections in immunosuppressed patients.

The major form of toxicity associated with foscarnet is renal impairment. Thus renal function should be monitored closely, particularly during the initial phase of therapy. Since foscarnet binds divalent metal ions, hypocalcemia, hypomagnesemia, hypokalemia, and hypo- or hyperphosphatemia can develop. Saline hydration and slow infusion appear to protect the patient against nephrotoxicity and electrolyte disturbances. Although hematologic abnormalities have been documented (most commonly anemia), foscarnet is not generally myelosuppressive and can be administered concomitantly with myelosuppressive medications such as zidovudine.

TRIFLURIDINE

Trifluridine is a pyrimidine nucleoside active against HSV-1, HSV-2, and CMV. Trifluridine monophosphate irreversibly inhibits thymidylate synthetase, and trifluridine triphosphate inhibits viral and, to a lesser extent, cellular DNA polymerases. Because of systemic toxicity, its use is limited to topical therapy. Trifluridine is approved for treatment of HSV keratitis, against which trials have shown that it is more effective than topical idoxuridine but similar in efficacy to topical vidarabine. The drug has benefited some patients with HSV keratitis who have failed to respond to idoxuridine or vidarabine. Topical application of trifluridine to sites of acyclovir-resistant HSV mucocutaneous infections has also been beneficial in some cases.

VIDARABINE

Vidarabine is a purine nucleoside analogue with activity against HSV-1, HSV-2, VZV, and EBV. Vidarabine inhibits viral DNA synthesis through its 5′-triphosphorylated metabolite, although its precise molecular mechanisms of action are not completely understood. IV-administered vidarabine has been shown to be effective in the treatment of herpes simplex encephalitis, mucocutaneous HSV infections, herpes zoster in immunocompromised patients, and neonatal HSV infections. Its use has been supplanted by that of IV acyclovir, which is more effective and easier to administer. Production of the IV preparation has been discontinued by the manufacturer, but vidarabine is available as an ophthalmic ointment, which is effective in the treatment of HSV keratitis.

ANTIVIRAL DRUGS ACTIVE AGAINST HEPATITIS VIRUSES

LAMIVUDINE

Lamivudine is a pyrimidine nucleoside analogue that is used primarily in combination therapy against HIV infection (Chap. 93). Its activity against hepatitis B virus (HBV) is attributable to inhibition of the viral DNA polymerase. This drug has also been approved for the treatment of chronic HBV infection. At doses of 100 mg/d given for 1 year to patients positive for hepatitis B e antigen (HBeAg), lamivudine is well tolerated and results in suppression of HBV DNA levels, normalization of serum aminotransferase levels in 40–75% of patients, and reduction of hepatic inflammation and fibrosis in 50–60% of patients. Loss of HBeAg occurs in 30% of patients. Lamivudine also appears to be useful in the prevention or suppression of HBV infection associated with liver transplantation.

Resistance to lamivudine develops in 24% of patients treated for 1 year and is associated with changes in the YMDD motif of HBV DNA polymerase. Because of the frequency of development of resistance, lamivudine has been largely supplanted by less-resistance-prone drugs for the treatment of HBV infection.

ADEFOVIR DIPIVOXIL

Adefovir dipivoxil is the oral prodrug of adefovir, an acyclic nucleotide analogue of adenosine monophosphate that has activity against HBV, HIV, HSV, CMV, and poxviruses. It is phosphorylated by cellular kinases to the active triphosphate moiety, which is a competitive inhibitor of HBV DNA polymerase and results in chain termination after incorporation into nascent viral DNA. Adefovir is administered orally and is eliminated primarily by the kidneys, with a plasma half-life of 5–7.5 h. In clinical studies, therapy with adefovir at a dose of 10 mg/d for 48 weeks resulted in normalization of serum alanine aminotransferase (ALT) levels in 48–72% of patients and improved liver histology in 53–64%; it also resulted in a 3.5- to 3.9-$\log_{10}$ reduction in the number of HBV DNA copies per milliliter of plasma. Adefovir was effective in treatment-naïve patients as well as in those infected with lamivudine-resistant HBV. Resistance to adefovir appears to develop less readily than that to lamivudine, but adefovir resistance rates of 15–18% have been reported after 192 weeks of treatment and may reach 30% after 5 years. This agent is generally well tolerated. Significant nephrotoxicity attributable to adefovir is uncommon at the dose employed in the treatment of HBV infections (10 mg/d) but is a treatment-limiting adverse effect at the higher doses used in therapy for HIV infections (30–120 mg/d). In any case, renal function should be monitored in patients taking adefovir, even at the lower dose. Adefovir is approved only for treatment of chronic HBV infection.

TENOFOVIR

Tenofovir disoproxil fumarate is a prodrug of tenofovir, a nucleotide analogue of adenosine monophosphate with activity against both retroviruses and hepadnaviruses. In both immunocompetent and immunocompromised patients (including those co-infected with HIV and HBV), tenofovir given at a dose of 300 mg/d for 48 weeks reduced HBV replication by 4.6–6 $\log_{10}$, normalized ALT levels in 68–76% of patients, and improved liver histopathology in 72–74% of patients. Resistance develops uncommonly during ≥2 years of therapy, and tenofovir is active against lamivudine-resistant HBV. The safety profile of tenofovir is similar to that of adefovir, but nephrotoxicity has not been encountered at the dose used for HBV therapy. Tenofovir is approved for the treatment of HIV and chronic HBV infections. For a more detailed discussion of tenofovir, see Chap. 93.

ENTECAVIR

Entecavir is a cyclopentyl 2′-deoxyguanosine analogue that inhibits HBV through interaction of entecavir triphosphate with several HBV DNA polymerase functions. At a dose of 0.5 mg/d given for 48 weeks, entecavir reduced HBV DNA copies by 5.0–6.9 $\log_{10}$, normalized serum aminotransferase levels in 68–78% of patients, and improved histopathology in 70–72% of patients. Entecavir inhibits lamivudine-resistant viruses that have M550I or M550V/L526M mutations but only at serum concentrations 20- or 30-fold higher than those obtained with the 0.5-mg/d dose. Thus, higher doses of entecavir (1 mg/d) are recommended for the treatment of patients infected with lamivudine-resistant HBV. Development of resistance to entecavir is uncommon in treatment-naïve patients but does occur at unacceptably high rates (43% after 4 years) in patients previously infected with lamivudine-resistant virus. Entecavir-resistant strains appear to be sensitive to adefovir and tenofovir.

Entecavir is highly bioavailable but should be taken on an empty stomach since food interferes with its absorption. The drug is eliminated primarily in unchanged form by the kidneys, and its dosage should be adjusted for patients with Cr_{Cl} values of <50 mL/min. Overall, entecavir is well tolerated, with a safety profile similar to that of lamivudine. As with other anti-HBV treatments, exacerbation of hepatitis may occur when entecavir therapy is stopped. Entecavir is approved for treatment of chronic hepatitis B, including infection with lamivudine-resistant viruses, in adults. Entecavir has some activity against HIV-1 (median effective concentration, 0.026 to >10 μM) but should not be used as monotherapy in HIV-positive patients because of the potential for development of HIV resistance due to the M184V mutation.

TELBIVUDINE

Telbivudine is a β-l enantiomer of thymidine and is a potent, selective inhibitor of HBV. Its active form is telbivudine triphosphate, which inhibits HBV DNA polymerase and causes chain termination but has little or no activity against human DNA polymerase. Administration of telbivudine at an oral dose of 600 mg/d for 52 weeks to patients with chronic hepatitis B resulted in reduction of HBV DNA by 5.2–6.4 $\log_{10}$ copies/mL along with normalization of ALT levels in 74–77% of recipients and improved histopathology in 65–67% of patients. Telbivudine-resistant HBV is generally cross-resistant with lamivudine-resistant virus but is usually susceptible to adefovir. After 2 years of therapy, resistance to telbivudine was noted in isolates from 22% of HBeAg-positive patients and in those from 9% of HBeAg-negative patients.

Orally administered telbivudine is rapidly absorbed; because it is eliminated primarily by the kidneys, its dosage should be reduced in patients with a Cr_{Cl} value of <50 mL/min. Telbivudine is generally well tolerated, but increases in serum levels of creatinine kinases as well as fatigue and myalgias have been observed. As with

other anti-HBV drugs, hepatitis may be exacerbated in patients who discontinue telbivudine therapy. Telbivudine has been approved for the treatment of adults with chronic hepatitis B who have evidence of viral replication and either persistently elevated serum aminotransferase levels or histopathologically active disease, but it has not been widely used because of the frequency of development of resistance noted earlier.

INTERFERONS

IFNs are cytokines that exhibit a broad spectrum of antiviral activities as well as immunomodulating and antiproliferative properties. IFNs are not available for oral administration but must be given IM, SC, or IV. Early studies with human leukocyte IFN demonstrated an effect in the prophylaxis of experimentally induced rhinovirus infections in humans and in the treatment of VZV infections in immunosuppressed patients. DNA recombinant technology has made available highly purified α, β, and γ IFNs that have been evaluated in a variety of viral infections. Results of such trials have confirmed the effectiveness of intranasally administered IFN in the prophylaxis of rhinovirus infections, although its use has been associated with nasal mucosal irritation. Studies have also demonstrated a beneficial effect of intralesionally or systemically administered IFNs on genital warts. The effect of systemic administration consists primarily of a reduction in the size of the warts, and this mode of therapy may be useful in persons who have numerous warts that cannot easily be treated by individual intralesional injections. However, lesions frequently recur after either intralesional or systemic IFN therapy is discontinued.

IFNs have undergone extensive study in the treatment of chronic HBV infection. The administration of standard IFN-α2b (5 million units daily or 10 million units three times a week for 16–24 weeks) to patients with stable chronic HBV infection resulted in loss of markers of HBV replication, such as HBeAg and HBV DNA, in 33–37% of cases; 8% of patients also became negative for hepatitis B surface antigen. In most patients who lose HBeAg and HBV DNA markers, serum aminotransferases return to normal levels, and both short- and long-term improvements in liver histopathology have been described. Predictors of a favorable response to standard IFN therapy include low pretherapy levels of HBV DNA, high pretherapy serum levels of ALT, a short duration of chronic HBV infection, and active inflammation in liver histopathology. Poor responses are seen in immunosuppressed patients, including those with HIV infection.

In pegylated IFNs, IFN alphas are linked to polyethylene glycol. This linkage results in slower absorption, decreased clearance, and more sustained serum concentrations, thereby permitting a more convenient, once-weekly dosing schedule; in many instances, pegylated IFN has supplanted standard IFN. After 48 weeks of treatment with 180 μg of pegylated IFN-α2a, HBV DNA was reduced by 4.1–4.5 $\log_{10}$ copies/mL, with normalization of serum ALT levels in 39% of patients and improved histology in 38%. Response rates were somewhat higher when lamivudine was administered with pegylated IFN-α2a. Adverse effects of IFN are common and include fever, chills, myalgia, fatigue, neurotoxicity (manifested primarily as somnolence, depression, anxiety, and confusion), and leukopenia. Autoantibodies (e.g., antithyroid antibodies) can also develop. IFN-α2b and pegylated IFN-α2a are approved for the treatment of patients with chronic hepatitis B. Data supporting the therapeutic efficacy of pegylated interferon-α2b in HBV infection have been published; the drug has not been approved for this indication in the United States but has been approved for treatment of chronic HBV infection in other countries.

Several IFN preparations, including IFN-α2a, IFN-α2b, IFN-alfacon-1, and IFN-αm1 (lymphoblastoid), have been studied as therapy for chronic HCV infections. A variety of monotherapy regimens have been studied, of which the most common for standard IFN is IFN-α2b or -α2a at 3 million units three times per week for 12–18 months. The addition of oral ribavirin to IFN-α2b—either as initial therapy or after failure of IFN therapy alone—results in significantly higher rates of sustained virologic and/or serum ALT responses (40–50%) than are obtained with monotherapy. Comparative studies indicate that pegylated IFN-α2b or -α2a therapy is more effective than standard IFN treatment against chronic HCV infection. The combination of SC pegylated IFN and oral ribavirin is more convenient and appears to be the most effective regimen for treatment of chronic hepatitis C. With this combination regimen, sustained virologic responses (SVRs) were seen in 42–51% of patients with genotype 1 infection and in 76–82% of patients with genotype 2 or 3 infection. Ribavirin appears to have a small antiviral effect in HCV infection but may also be working through an immunomodulatory effect in combination with IFN. Optimal results with ribavirin appear to be associated with weight-based dosing. Prognostic factors for a favorable response include an age of <40 years, a short duration of infection, low levels of HCV RNA, a lesser degree of liver histopathology, and infection with HCV genotypes other than 1. IFN-alfacon, a synthetic "consensus" α interferon, appears to produce response rates similar to those elicited by standard IFN-α2a or -α2b alone and is also approved in the United States for the treatment of chronic hepatitis C.

The efficacy of IFN-α treatment for chronic hepatitis D remains unestablished. Anecdotal reports suggested that doses ranging from 5 million units daily to 9 million units three times per week for 12 months elicit biochemical and virologic responses. Results from small controlled trials have been inconsistent, and observed responses have not generally been sustained. Limited experience has been published with the use of pegylated IFN-α2a or -α2b for treatment of hepatitis D, but some consultants prefer these agents for this indication because of their pharmacologic advantages over standard IFN.

PROTEASE INHIBITORS

This drug class is specifically designed to inhibit the 3/4A (NS3/4A) HCV protease. These agents resemble the HCV polypeptide and, when processed by the viral protease, form a covalent bond with the catalytic serine residues and block further activity. The most clinically advanced compound in this class is telaprevir. In initial phase 1 and 2 clinical studies, telaprevir monotherapy decreased the HCV load by 2–5 $\log_{10}$. Telaprevir in combination with IFN and ribavirin increased the SVR rate from ~40% to 60% when used as primary therapy for genotype 1 infections. For re-treatment of HCV-infected patients in whom prior IFN/ribavirin therapy had failed, the addition of telaprevir plus pegylated IFN/ribavirin increased the SVR rate to 51–53%. The combination of telaprevir/pegylated IFN and ribavirin is superior to this combination without ribavirin. Typically, an oral loading dose of 1125 mg is followed by 750 mg every 8 h orally for 12–24 weeks. Monotherapy is associated with the rapid emergence of antiviral resistance; substitutions are found in the NS3 protease, especially double variants at positions V35M and R155K. Telaprevir therapy is associated with rashes in ~50% of patients; these eruptions are severe in ~5% of cases and often develop weeks after therapy has begun. Data suggest that telaprevir has the potential to increase the SVR rate and may shorten the overall duration of HCV therapy from 48 to 24 weeks when used in conjunction with pegylated IFN and ribavirin. As of this writing (February 2011), protease inhibitors have not been approved for treatment of HCV.

CHAPTER 84

HERPES SIMPLEX VIRUS INFECTIONS

Lawrence Corey

DEFINITION

Herpes simplex viruses (HSV-1, HSV-2; *Herpesvirus hominis*) produce a variety of infections involving mucocutaneous surfaces, the central nervous system (CNS), and—on occasion—visceral organs. Prompt recognition and treatment reduce the morbidity and mortality rates associated with HSV infections.

ETIOLOGIC AGENT

The genome of HSV is a linear, double-strand DNA molecule (molecular weight, ~100 × 10^6) that encodes >90 transcription units with 84 identified proteins. The genomic structures of the two HSV subtypes are similar. The overall genomic sequence homology between HSV-1 and HSV-2 is ~50%, while the proteome homology is >80%. The homologous sequences are distributed over the entire genome map, and most of the polypeptides specified by one viral type are antigenically related to polypeptides of the other viral type. Many type-specific regions unique to HSV-1 and HSV-2 proteins do exist, however, and a number of them appear to be important in host immunity. These type-specific regions have been used to develop serologic assays that distinguish between the two viral subtypes. Either restriction endonuclease analysis or sequencing of viral DNA can be used to distinguish between the two subtypes and among strains of each subtype. The variability of nucleotide sequences from clinical strains of HSV-1 and HSV-2 is such that HSV isolates obtained from two individuals can be differentiated by restriction enzyme patterns or genomic sequences. Moreover, epidemiologically related sources, such as sexual partners, mother-infant pairs, or persons involved in a common-source outbreak, can be inferred from such patterns.

The viral genome is packaged in a regular icosahedral protein shell (capsid) composed of 162 capsomeres (see Fig. 82-1). The outer covering of the virus is a lipid-containing membrane (envelope) acquired as the DNA-containing capsid buds through the inner nuclear membrane of the host cell. Between the capsid and lipid bilayer of the envelope is the tegument. Viral replication has both nuclear and cytoplasmic phases. Initial attachment

to the cell membrane involves interactions of viral glycoproteins C and B with several cellular heparan sulfate–like surface receptors. Subsequently, viral glycoprotein D binds to cellular co-receptors that belong to the tumor necrosis factor receptor family of proteins, the immunoglobulin superfamily (nectin family), or both. The ubiquity of these receptors contributes to the wide host range of herpesviruses. Replication is highly regulated. After fusion and entry, the nucleocapsid enters the cytoplasm and several viral proteins are released from the virion. Some of these viral proteins shut off host protein synthesis (by increasing cellular RNA degradation), while others "turn on" the transcription of early genes of HSV replication. These early gene products, designated α *genes*, are required for synthesis of the subsequent polypeptide group, the β polypeptides, many of which are regulatory proteins and enzymes required for DNA replication. Most current antiviral drugs interfere with β proteins, such as viral DNA polymerase. The third (γ) class of HSV genes requires viral DNA replication for expression and constitutes most structural proteins specified by the virus.

After viral genome replication and structural protein synthesis, nucleocapsids are assembled in the cell's nucleus. Envelopment occurs as the nucleocapsids bud through the inner nuclear membrane into the perinuclear space. In some cells, viral replication in the nucleus forms two types of inclusion bodies: type A basophilic Feulgen-positive bodies that contain viral DNA and eosinophilic inclusion bodies that are devoid of viral nucleic acid or protein and represent a "scar" of viral infection. Enveloped virions are then transported via the endoplasmic reticulum and the Golgi apparatus to the cell surface.

Viral genomes are maintained by some neuronal cells in a repressed state called *latency*. Latency, which is associated with transcription of only a limited number of virus-encoded RNAs, accounts for the presence of viral DNA and RNA in neural tissue at times when infectious virus cannot be isolated. Maintenance and growth of neural cells from latently infected ganglia in tissue culture result in production of infectious virions (explantation) and in subsequent permissive infection of susceptible cells (cocultivation). Activation of the viral genome may then occur, resulting in *reactivation*, the normal pattern of regulated viral gene expression, replication, and release of HSV. The release of virions from the neuron follows a complex process of anterograde transport down the length of neuronal axons. In experimental animals, ultraviolet light, systemic and local immunosuppression, and trauma to the skin or ganglia are associated with reactivation.

To date, three noncoding RNA latency-associated transcripts (LATs) are the only abundant transcripts in the nuclei of latently infected neurons. Deletion mutants of the genomic region that can become latent have been made, and the efficiency of their later reactivation is reduced. In addition, substitution of HSV-1 LATs for HSV-2 LATs induces an HSV-1 reactivation pattern. Thus, LATs appear to maintain—rather than establish—latency. HSV-1 LATs promote the survival of acutely infected neurons, perhaps by inhibiting apoptotic pathways. Highly expressed during latency, LAT-derived micro-RNA appears to silence expression of the key neurovirulence factor infected-cell protein 34.5 (ICP34.5) and to bind in an antisense configuration to ICP0 messenger RNA to prevent expression of this immediate-early protein, which is vital to HSV reactivation. Studies of individual neurons from cadaveric trigeminal ganglionic explants by microdissection and real-time polymerase chain reaction (PCR) revealed that many more neurons (2–11%) harbor HSV than would be predicted by in situ hybridization studies for LAT and that DNA copy number is similar in LAT-positive and LAT-negative neurons. These findings make it less clear what role LATs play in preventing reactivation. At present, the molecular mechanisms of HSV latency are not completely understood; CD8+ T cells have been found in ganglia of experimental animals and humans and appear to influence the process of reactivation, possibly by inducing antiviral factors such as interferon (IFN) γ. Strategies to interrupt or maintain latency in neurons are not available.

PATHOGENESIS

Exposure to HSV at mucosal surfaces or abraded skin sites permits entry of the virus into cells of the epidermis and dermis and initiation of viral replication therein. HSV infections are usually acquired subclinically. Whether clinical or subclinical, HSV acquisition is associated with sufficient viral replication to permit infection of either sensory or autonomic nerve endings. On entry into the neuronal cell, the virus—or, more likely, the nucleocapsid—is transported intra-axonally to the nerve cell bodies in ganglia. In humans, the transit interval from inoculation of virus in peripheral tissue to spread to the ganglia is unknown. During the initial phase of infection, viral replication occurs in ganglia and contiguous neural tissue. Virus then spreads to other mucocutaneous surfaces through centrifugal migration of infectious virions via peripheral sensory nerves. This mode of spread helps explain the large surface area involved, the high frequency of new lesions distant from the initial crop of vesicles that is characteristic in patients with primary genital or oral-labial HSV infection, and the ability to recover virus from neural tissue distant from neurons innervating the inoculation site. Contiguous spread of locally inoculated virus also may take place and allow further mucosal extension of disease. Recent studies have demonstrated HSV viremia—another mechanism for extension of infection throughout the body—in ~30–40% of persons with primary HSV-2 infection. Latent infection with both viral subtypes in both sensory and autonomic ganglia has been demonstrated. For HSV-1 infection, trigeminal ganglia

are most commonly infected, although extension to the inferior and superior cervical ganglia also occurs. With genital infection, sacral nerve root ganglia (S2–S5) are most commonly affected.

After resolution of primary disease, infectious HSV can no longer be cultured from the ganglia; however, latent infection, as defined by the presence of viral DNA, persists in 2–11% of ganglionic cells in the anatomic region of the initial infection. The mechanism of reactivation from latency is unknown. Increasingly, studies indicate that host T cell responses at the ganglionic and peripheral mucosal level influence the frequency and severity of HSV reactivation. HSV-specific T cells have been recovered from peripheral nerve root ganglia. Many of these resident CD8+ T cells are juxtaposed with latently HSV-1-infected neurons in the trigeminal ganglia and can block reactivation with both IFN-γ release and granzyme B degradation of the immediate-early protein ICP4. In addition, there appears to be a latent viral load in the ganglia that correlates positively with the number of neurons infected and the rate of reactivation but inversely with the number of CD8+ cells present. It is not known whether reactivating stimuli transiently suppress these immune cells, independently upregulate transcription of lytic genes, or both. However, once virus reaches the dermal-epidermal junction, there are two possible outcomes: subclinical shedding or recurrence (the latter defined clinically by a skin blister and ulceration). Histologically, herpetic lesions involve a thin-walled vesicle or ulceration in the basal region, multinucleated cells that may include intranuclear inclusions, necrosis, and an acute inflammatory infection. Re-epithelialization occurs once viral replication is restricted, almost always in the absence of a scar.

Analysis of the DNA from sequential isolates of HSV or from isolates from multiple infected ganglia in any one individual has revealed similar, if not identical, restriction endonuclease or DNA sequence patterns in most persons. The finding of individual neurons infected with multiple strains of drug-susceptible and drug-resistant virus in severely immunosuppressed patients indicates that ganglia can be reseeded during chronic infection. As exposure to mucosal shedding is relatively common during a person's lifetime, current data suggest that exogenous infection with different strains of the same subtype, while possible, is uncommon.

IMMUNITY

Host responses influence the acquisition of HSV disease, the severity of infection, resistance to the development of latency, the maintenance of latency, and the frequency of recurrences. Both antibody-mediated and cell-mediated reactions are clinically important. Immunocompromised patients with defects in cell-mediated immunity experience more severe and more extensive HSV infections than those with deficits in humoral immunity, such as agammaglobulinemia. Experimental ablation of lymphocytes indicates that T cells play a major role in preventing lethal disseminated disease, although antibodies help reduce titers of virus in neural tissue. Some clinical manifestations of HSV appear to be related to the host immune response (e.g., stromal opacities associated with recurrent herpetic keratitis). The surface viral glycoproteins have been shown to be targets of antibodies that mediate neutralization and immune-mediated cytolysis (antibody-dependent cell-mediated cytotoxicity). Monoclonal antibodies specific for each of the known viral glycoproteins have, in experimental infections, conferred protection against subsequent neurologic disease or ganglionic latency. In humans, however, subunit glycoprotein vaccines have been only partially successful in reducing acquisition of infection. Multiple cell populations, including natural killer cells, macrophages, and a variety of T lymphocytes, play a role in host defenses against HSV infections, as do lymphokines generated by T lymphocytes. In animals, passive transfer of primed lymphocytes confers protection from subsequent challenge. Maximal protection usually requires the activation of multiple T cell subpopulations, including cytotoxic T cells and T cells responsible for delayed hypersensitivity. The latter cells may confer protection by the antigen-stimulated release of lymphokines (e.g., IFNs), which in turn have a direct antiviral effect and both activate and enhance a variety of specific and nonspecific effector cells. Increasing evidence suggests that HSV-specific CD8+ T cell responses are critical for clearance of virus from lesions. In addition, immunosuppressed patients with frequent and prolonged HSV lesions have fewer functional CD8+ T cells directed at HSV. The HSV virion contains a variety of genes that are directed at the inhibition of host responses. These include gene no. 12 (*US-12*), which can bind to the cellular transporter-activating protein TAP-1 and reduce the ability of this protein to bind HSV peptides to human leukocyte antigen (HLA) class I, thereby reducing recognition of viral proteins by cytotoxic T cells of the host. This effect can be overcome by the addition of IFN-γ, but this reversal requires 24–48 h; thus, the virus has time to replicate and invade other host cells. Entry of infectious HSV-1 and HSV-2 inhibits several signaling pathways of both CD4+ and CD8+ T cells, leading to their functional impairment in killing and influencing the spectrum of their cytokine secretion.

Recent studies suggest that the rate of HSV reactivation is far more frequent than previously recognized. PCR analysis of daily anogenital swab samples has shown that the virus is shed on a median of 25% of days by the 95% of patients who are positive for antibody to HSV-2 and who shed virus, with a wide range of interpatient variability (range, 2–75%). In studies with sampling performed every 6 h, 49% of genital reactivation episodes lasted <12 h and 29% lasted <6 h. Many of these short bursts of reactivation were associated with copy numbers thought to be high enough to cause transmission to susceptible sexual partners. These data

suggest that peripheral immune control may dictate the likelihood and severity of recurrences as well as the frequency of subclinical shedding. There is a strong association between the magnitude of the CD8+ T lymphocyte response and the clearance of virus from genital lesions. The lack of this response, rather than a low CD4+ T lymphocyte count, also predicts frequent and severe HSV-2 recurrences in untreated as well as treated HIV-1-infected patients. HSV-2-specific CD8+ and CD4+ T cells appear to persist for prolonged periods (months) in genital skin previously involved in an HSV-2 reactivation. The location, effectiveness, and longevity of the T lymphocytes (and perhaps of other immune effector cells) may be important in the expression of disease and the likelihood of transmission over time.

EPIDEMIOLOGY

Seroepidemiologic studies have documented HSV infections worldwide. Serologic assays with whole-virus antigen preparations, such as complement fixation, neutralization, indirect immunofluorescence, passive hemagglutination, radioimmunoassay, and enzyme-linked immunosorbent assay, are useful for differentiating uninfected (seronegative) persons from those with past HSV-1 or HSV-2 infection, but they do not reliably distinguish between the two viral subtypes. Serologic assays that identify antibodies to type-specific surface proteins (epitopes) of the two viral subtypes have been developed and can distinguish reliably between the human antibody responses to HSV-1 and HSV-2. The most commonly used assays are those that measure antibodies to glycoprotein G of HSV-1 (gG1) and HSV-2 (gG2). A western blot assay that can detect several HSV type-specific proteins can also be used.

Infection with HSV-1 is acquired more frequently and earlier than infection with HSV-2. More than 90% of adults have antibodies to HSV-1 by the fifth decade of life. In populations of low socioeconomic status, most persons acquire HSV-1 infection before the third decade of life. Antibodies to HSV-2 are not detected routinely until puberty. Antibody prevalence rates correlate with past sexual activity and vary greatly among different population groups. There is some evidence that the prevalence of HSV-2 has decreased slightly over the past decade in the United States. Serosurveys indicate that 15–20% of the U.S. population has antibodies to HSV-2. In most routine obstetric and family planning clinics, 25% of women have HSV-2 antibodies, although only 10% of those who are seropositive for HSV-2 report a history of genital lesions. As many as 50% of heterosexual adults attending sexually transmitted disease clinics have antibodies to HSV-2.

A wide variety of serologic surveys have indicated a similar or even higher seroprevalence of HSV-2 in most parts of Central America, South America, and Africa. There is an epidemiologic synergy between HSV-2 and HIV-1. HSV-2 infection is associated with a two- to fourfold increase in HIV-1 acquisition. In addition, HSV-2 is reactivated and transmitted more frequently in persons co-infected with HIV-1 and HSV-2 than in persons not infected with HIV-1. Thus, most areas of the world with a high HIV-1 prevalence also have a high HSV-2 prevalence. In Africa, HSV-2 seroprevalence has ranged from 40% to 70% in obstetric and other sexually experienced populations. Antibody prevalence rates average ~5–10% higher among women than among men.

Several studies suggest that many cases of "asymptomatic" genital HSV-2 infection are, in fact, simply unrecognized: when "asymptomatic" seropositive persons are shown pictures of genital lesions, >60% subsequently identify episodes of symptomatic reactivation. Most important, these asymptomatic seropositive persons with reactivation shed virus on mucosal surfaces almost as frequently as do those with symptomatic disease. The large reservoir of unidentified carriers of HSV-2 and the frequent asymptomatic reactivation of the virus from the genital tract have fostered the continued spread of genital herpes throughout the world. HSV-2 infection is an independent risk factor for the acquisition and transmission of infection with HIV-1. Among co-infected persons, HIV-1 virions can be shed from herpetic lesions of the genital region. This shedding may facilitate the spread of HIV through sexual contact. HSV-2 reactivation is associated with a localized persistent inflammatory response consisting of high concentrations of CCR5-enriched CD4+ T cells as well as inflammatory dendritic cells in the submucosa of the genital skin. These cells can support HIV infection and replication and hence are likely to account for the two- to threefold increase in HIV acquisition among persons with genital herpes. Unfortunately, antiviral therapy does not reduce this subclinical postreactivation inflammation, probably because of the inability of current antiviral agents to prevent the release of small amounts of HSV antigen into the genital mucosa.

HSV infections occur throughout the year. Transmission can result from contact with persons who have active ulcerative lesions or with persons who have no clinical manifestations of infection but who are shedding HSV from mucocutaneous surfaces. HSV reactivation on genital skin and mucosal surfaces is common. With once-daily sampling of immunocompetent adults, HSV-2 can be cultured from the genital tract on 2–10% of days tested, and HSV DNA can be detected on 20–30% of days by PCR. Corresponding figures for HSV-1 in oral secretions are similar. Rates of shedding are highest during the initial years after acquisition, with viral shedding occurring on as many as 30–50% of days during this period. Immunosuppressed patients shed HSV from mucosal sites at an even higher frequency (20–80% of days). With increased sampling frequency (e.g., four times daily), the rates of reactivation are two- to fourfold higher, with many episodes lasting <12 h. These high rates of mucocutaneous reactivation suggest that exposure to HSV from sexual or other close contact (kissing, sharing of glasses or silverware) is common and help explain the continuing spread and high seroprevalence of HSV infections worldwide. Reactivation rates vary widely among individuals. Among HIV-positive patients, a low CD4+ T cell count and a heavy viral load

are associated with increased rates of HSV reactivation. Daily antiviral chemotherapy for HSV-2 infection can reduce shedding rates but does not eliminate shedding, as measured by PCR or culture.

CLINICAL SPECTRUM

HSV has been isolated from nearly all visceral and mucocutaneous sites. The clinical manifestations and course of HSV infection depend on the anatomic site involved, the age and immune status of the host, and the antigenic type of the virus. Primary HSV infections (i.e., first infections with either HSV-1 or HSV-2 in which the host lacks HSV antibodies in acute-phase serum) are frequently accompanied by systemic signs and symptoms. Compared with recurrent episodes, primary infections, which involve both mucosal and extramucosal sites, are characterized by a longer duration of symptoms and virus isolation from lesions. The incubation period ranges from 1 to 26 days (median, 6–8 days). Both viral subtypes can cause genital and oral-facial infections, and the infections caused by the two subtypes are clinically indistinguishable. However, the frequency of reactivation of infection is influenced by anatomic site and virus type. Genital HSV-2 infection is twice as likely to reactivate and recurs 8–10 times more frequently than genital HSV-1 infection. Conversely, oral-labial HSV-1 infection recurs more frequently than oral-labial HSV-2 infection. Asymptomatic shedding rates follow the same pattern.

Oral-facial infections

Gingivostomatitis and pharyngitis are the most common clinical manifestations of first-episode HSV-1 infection, while recurrent herpes labialis is the most common clinical manifestation of reactivation HSV-1 infection. HSV pharyngitis and gingivostomatitis usually result from primary infection and are most commonly seen among children and young adults. Clinical symptoms and signs, which include fever, malaise, myalgias, inability to eat, irritability, and cervical adenopathy, may last 3–14 days. Lesions may involve the hard and soft palate, gingiva, tongue, lip, and facial area. HSV-1 or HSV-2 infection of the pharynx usually results in exudative or ulcerative lesions of the posterior pharynx and/or tonsillar pillars. Lesions of the tongue, buccal mucosa, or gingiva may occur later in the course in one-third of cases. Fever lasting 2–7 days and cervical adenopathy are common. It can be difficult to differentiate HSV pharyngitis clinically from bacterial pharyngitis, *Mycoplasma pneumoniae* infections, and pharyngeal ulcerations of noninfectious etiologies (e.g., Stevens-Johnson syndrome). No substantial evidence suggests that reactivation of oral-labial HSV infection is associated with symptomatic recurrent pharyngitis.

Reactivation of HSV from the trigeminal ganglia may be associated with asymptomatic virus excretion in the saliva, development of intraoral mucosal ulcerations, or herpetic ulcerations on the vermilion border of the lip or external facial skin. About 50–70% of seropositive patients undergoing trigeminal nerve-root decompression and 10–15% of those undergoing dental extraction develop oral-labial HSV infection a median of 3 days after these procedures. Clinical differentiation of intraoral mucosal ulcerations due to HSV from aphthous, traumatic, or drug-induced ulcerations is difficult.

In immunosuppressed patients, HSV infection may extend into mucosal and deep cutaneous layers. Friability, necrosis, bleeding, severe pain, and inability to eat or drink may result. The lesions of HSV mucositis are clinically similar to mucosal lesions caused by cytotoxic drug therapy, trauma, or fungal or bacterial infections. Persistent ulcerative HSV infections are among the most common infections in patients with AIDS. HSV and *Candida* infections often occur concurrently. Systemic antiviral therapy speeds the rate of healing and relieves the pain of mucosal HSV infections in immunosuppressed patients. The frequency of HSV reactivation during the early phases of transplantation or induction chemotherapy is high (50–90%), and prophylactic systemic antiviral agents such as IV acyclovir and penciclovir or the oral congeners of these drugs are used to reduce reactivation rates. Patients with atopic eczema may also develop severe oral-facial HSV infections (*eczema herpeticum*), which may rapidly involve extensive areas of skin and occasionally disseminate to visceral organs. Extensive eczema herpeticum has resolved promptly with the administration of IV acyclovir. Erythema multiforme may also be associated with HSV infections (see Fig. 11-25); some evidence suggests that HSV infection is the precipitating event in ~75% of cases of cutaneous erythema multiforme. HSV antigen has been demonstrated both in circulatory immune complexes and in skin lesion biopsy samples from these cases. Patients with severe HSV-associated erythema multiforme are candidates for chronic suppressive oral antiviral therapy.

HSV-1 and varicella-zoster virus (VZV) have been implicated in the etiology of Bell's palsy (flaccid paralysis of the mandibular portion of the facial nerve). Some but not all trials have documented quicker resolution of facial paralysis with the prompt initiation of antiviral therapy, with or without glucocorticoids. However, other trials have shown little benefit. Thus there is no consensus on the relative value of antiviral drugs alone, glucocorticoids alone, and the two modalities combined for the treatment of Bell's palsy.

Genital infections

First-episode primary genital herpes is characterized by fever, headache, malaise, and myalgias. Pain, itching, dysuria, vaginal and urethral discharge, and tender inguinal lymphadenopathy are the predominant local symptoms. Widely spaced bilateral lesions of the external genitalia are characteristic **(Fig. 84-1)**. Lesions may be present in varying stages, including vesicles, pustules, or painful erythematous ulcers. The cervix and urethra are involved in >80% of women with first-episode

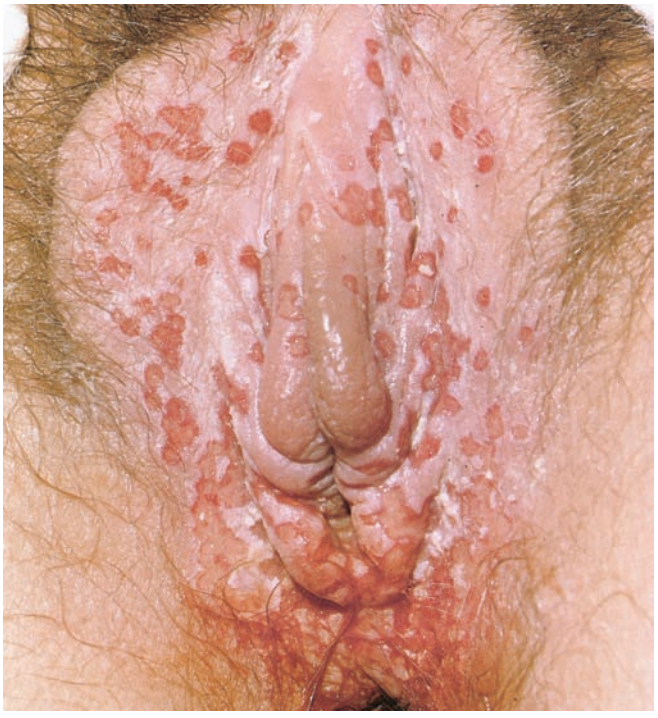


FIGURE 84-1
Genital herpes: primary vulvar infection. Multiple, extremely painful, punched-out, confluent, shallow ulcers on the edematous vulva and perineum. Micturition is often very painful. Associated inguinal lymphadenopathy is common. (*Reprinted with permission from K Wolff, RA Johnson, D Summond: Fitzpatrick's Color Atlas and Synopsis of Clinical Dermatology, 5th ed, New York, McGraw-Hill, 2005.*)

infections. First episodes of genital herpes in patients who have had prior HSV-1 infection are associated with systemic symptoms in a few patients and with faster healing than primary genital herpes. Subclinical DNAemia has been found in ~30% of cases of true primary genital herpes. The clinical courses of acute first-episode genital herpes are similar for HSV-1 and HSV-2 infection. However, the recurrence rates of genital disease differ with the viral subtype: the 12-month recurrence rates among patients with first-episode HSV-2 and HSV-1 infections are ~90% and ~55%, respectively (median number of recurrences, 4 and <1, respectively). Recurrence rates for genital HSV-2 infections vary greatly among individuals and over time within the same individual. HSV has been isolated from the urethra and urine of men and women without external genital lesions. A clear mucoid discharge and dysuria are characteristics of symptomatic HSV urethritis. HSV has been isolated from the urethra of 5% of women with the dysuria-frequency syndrome. Occasionally, HSV genital tract disease is manifested by endometritis and salpingitis in women and by prostatitis in men. About 15% of cases of HSV-2 acquisition are associated with nonlesional clinical syndromes, such as aseptic meningitis, cervicitis, or urethritis. A more complete discussion of the differential diagnosis of genital herpes is presented in Chap. 30.

Both HSV-1 and HSV-2 can cause symptomatic or asymptomatic rectal and perianal infections. HSV proctitis is usually associated with rectal intercourse. However, subclinical perianal shedding of HSV is detected in women and men who report no rectal intercourse. This phenomenon is due to the establishment of latency in the sacral dermatome from prior genital tract infection, with subsequent reactivation in epithelial cells in the perianal region. Such reactivations are often subclinical. Symptoms of HSV proctitis include anorectal pain, anorectal discharge, tenesmus, and constipation. Sigmoidoscopy reveals ulcerative lesions of the distal 10 cm of the rectal mucosa. Rectal biopsies show mucosal ulceration, necrosis, polymorphonuclear and lymphocytic infiltration of the lamina propria, and (in occasional cases) multinucleated intranuclear inclusion–bearing cells. Perianal herpetic lesions are also found in immunosuppressed patients receiving cytotoxic therapy. Extensive perianal herpetic lesions and/or HSV proctitis is common among patients with HIV infection.

Herpetic whitlow

Herpetic whitlow—HSV infection of the finger—may occur as a complication of primary oral or genital herpes by inoculation of virus through a break in the epidermal surface or by direct introduction of virus into the hand through occupational or some other type of exposure. Clinical signs and symptoms include abrupt-onset edema, erythema, and localized tenderness of the infected finger. Vesicular or pustular lesions of the fingertip that are indistinguishable from lesions of pyogenic bacterial infection are seen. Fever, lymphadenitis, and epitrochlear and axillary lymphadenopathy are common. The infection may recur. Prompt diagnosis (to avoid unnecessary and potentially exacerbating surgical therapy and/or transmission) is essential. Antiviral chemotherapy is usually recommended (see later in the chapter).

Herpes gladiatorum

HSV may infect almost any area of skin. Mucocutaneous HSV infections of the thorax, ears, face, and hands have been described among wrestlers. Transmission of these infections is facilitated by trauma to the skin sustained during wrestling. Several recent outbreaks have illustrated the importance of prompt diagnosis and therapy to contain the spread of this infection.

Eye infections

HSV infection of the eye is the most common cause of corneal blindness in the United States. HSV keratitis presents as an acute onset of pain, blurred vision, chemosis, conjunctivitis, and characteristic dendritic lesions of the cornea. Use of topical glucocorticoids may exacerbate symptoms and lead to involvement of deep structures of the eye. Debridement, topical antiviral treatment, and/or IFN therapy hastens healing. However, recurrences

are common, and the deeper structures of the eye may sustain immunopathologic injury. Stromal keratitis due to HSV appears to be related to T cell–dependent destruction of deep corneal tissue. An HSV-1 epitope that is autoreactive with T cell–targeting corneal antigens has been postulated to be a factor in this infection. Chorioretinitis, usually a manifestation of disseminated HSV infection, may occur in neonates or in patients with HIV infection. HSV and VZV can cause acute necrotizing retinitis as an uncommon but severe manifestation.

Central and peripheral nervous system infections

HSV accounts for 10–20% of all cases of sporadic viral encephalitis in the United States. The estimated incidence is ~2.3 cases per 1 million persons per year. Cases are distributed throughout the year, and the age distribution appears to be biphasic, with peaks at 5–30 and >50 years of age. HSV-1 causes >95% of cases.

The pathogenesis of HSV encephalitis varies. In children and young adults, primary HSV infection may result in encephalitis; presumably, exogenously acquired virus enters the CNS by neurotropic spread from the periphery via the olfactory bulb. However, most adults with HSV encephalitis have clinical or serologic evidence of mucocutaneous HSV-1 infection before the onset of CNS symptoms. In ~25% of the cases examined, the HSV-1 strains from the oropharynx and brain tissue of the same patient differ; thus, some cases may result from reinfection with another strain of HSV-1 that reaches the CNS. Two theories have been proposed to explain the development of actively replicating HSV in localized areas of the CNS in persons whose ganglionic and CNS isolates are similar. Reactivation of latent HSV-1 infection in trigeminal or autonomic nerve roots may be associated with extension of virus into the CNS via nerves innervating the middle cranial fossa. HSV DNA has been demonstrated by DNA hybridization in brain tissue obtained at autopsy—even from healthy adults. Thus, reactivation of long-standing latent CNS infection may be another mechanism for the development of HSV encephalitis.

Recent studies have identified genetic polymorphisms in two separate genes among families with a high frequency of HSV encephalitis. Peripheral-blood mononuclear cells from these patients (predominantly children) appear to secrete reduced levels of IFN in response to HSV. These observations suggest that some cases of sporadic HSV encephalitis may be related to host genetic determinants.

The clinical hallmark of HSV encephalitis has been the acute onset of fever and focal neurologic symptoms and signs, especially in the temporal lobe **(Fig. 84-2)**. Clinical differentiation of HSV encephalitis from other viral encephalitides, focal infections, or noninfectious processes is difficult. Elevated cerebrospinal fluid (CSF) protein levels, leukocytosis (predominantly lymphocytes), and red blood cell counts due to hemorrhagic necrosis are common. While brain biopsy has been the gold standard for defining HSV encephalitis, a highly sensitive and specific PCR for detection of HSV DNA in CSF

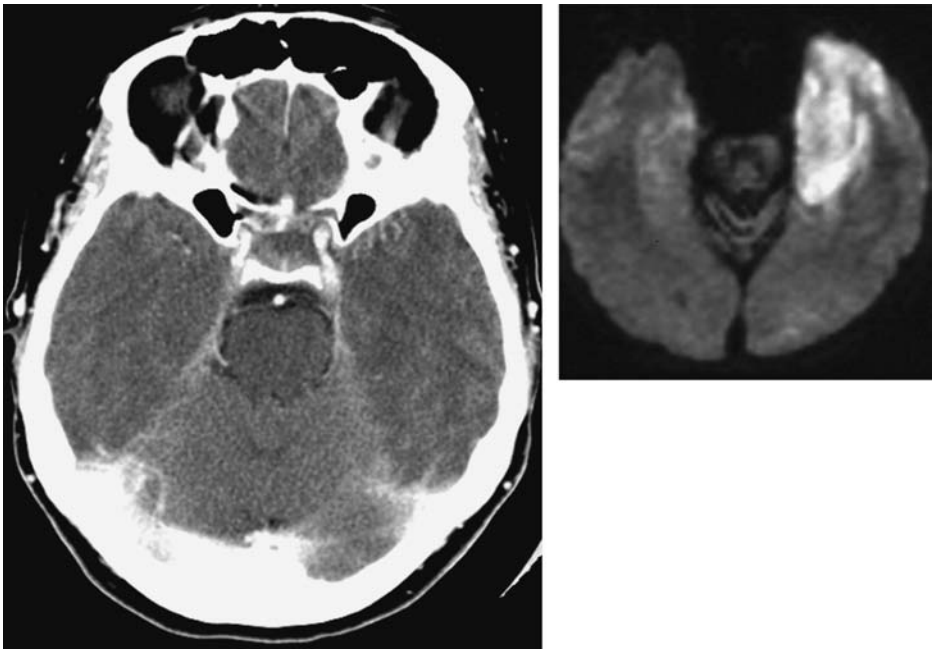


FIGURE 84-2
CT and diffusion-weighted MRI scans of the brain of a patient with left-temporal-lobe HSV encephalitis.

has largely replaced biopsy for defining CNS infection. Although titers of antibody to HSV in CSF and serum increase in most cases of HSV encephalitis, they rarely do so earlier than 10 days into the illness and therefore, while useful retrospectively, are generally not helpful in establishing an early clinical diagnosis. Demonstration of HSV antigen, HSV DNA, or HSV replication in brain tissue obtained by biopsy is highly sensitive and has a low complication rate; examination of such tissue also provides the best opportunity to identify alternative, potentially treatable causes of encephalitis. Antiviral chemotherapy with acyclovir reduces the rate of death from HSV encephalitis. Even with therapy, however, neurologic sequelae are common, especially among persons >50 years of age. Most authorities recommend the administration of IV acyclovir to patients with presumed HSV encephalitis until the diagnosis is confirmed or an alternative diagnosis is made. All confirmed cases should be treated with IV acyclovir (30 mg/kg per day in three divided doses for 14–21 days). After the completion of therapy, the clinical recurrence of encephalitis requiring more treatment has been reported. For this reason, some authorities prefer to treat initially for 21 days, and many continue therapy until HSV DNA has been eliminated from the CSF. Even with therapy, neurologic sequelae are common, especially among persons >35 years of age.

HSV DNA has been detected in CSF from 3–15% of persons presenting to the hospital with aseptic meningitis. HSV meningitis, which is usually seen in association with primary genital HSV infection, is an acute, self-limited disease manifested by headache, fever, and mild photophobia and lasting 2–7 days. Lymphocytic pleocytosis in the CSF is characteristic. Neurologic sequelae of HSV meningitis are rare. HSV is the most commonly identified cause of recurrent lymphocytic meningitis (Mollaret's meningitis). Demonstration of HSV antibodies in CSF or persistence of HSV DNA in CSF can establish the diagnosis. For persons with frequent recurrences of HSV meningitis, daily antiviral therapy has reduced the occurrence of such episodes.

Autonomic nervous system dysfunction, especially of the sacral region, has been reported in association with both HSV and VZV infections. Numbness, tingling of the buttocks or perineal areas, urinary retention, constipation, CSF pleocytosis, and (in males) impotence may occur. Symptoms appear to resolve slowly over days or weeks. Occasionally, hypoesthesia and/or weakness of the lower extremities persists for many months. Rarely, transverse myelitis, manifested by a rapidly progressive symmetric paralysis of the lower extremities or Guillain-Barré syndrome, follows HSV infection. Similarly, peripheral nervous system involvement (Bell's palsy) or cranial polyneuritis may be related to reactivation of HSV-1 infection. Transitory hypoesthesia of the area of skin innervated by the trigeminal nerve and vestibular system dysfunction (as measured by electronystagmography) are the predominant signs of disease. Whether antiviral chemotherapy can abort these signs or reduce their frequency and severity is not yet known.

Visceral infections

HSV infection of visceral organs usually results from viremia, and multiple-organ involvement is common. Occasionally, however, the clinical manifestations of HSV infection involve only the esophagus, lung, or liver. HSV esophagitis may result from direct extension of oral-pharyngeal HSV infection into the esophagus or may occur de novo by reactivation and spread of HSV to the esophageal mucosa via the vagus nerve. The predominant symptoms of HSV esophagitis are odynophagia, dysphagia, substernal pain, and weight loss. Multiple oval ulcerations appear on an erythematous base with or without a patchy white pseudomembrane. The distal esophagus is most commonly involved. With extensive disease, diffuse friability may spread to the entire esophagus. Neither endoscopic nor barium examination can reliably differentiate HSV esophagitis from *Candida* esophagitis or from esophageal ulcerations due to thermal injury, radiation, or corrosives. Endoscopically obtained secretions for cytologic examination and culture or DNA detection by PCR provide the most useful material for diagnosis. Systemic antiviral chemotherapy usually reduces the severity and duration of symptoms and heals esophageal ulcerations.

HSV pneumonitis is uncommon except in severely immunosuppressed patients and may result from extension of herpetic tracheobronchitis into lung parenchyma. Focal necrotizing pneumonitis usually ensues. Hematogenous dissemination of virus from sites of oral or genital mucocutaneous disease may also occur, producing bilateral interstitial pneumonitis. Bacterial, fungal, and parasitic pathogens are commonly present in HSV pneumonitis. The mortality rate from untreated HSV pneumonia in immunosuppressed patients is high (>80%). HSV has also been isolated from the lower respiratory tract of persons with adult respiratory distress syndrome and prolonged intubation. Most authorities believe that the presence of HSV in tracheal aspirates in such settings is due to reactivation of HSV in the tracheal region and localized tracheitis in persons with long-standing intubation. Such patients should be evaluated for extension of HSV infection into the lung parenchyma. Controlled trials evaluating the role of antiviral agents used against HSV in morbidity and mortality associated with acute respiratory distress syndrome have not been conducted. The role of lower respiratory tract HSV infection in overall rates of morbidity and mortality associated with these conditions is unclear. HSV is an uncommon cause of hepatitis in immunocompetent patients. HSV infection of the liver is associated with fever, abrupt elevations of bilirubin and serum aminotransferase levels, and leukopenia (<4000 white blood cells/μL). Disseminated intravascular coagulation may also develop.

Other reported complications of HSV infection include monarticular arthritis, adrenal necrosis, idiopathic thrombocytopenia, and glomerulonephritis. Disseminated HSV infection in immunocompetent patients is rare. In immunocompromised, burned, or malnourished patients, HSV occasionally disseminates to other visceral organs,

such as the adrenal glands, pancreas, small and large intestines, and bone marrow. Rarely, primary HSV infection in pregnancy disseminates and may be associated with the death of both mother and fetus. This uncommon event is usually related to the acquisition of primary infection in the third trimester. Disseminated HSV infection is best detected by the presence of HSV DNA in plasma or blood.

Neonatal HSV infections

Of all HSV-infected populations, neonates (infants younger than 6 weeks) have the highest frequency of visceral and/or CNS infection. Without therapy, the overall rate of death from neonatal herpes is 65%; <10% of neonates with CNS infection develop normally. Although skin lesions are the most commonly recognized features of disease, many infants do not develop lesions at all or do so only well into the course of disease. Neonatal infection is usually acquired perinatally from contact with infected genital secretions at delivery. Congenitally infected infants have been reported. In most series, 30% of neonatal HSV infections are due to HSV-1 and 70% to HSV-2. The risk of developing neonatal HSV infection is 10 times higher for an infant born to a mother who has recently acquired HSV than for other infants. Neonatal HSV-1 infections may also be acquired through postnatal contact with immediate family members who have symptomatic or asymptomatic oral-labial HSV-1 infection or through nosocomial transmission within the hospital. All neonates with presumed herpes should be treated with IV acyclovir. Antiviral chemotherapy with high-dose IV acyclovir (60 mg/kg per day) has reduced the mortality rate from neonatal herpes to ~15%. However, rates of morbidity, especially among infants with HSV-2 infection involving the CNS, are still very high.

HSV in Pregnancy

In the United States, 22% of all pregnant women and 55% of non-Hispanic black pregnant women are seropositive for HSV-2. However, the risk of mother-to-child transmission of HSV in the perinatal period is highest when the infection is acquired near the time of labor—that is, in previously HSV-seronegative women. The clinical manifestations of recurrent genital herpes—including the frequency of subclinical versus clinical infection, duration of lesions, pain, and constitutional symptoms—are similar in pregnant and nonpregnant women. Recurrences increase in frequency over the course of pregnancy. However, when women are seropositive for HSV-2 at the outset of pregnancy, no effect on neonatal outcomes (including birth weight and gestational age) is seen. First-episode infections in pregnancy have more severe consequences for mother and infant. Maternal visceral dissemination during the third trimester occasionally occurs, as does premature birth or intrauterine growth retardation. The acquisition of primary disease in pregnancy, whether related to HSV-1 or HSV-2, carries the risk of transplacental transmission of virus to the neonate and can result in spontaneous abortion, although this outcome is relatively uncommon. Most authorities recommend antiviral treatment for newly acquired genital HSV infection during pregnancy with acyclovir (400 mg three times daily) or valacyclovir (500–1000 mg twice daily) administered for 7–10 days. However, the impact of this intervention on transmission is unknown. The high HSV-2 prevalence rate in pregnancy and the low incidence of neonatal disease (1 case per 6000–20,000 live births) indicate that only a few infants are at risk of acquiring HSV. Therefore, cesarean section is not warranted for all women with recurrent genital disease. Because intrapartum transmission of infection accounts for the majority of cases, only women who are shedding HSV at delivery need be considered for abdominal delivery. Several studies have shown no correlation between recurrence of viral shedding before delivery and viral shedding at term. Hence, weekly virologic monitoring and amniocentesis are not recommended.

The frequency of transmission from mother to infant is markedly higher among women who acquire HSV near term (30–50%) than among those in whom HSV-2 infection is reactivated at delivery (<1%). Although maternal antibody to HSV-2 is protective, antibody to HSV-1 offers little or no protection against neonatal HSV-2 infection. Primary genital infection with HSV-1 leads to a particularly high risk of transmission during pregnancy and accounts for an increasing proportion of neonatal HSV cases. Moreover, during reactivation, HSV-1 appears more transmissible to the neonate than HSV-2. Only 2% of women who are seropositive for HSV-2 have HSV-2 isolated from cervical secretions at delivery, and only 1% of infants exposed in this manner develop infection, presumably because of the protective effects of maternally transferred antibodies and perhaps lower viral titers during reactivation. Despite the low frequency of transmission of HSV in this setting, 30–50% of infants with neonatal HSV are born to mothers with established genital herpes.

Isolation of HSV by cervicovaginal swab at the time of delivery is the greatest risk factor for intrapartum HSV transmission (relative risk = 346); however, culture-negative, PCR-positive cases of intrapartum transmission are well described. New acquisition of HSV (odds ratio [OR] = 49), isolation of HSV-1 versus HSV-2 (OR = 35), cervical versus vulvar HSV detection (OR = 15), use of fetal scalp electrodes (OR = 3.5), and young age confer further risk of transmission, whereas abdominal delivery is protective (OR = 0.14). Physical examination poorly predicts the absence of shedding, and PCR far exceeds culture in terms of sensitivity and speed. Therefore, PCR detection at the onset of labor should be used to aid clinical decision-making for women with HSV-2 antibody. Because cesarean section appears to be an effective means of reducing maternal-fetal transmission, patients with recurrent genital herpes should be encouraged to come to the hospital early at the time of delivery for careful examination of

the external genitalia and cervix as well as collection of a swab sample for viral isolation. Women who have no evidence of lesions should have a vaginal delivery. The presence of active lesions on the cervix or external genitalia is an indication for abdominal delivery.

If first-episode exposure has occurred (e.g., if HSV serologies show that the mother is seronegative or if the mother is HSV-1-seropositive and the isolate at delivery is found to be HSV-2), many authorities would initiate antiviral therapy for the infant with IV acyclovir. At a minimum, samples for viral cultures and PCR should be obtained from the throat, nasopharynx, eyes, and rectum of these infants immediately and at 5- to 10-day intervals. Lethargy, skin lesions, or fever should be evaluated promptly. All infants from whom HSV is isolated 24 h after delivery should be treated with IV acyclovir at recommended doses.

DIAGNOSIS

Both clinical and laboratory criteria are useful for diagnosing HSV infections. A clinical diagnosis can be made accurately when characteristic multiple vesicular lesions on an erythematous base are present. However, herpetic ulcerations may resemble skin ulcerations of other etiologies. Mucosal HSV infections may also present as urethritis or pharyngitis without cutaneous lesions. Thus, laboratory studies to confirm the diagnosis and to guide therapy are recommended. While staining of scrapings from the base of the lesions with Wright's, Giemsa's (Tzanck preparation), or Papanicolaou's stain to detect giant cells or intranuclear inclusions of *Herpesvirus* infection is a well-described procedure, few clinicians are skilled in these techniques, the sensitivity of staining is low (<30% for mucosal swabs), and these cytologic methods do not differentiate between HSV and VZV infections.

HSV infection is best confirmed in the laboratory by detection of virus, viral antigen, or viral DNA in scrapings from lesions. HSV DNA detection by PCR is the most sensitive laboratory technique for detecting mucosal or visceral HSV infections and should be utilized when available. HSV causes a discernible cytopathic effect in a variety of cell culture systems, and this effect can be identified within 48–96 h after inoculation. Spin-amplified culture with subsequent staining for HSV antigen has shortened the time needed to identify HSV to <24 h. The sensitivity of all detection methods depends on the stage of the lesions (with higher sensitivity for vesicular than for ulcerative lesions), on whether the patient has a first or a recurrent episode of the disease (with higher sensitivity in first than in recurrent episodes), and on whether the sample is from an immunosuppressed or an immunocompetent patient (with more antigen or DNA in immunosuppressed patients). Laboratory confirmation permits subtyping of the virus; information on subtype may be useful epidemiologically and may help to predict the frequency of reactivation after first-episode oral-labial or genital HSV infection.

Acute- and convalescent-phase serum can be useful in demonstrating seroconversion during primary HSV-1 or HSV-2 infection. However, few available tests report titers, and increases in index values do not reflect first episodes in all patients. Serologic assays based on type-specific proteins should be used to identify asymptomatic carriers of HSV-1 or HSV-2. No reliable IgM method for defining acute HSV infection is available.

Several studies have shown that persons with previously unrecognized HSV-2 infection can be taught to identify symptomatic reactivations. Individuals seropositive for HSV-2 should be told about the high frequency of subclinical reactivation in mucosal surfaces that are not visible to the eye (e.g., cervix, urethra, perianal skin) or in microscopic ulcerations that may not be clinically symptomatic. Transmission of infection during such episodes is well established. HSV-2-seropositive persons should be educated about the high likelihood of subclinical shedding and the role condoms (male or female) may play in reducing transmission. Antiviral therapy with valacyclovir (500 mg once daily) has been shown to reduce the transmission of HSV-2 between sexual partners.

TREATMENT Herpes Simplex Virus Infections

Many aspects of mucocutaneous and visceral HSV infections are amenable to antiviral chemotherapy. For mucocutaneous infections, acyclovir and its congeners famciclovir and valacyclovir have been the mainstays of therapy. Several antiviral agents are available for topical use in HSV eye infections: idoxuridine, trifluorothymidine, topical vidarabine, and cidofovir. For HSV encephalitis and neonatal herpes, IV acyclovir is the treatment of choice.

All licensed antiviral agents for use against HSV inhibit the viral DNA polymerase. One class of drugs, typified by the drug acyclovir, is made up of substrates for the HSV enzyme thymidine kinase (TK). Acyclovir, ganciclovir, famciclovir, and valacyclovir are all selectively phosphorylated to the monophosphate form in virus-infected cells. Cellular enzymes convert the monophosphate form of the drug to the triphosphate, which is then incorporated into the viral DNA chain. Acyclovir is the agent most frequently used for the treatment of HSV infections and is available in IV, oral, and topical formulations. Valacyclovir, the valyl ester of acyclovir, offers greater bioavailability than acyclovir and thus can be administered less frequently. Famciclovir, the oral formulation of penciclovir, is clinically effective in the treatment of a variety of HSV-1 and HSV-2 infections. Ganciclovir is active against both HSV-1 and HSV-2; however, it is more toxic than acyclovir, valacyclovir, and famciclovir and generally is not recommended for the treatment of HSV infections. Anecdotal case reports suggest that ganciclovir may also be less effective than acyclovir for treatment of HSV infections. All three recommended compounds—acyclovir, valacyclovir, and famciclovir—have proved effective in shortening the duration of symptoms and lesions of mucocutaneous HSV infections in both immunocompromised and immunocompetent patients (Table 84-1). IV and oral formulations prevent reactivation of HSV in seropositive immunocompromised patients during induction

TABLE 84-1

ANTIVIRAL CHEMOTHERAPY FOR HSV INFECTION

I. Mucocutaneous HSV infections

A. Infections in immunosuppressed patients

1. *Acute symptomatic first or recurrent episodes:* IV acyclovir (5 mg/kg q8h) or oral acyclovir (400 mg qid), famciclovir (500 mg bid or tid), or valacyclovir (500 mg bid) is effective. Treatment duration may vary from 7 to 14 days.
2. *Suppression of reactivation disease (genital or oral-labial):* IV acyclovir (5 mg/kg q8h) or oral valacyclovir (500 mg bid) or acyclovir (400–800 mg 3–5 times per day) prevents recurrences during the 30-day period immediately after transplantation. Longer-term HSV suppression is often used for persons with continued immunosuppression. In bone marrow and renal transplant recipients, oral valacyclovir (2 g/d) is also effective in reducing cytomegalovirus infection. Oral valacyclovir at a dose of 4 g/d has been associated with thrombotic thrombocytopenic purpura after extended use in HIV-positive persons. In HIV-infected persons, oral acyclovir (400–800 mg bid), valacyclovir (500 mg bid), or famciclovir (500 mg bid) is effective in reducing clinical and subclinical reactivations of HSV-1 and HSV-2.

B. Infections in immunocompetent patients

1. *Genital herpes*
   a. *First episodes:* Oral acyclovir (200 mg 5 times per day or 400 mg tid), valacyclovir (1 g bid), or famciclovir (250 mg bid) for 7–14 days is effective. IV acyclovir (5 mg/kg q8h for 5 days) is given for severe disease or neurologic complications such as aseptic meningitis.
   b. *Symptomatic recurrent genital herpes:* Short-course (1- to 3-day) regimens are preferred because of low cost, likelihood of adherence, and convenience. Oral acyclovir (800 mg tid for 2 days), valacyclovir (500 mg bid for 3 days), or famciclovir (750 or 1000 mg bid for 1 day, a 1500-mg single dose, or 500 mg stat followed by 250 mg q12h for 3 days) effectively shortens lesion duration. Other options include oral acyclovir (200 mg 5 times per day), valacyclovir (500 mg bid), and famciclovir (125 mg bid for 5 days).
   c. *Suppression of recurrent genital herpes:* Oral acyclovir (400–800 mg bid) or valacyclovir (500 mg daily) is given. Patients with >9 episodes per year should take oral valacyclovir (1 g daily or 500 mg bid) or famciclovir (250 mg bid or 500 mg bid).
2. *Oral-labial HSV infections*
   a. *First episode:* Oral acyclovir (200 mg) is given 4 or 5 times per day; an oral acyclovir suspension can be used (600 mg/m^2 qid). Oral famciclovir (250 mg bid) or valacyclovir (1 g bid) has been used clinically.
   b. *Recurrent episodes:* If initiated at the onset of the prodrome, single-dose or 1-day therapy effectively reduces pain and speeds healing. Regimens include oral famciclovir (a 1500-mg single dose or 750 mg bid for 1 day) or valacyclovir (a 2-g single dose or 2 g bid for 1 day). Self-initiated therapy with 6-times-daily topical penciclovir cream effectively speeds healing of oral-labial HSV. Topical acyclovir cream has also been shown to speed healing.
   c. *Suppression of reactivation of oral-labial HSV:* If started before exposure and continued for the duration of exposure (usually 5–10 days), oral acyclovir (400 mg bid) prevents reactivation of recurrent oral-labial HSV infection associated with severe sun exposure.
3. *Surgical prophylaxis of oral or genital HSV infection:* Several surgical procedures, such as laser skin resurfacing, trigeminal nerve-root decompression, and lumbar disk surgery, have been associated with HSV reactivation. IV acyclovir (3–5 mg/kg q8h) or oral acyclovir (800 mg bid), valacyclovir (500 mg bid), or famciclovir (250 mg bid) effectively reduces reactivation. Therapy should be initiated 48 h before surgery and continued for 3–7 days.
4. *Herpetic whitlow:* Oral acyclovir (200 mg; alternative: 400 mg tid) is given 5 times daily for 7–10 days.
5. *HSV proctitis:* Oral acyclovir (400 mg 5 times per day) is useful in shortening the course of infection. In immunosuppressed patients or in patients with severe infection, IV acyclovir (5 mg/kg q8h) may be useful.
6. *Herpetic eye infections:* In acute keratitis, topical trifluorothymidine, vidarabine, idoxuridine, acyclovir, penciclovir, and interferon are all beneficial. Debridement may be required. Topical steroids may worsen disease.

II. CNS HSV infections

A. HSV encephalitis: IV acyclovir (10 mg/kg q8h; 30 mg/kg per day) is given for 10 days or until HSV DNA is no longer detected in CSF.

B. HSV aseptic meningitis: No studies of systemic antiviral chemotherapy exist. If therapy is to be given, IV acyclovir (15–30 mg/kg per day) should be used.

C. Autonomic radiculopathy: No studies are available. Most authorities recommend a trial of IV acyclovir.

III. Neonatal HSV infections: Oral acyclovir (60 mg/kg per day, divided into 3 doses) is given. The recommended duration of treatment is 21 days. Monitoring for relapse should be undertaken, and some authorities recommend continued suppression with oral acyclovir suspension for 3–4 months.

IV. Visceral HSV infections

A. HSV esophagitis: IV acyclovir (15 mg/kg per day) is given. In some patients with milder forms of immunosuppression, oral therapy with valacyclovir or famciclovir is effective.

B. HSV pneumonitis: No controlled studies exist. IV acyclovir (15 mg/kg per day) should be considered.

(*continued*)

TABLE 84-1

ANTIVIRAL CHEMOTHERAPY FOR HSV INFECTION (*CONTINUED*)

V. Disseminated HSV infections: No controlled studies exist. IV acyclovir (5 mg/kg q8h) should be tried. Adjustments for renal insufficiency may be needed. No definite evidence indicates that therapy will decrease the risk of death.

VI. Erythema multiforme associated with HSV: Anecdotal observations suggest that oral acyclovir (400 mg bid or tid) or valacyclovir (500 mg bid) will suppress erythema multiforme.

VII. Infections due to acyclovir-resistant HSV: IV foscarnet (40 mg/kg IV q8h) should be given until lesions heal. The optimal duration of therapy and the usefulness of its continuation to suppress lesions are unclear. Some patients may benefit from cutaneous application of trifluorothymidine or 5% cidofovir gel.

chemotherapy or in the period immediately after bone marrow or solid organ transplantation. Chronic daily suppressive therapy reduces the frequency of reactivation disease among patients with frequent genital or oral-labial herpes. Only valacyclovir has been subjected to clinical trials that demonstrated reduced transmission of HSV-2 infection between sexual partners. IV acyclovir (30 mg/kg per day, given as a 10-mg/kg infusion over 1 h at 8-h intervals) is effective in reducing rates of death and morbidity from HSV encephalitis. Early initiation of therapy is a critical factor in outcome. The major side effect associated with IV acyclovir is transient renal insufficiency, usually due to crystallization of the compound in the renal parenchyma. This adverse reaction can be avoided if the medication is given slowly over 1 h and the patient is well hydrated. Because CSF levels of acyclovir average only 30–50% of plasma levels, the dosage of acyclovir used for treatment of CNS infection (30 mg/kg per day) is double that used for treatment of mucocutaneous or visceral disease (15 mg/kg per day). Even higher doses of IV acyclovir are used for neonatal HSV infection (60 mg/kg per day in three divided doses).

Increasingly, shorter courses of therapy are being used for treatment of recurrent mucocutaneous infection with HSV-1 or HSV-2 in immunocompetent patients. One-day courses of famciclovir and valacyclovir are clinically effective, more convenient, and generally less costly than longer courses of therapy (Table 84-1). These short-course regimens should be reserved for immunocompetent hosts.

SUPPRESSION OF MUCOCUTANEOUS HERPES Recognition of the high frequency of subclinical reactivation provides a well-accepted rationale for the use of daily antiviral therapy to suppress reactivations of HSV, especially in persons with frequent clinical reactivations (e.g., those with recently acquired genital HSV infection). Immunosuppressed persons, including those with HIV infection, may also benefit from daily antiviral therapy. Recent studies have shown the efficacy of daily acyclovir and valacyclovir in reducing the frequency of HSV reactivations among HIV-positive persons. Regimens used include acyclovir (400–800 mg twice daily), famciclovir (500 mg twice daily), and valacyclovir (500 mg twice daily); valacyclovir at a dose of 4 g daily was associated with thrombotic thrombocytopenic purpura in one study of HIV-infected persons. In addition, daily treatment of HSV-2 reduces the titer of HIV RNA in plasma (0.5-log reduction) and in genital mucosa (0.33-log reduction).

REDUCED HSV TRANSMISSION TO SEXUAL PARTNERS Once-daily valacyclovir (500 mg) has been shown to reduce transmission of HSV-2 between sexual partners. Transmission rates are higher from males to females and among persons with frequent HSV-2 reactivation. Serologic screening can be used to identify at-risk couples. Daily valacyclovir appears to be more effective at reducing subclinical shedding than daily famciclovir.

ACYCLOVIR RESISTANCE Acyclovir-resistant strains of HSV have been identified. Most of these strains have an altered substrate specificity for phosphorylating acyclovir. Thus, cross-resistance to famciclovir and valacyclovir is usually found. Occasionally, an isolate with altered TK specificity arises and is sensitive to famciclovir but not to acyclovir. In some patients infected with TK-deficient virus, higher doses of acyclovir are associated with clearing of lesions. In others, clinical disease progresses despite high-dose therapy. Almost all clinically significant acyclovir resistance has been seen in immunocompromised patients, and HSV-2 isolates are more often resistant than HSV-1 strains. A study by the Centers for Disease Control and Prevention indicated that ~5% of HSV-2 isolates from HIV-positive persons exhibit some degree of in vitro resistance to acyclovir. Of HSV-2 isolates from immunocompetent patients attending sexually transmitted disease clinics, <0.5% show reduced in vitro sensitivity to acyclovir. The lack of appreciable change in the frequency of detection of such isolates in the past 20 years probably reflects the reduced transmission of TK-deficient mutants. Isolation of HSV from lesions persisting despite adequate dosages and blood levels of acyclovir should raise the suspicion of acyclovir resistance. Therapy with the antiviral drug foscarnet is useful in acyclovir-resistant cases (Chap. 83). Because of its toxicity and cost, this drug is usually reserved for patients with extensive mucocutaneous infections. Cidofovir is a nucleotide analogue and exists as a phosphonate or monophosphate form. Most TK-deficient strains of HSV are sensitive to cidofovir. Cidofovir ointment speeds healing of acyclovir-resistant lesions. No well-controlled

trials of systemic cidofovir have been reported. True TK-negative variants of HSV appear to have a reduced capacity to spread because of altered neurovirulence—a feature important in the relatively infrequent presence of such strains in immunocompetent populations, even with increasing use of antiviral drugs.

PREVENTION

The success of efforts to control HSV disease on a population basis through suppressive antiviral chemotherapy and/or educational programs will be limited. Barrier forms of contraception (especially condoms) decrease the likelihood of transmission of HSV infection, particularly during periods of asymptomatic viral excretion. When lesions are present, HSV infection may be transmitted by skin-to-skin contact despite the use of a condom. Nevertheless, the available data suggest that consistent condom use is an effective means of reducing the risk of genital HSV-2 transmission. Chronic daily antiviral therapy with valacyclovir can also be partially effective in reducing acquisition of HSV-2, especially among susceptible women. There are no comparative efficacy studies of valacyclovir versus condom use. Most authorities suggest both approaches. The need for a vaccine to prevent acquisition of HSV infection is great, especially in light of the role HSV-2 plays in enhancing the acquisition and transmission of HIV-1.

A substantial portion of neonatal HSV cases could be prevented by reducing the acquisition of HSV by women in the third trimester of pregnancy. Neonatal HSV infection can result from either the acquisition of maternal infection near term or the reactivation of infection at delivery in the already-infected mother. Thus strategies for reducing neonatal HSV are complex. Some authorities have recommended that antiviral therapy with acyclovir or valacyclovir be given to HSV-2-infected women in late pregnancy as a means of reducing reactivation of HSV-2 at term. Data are not available to support the efficacy of this approach. Moreover, the high treatment-to-prevention ratio makes this a dubious public health approach, even though it can reduce the frequency of HSV-associated cesarean delivery.

CHAPTER 85

VARICELLA-ZOSTER VIRUS INFECTIONS

Richard J. Whitley

DEFINITION

Varicella-zoster virus (VZV) causes two distinct clinical entities: varicella (chickenpox) and herpes zoster (shingles). Chickenpox, a ubiquitous and extremely contagious infection, is usually a benign illness of childhood characterized by an exanthematous vesicular rash. With reactivation of latent VZV (which is most common after the sixth decade of life), herpes zoster presents as a dermatomal vesicular rash, usually associated with severe pain.

ETIOLOGY

A clinical association between varicella and herpes zoster has been recognized for nearly 100 years. Early in the twentieth century, similarities in the histopathologic features of skin lesions resulting from varicella and herpes zoster were demonstrated. Viral isolates from patients with chickenpox and herpes zoster produced similar alterations in tissue culture—specifically, the appearance of eosinophilic intranuclear inclusions and multinucleated giant cells. These results suggested that the viruses were biologically similar. Restriction endonuclease analyses of viral DNA from a patient with chickenpox who subsequently developed herpes zoster verified the molecular identity of the two viruses responsible for these different clinical presentations.

VZV is a member of the family Herpesviridae, sharing with other members such structural characteristics as a lipid envelope surrounding a nucleocapsid with icosahedral symmetry, a total diameter of ~180–200 nm, and centrally located double-stranded DNA that is ~125,000 bp in length.

PATHOGENESIS AND PATHOLOGY

Primary infection

Transmission occurs readily by the respiratory route; the subsequent localized replication of the virus at an undefined site (presumably the nasopharynx) leads to seeding of the reticuloendothelial system and ultimately to the development of viremia. Viremia in patients with chickenpox is reflected in the diffuse and scattered nature of the skin lesions and can be verified in selected cases by the recovery of VZV from the blood or routinely by the detection of viral DNA in either blood or lesions by polymerase chain reaction (PCR). Vesicles involve the corium and dermis, with degenerative changes characterized by ballooning, the presence of multinucleated giant cells, and eosinophilic intranuclear inclusions. Infection may involve localized blood vessels of the skin, resulting in necrosis and epidermal hemorrhage. With the evolution of disease, the vesicular fluid becomes cloudy because of the recruitment of polymorphonuclear leukocytes and the presence of degenerated cells and fibrin. Ultimately, the vesicles either rupture and release their fluid (which includes infectious virus) or are gradually reabsorbed.

Recurrent infection

The mechanism of reactivation of VZV that results in herpes zoster is unknown. Presumably, the virus infects dorsal root ganglia during chickenpox, where it remains latent until reactivated. Histopathologic examination of representative dorsal root ganglia during active herpes zoster demonstrates hemorrhage, edema, and lymphocytic infiltration.

Active replication of VZV in other organs, such as the lung or the brain, can occur during either chickenpox or herpes zoster but is uncommon in the immunocompetent host. Pulmonary involvement is characterized by interstitial pneumonitis, multinucleated giant cell formation, intranuclear inclusions, and pulmonary hemorrhage. Central nervous system (CNS) infection leads to histopathologic evidence of perivascular cuffing similar to that encountered in measles and other viral encephalitides. Focal hemorrhagic necrosis of the brain, characteristic of herpes simplex virus (HSV) encephalitis, is uncommon in VZV infection.

EPIDEMIOLOGY AND CLINICAL MANIFESTATIONS

Chickenpox

Humans are the only known reservoir for VZV. Chickenpox is highly contagious, with an attack rate of at least 90% among susceptible (seronegative) individuals. Persons of both sexes and all races are infected equally. The virus is endemic in the population at large; however, it becomes epidemic among susceptible individuals during seasonal peaks—namely, late winter and early spring in the temperate zone. Much of our knowledge of the disease's natural history and incidence predates the licensure of the chickenpox vaccine in 1995. Historically, children 5–9 years old are most commonly affected and account for 50% of all cases. Most other cases involve children 1–4 and 10–14 years old. Approximately 10% of the population of the United States over the age of 15 is susceptible to infection. VZV vaccination during the second year of life has dramatically changed the epidemiology of infection, causing a significant decrease in the annualized incidence of chickenpox.

The incubation period of chickenpox ranges from 10–21 days but is usually 14–17 days. Secondary attack rates in susceptible siblings within a household are 70–90%. Patients are infectious ~48 h before onset of the vesicular rash, during the period of vesicle formation (which generally lasts 4–5 days), and until all vesicles are crusted.

Clinically, chickenpox presents with a rash, low-grade fever, and malaise, although a few patients develop a prodrome 1–2 days before onset of the exanthem. In the immunocompetent patient, chickenpox is usually a benign illness associated with lassitude and with body temperatures of 37.8°–39.4°C (100°–103°F) of 3–5 days' duration. The skin lesions—the hallmark of the infection—include maculopapules, vesicles, and scabs in various stages of evolution **(Fig. 85-1)**. These lesions, which evolve from maculopapules to vesicles over hours to days, appear on the trunk and face and rapidly spread to involve other areas of the body. Most are small and have an erythematous base with a diameter of 5–10 mm. Successive crops appear over a 2- to 4-day period. Lesions can also be found on the mucosa of the pharynx and/or the vagina. Their severity varies from one person to another. Some individuals have very few lesions, while others have as many as 2000. Younger children tend to have fewer vesicles than older individuals.

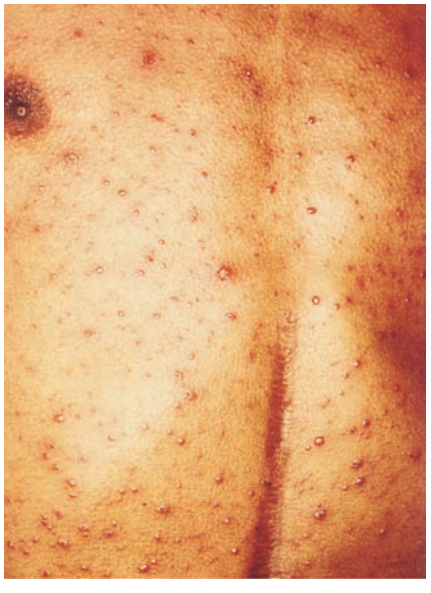


FIGURE 85-1
Varicella lesions at various stages of evolution: vesicles on an erythematous base, umbilical vesicles, and crusts.

Secondary and tertiary cases within families are associated with a relatively large number of vesicles. Immunocompromised patients—both children and adults, particularly those with leukemia—have lesions (often with a hemorrhagic base) that are more numerous and take longer to heal than those of immunocompetent patients. Immunocompromised individuals are also at greater risk for visceral complications, which occur in 30–50% of cases and are fatal 15% of the time in the absence of antiviral therapy.

The most common infectious complication of varicella is secondary bacterial superinfection of the skin, which is usually caused by *Streptococcus pyogenes* or *Staphylococcus aureus,* including strains that are methicillin-resistant. Skin infection results from excoriation of lesions after scratching. Gram's staining of skin lesions should help clarify the etiology of unusually erythematous and pustulated lesions.

The most common extracutaneous site of involvement in children is the CNS. The syndrome of acute cerebellar ataxia and meningeal inflammation generally appears ~21 days after onset of the rash and rarely develops in the preeruptive phase. The cerebrospinal fluid (CSF) contains lymphocytes and elevated levels of protein. CNS involvement is a benign complication of VZV infection in children and generally does not require hospitalization. Aseptic meningitis, encephalitis, transverse myelitis, and Guillain-Barré syndrome can also occur. Reye's syndrome has been reported in children concomitantly treated with aspirin. Encephalitis is reported in 0.1–0.2% of children with chickenpox. Other than supportive care, no specific therapy (e.g., acyclovir administration) has proved efficacious for patients with CNS involvement.

Varicella pneumonia, the most serious complication following chickenpox, develops more commonly in adults (up to 20% of cases) than in children and is particularly severe in pregnant women. Pneumonia due to VZV usually has its onset 3–5 days into the illness and is associated with tachypnea, cough, dyspnea, and fever. Cyanosis, pleuritic chest pain, and hemoptysis are common. Roentgenographic evidence of disease consists of nodular infiltrates and interstitial pneumonitis. Resolution of pneumonitis parallels improvement of the skin rash; however, patients may have persistent fever and compromised pulmonary function for weeks.

Other complications of chickenpox include myocarditis, corneal lesions, nephritis, arthritis, bleeding diatheses, acute glomerulonephritis, and hepatitis. Hepatic involvement, distinct from Reye's syndrome and usually asymptomatic, is common in chickenpox and is generally characterized by elevated levels of liver enzymes, particularly aspartate and alanine aminotransferases.

Perinatal varicella is associated with a high mortality rate when maternal disease develops within 5 days before delivery or within 48 h thereafter. Because the newborn does not receive protective transplacental antibodies and has an immature immune system, the illness may be unusually severe. The reported mortality rate is as high as 30% in this group. *Congenital varicella*, with clinical manifestations of limb hypoplasia, cicatricial skin lesions, and microcephaly at birth, is extremely uncommon.

Herpes zoster

Herpes zoster (shingles) is a sporadic disease that results from reactivation of latent VZV from dorsal root ganglia. Most patients with shingles have no history of recent exposure to other individuals with VZV infection. Herpes zoster occurs at all ages, but its incidence is highest (5–10 cases per 1000 persons) among individuals in the sixth decade of life and beyond. Data suggest that 1.2 million cases occur annually in the United States. Recurrent herpes zoster is exceedingly rare except in immunocompromised hosts, especially those with AIDS.

Herpes zoster is characterized by a unilateral vesicular dermatomal eruption, often associated with severe pain. The dermatomes from T3 to L3 are most frequently involved. If the ophthalmic branch of the trigeminal nerve is involved, *zoster ophthalmicus* results. The factors responsible for the reactivation of VZV are not known. In children, reactivation is usually benign; in adults, it can be debilitating because of pain. The onset of disease is heralded by pain within the dermatome, which may precede lesions by 48–72 h; an erythematous maculopapular rash evolves rapidly into vesicular lesions **(Fig. 85-2)**. In the normal host, these lesions may remain few in number and continue to form for only 3–5 days. The total duration of disease is generally 7–10 days; however, it may take as long as 2–4 weeks for the skin to return to normal.

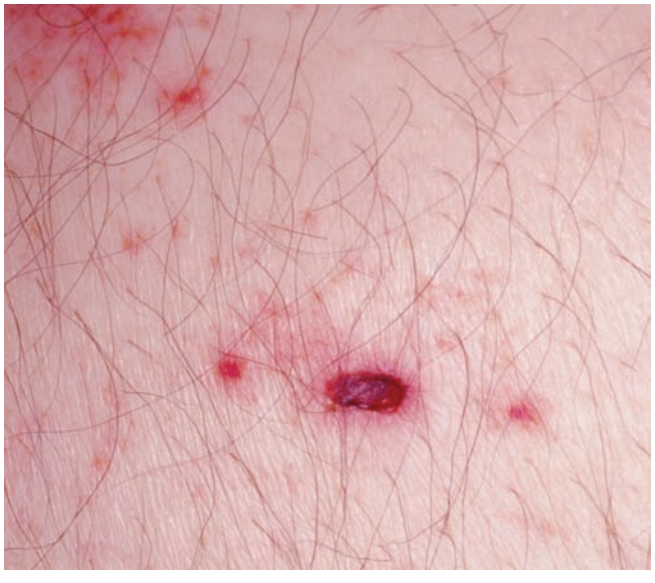


FIGURE 85-2
Close-up of lesions of disseminated zoster. Note lesions at different stages of evolution, including pustules and crusting. *(Photo courtesy of Lindsey Baden; with permission.)*

Patients with herpes zoster can transmit infection to seronegative individuals, with consequent chickenpox. In a few patients, characteristic localization of pain to a dermatome with serologic evidence of herpes zoster has been reported in the absence of skin lesions, an entity known as *zoster sine herpetica*. When branches of the trigeminal nerve are involved, lesions may appear on the face, in the mouth, in the eye, or on the tongue. *Zoster ophthalmicus* is usually a debilitating condition that can result in blindness in the absence of antiviral therapy. In the *Ramsay Hunt syndrome*, pain and vesicles appear in the external auditory canal, and patients lose their sense of taste in the anterior two-thirds of the tongue while developing ipsilateral facial palsy. The geniculate ganglion of the sensory branch of the facial nerve is involved.

In both normal and immunocompromised hosts, the most debilitating complication of herpes zoster is pain associated with acute neuritis and postherpetic neuralgia. Postherpetic neuralgia is uncommon in young individuals; however, at least 50% of zoster patients over age 50 report some degree of pain in the involved dermatome months after the resolution of cutaneous disease. Changes in sensation in the dermatome, resulting in either hypo- or hyperesthesia, are common.

CNS involvement may follow localized herpes zoster. Many patients without signs of meningeal irritation have CSF pleocytosis and moderately elevated levels of CSF protein. Symptomatic meningoencephalitis is characterized by headache, fever, photophobia, meningitis, and vomiting. A rare manifestation of CNS involvement is granulomatous angiitis with contralateral hemiplegia, which can be diagnosed by cerebral arteriography. Other neurologic manifestations include transverse myelitis with or without motor paralysis.

Like chickenpox, herpes zoster is more severe in immunocompromised than immunocompetent individuals. Lesions continue to form for >1 week, and scabbing is not complete in most cases until 3 weeks into the illness. Patients with Hodgkin's disease and non-Hodgkin's lymphoma are at greatest risk for progressive herpes zoster. Cutaneous dissemination **(Fig. 85-3)** develops in ~40% of these patients. Among patients with cutaneous dissemination, the risk of pneumonitis, meningoencephalitis, hepatitis, and other serious complications is increased by 5–10%. However, even in immunocompromised patients, disseminated zoster is rarely fatal.

Recipients of hematopoietic stem cell transplants are at particularly high risk of VZV infection. Of all cases of posttransplantation VZV infection, 30% occur within 1 year (50% of these within 9 months); 45% of the patients involved have cutaneous or visceral dissemination. The mortality rate in this situation is 10%. Postherpetic neuralgia, scarring, and bacterial superinfection are especially common in VZV infections occurring within 9 months of transplantation. Among infected patients, concomitant graft-versus-host disease increases the chance of dissemination and/or death.

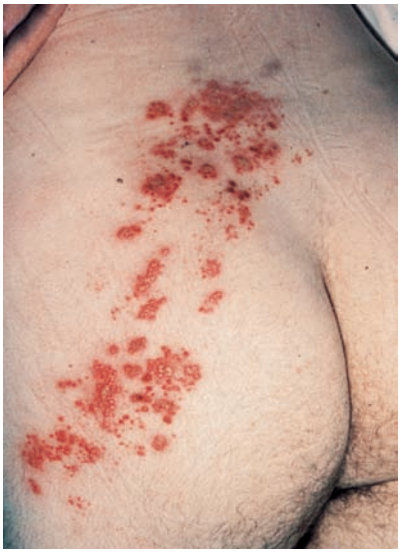


FIGURE 85-3
Herpes zoster in an HIV-infected patient is seen as hemorrhagic vesicles and pustules on an erythematous base grouped in a dermatomal distribution.

DIFFERENTIAL DIAGNOSIS

(See also Chap. 11) The diagnosis of chickenpox is not difficult. The characteristic rash and a history of recent exposure should lead to a prompt diagnosis. Other viral infections that can mimic chickenpox include disseminated HSV infection in patients with atopic dermatitis and the disseminated vesiculopapular lesions sometimes associated with coxsackievirus infection, echovirus infection, or atypical measles. However, these rashes are more commonly morbilliform with a hemorrhagic component rather than vesicular or vesiculopustular. Rickettsialpox (Chap. 79) can be confused with chickenpox; however, rickettsialpox can be distinguished easily by detection of the "herald spot" at the site of the mite bite and the development of a more pronounced headache. Serologic testing is also useful in differentiating rickettsialpox from varicella and can confirm susceptibility in adults unsure of their chickenpox history. Concern about smallpox has recently increased because of the threat of bioterrorism (Chap. 7). The lesions of smallpox are larger than those of chickenpox and are all at the same stage of evolution at any given time.

Unilateral vesicular lesions in a dermatomal pattern should lead rapidly to the diagnosis of herpes zoster, although the occurrence of shingles without a rash has been reported. Both HSV and coxsackievirus infections can cause dermatomal vesicular lesions. Supportive diagnostic virology and fluorescent staining of skin scrapings with monoclonal antibodies are helpful in ensuring the proper diagnosis. In the prodromal stage of herpes zoster, the diagnosis can be exceedingly difficult and may be made only after lesions have appeared or by retrospective serologic assessment.

LABORATORY FINDINGS

Unequivocal confirmation of the diagnosis is possible only through the isolation of VZV in susceptible tissue-culture cell lines, the demonstration of either seroconversion or a fourfold or greater rise in antibody titer between acute-phase and convalescent-phase serum specimens, or the detection of VZV DNA by PCR. A rapid impression can be obtained by a Tzanck smear, with scraping of the base of the lesions in an attempt to demonstrate multinucleated giant cells; however, the sensitivity of this method is low (~60%). PCR technology for the detection of viral DNA in vesicular fluid is available in a limited number of diagnostic laboratories. Direct immunofluorescent staining of cells from the lesion base or detection of viral antigens by other assays (such as the immunoperoxidase assay) is also useful, although these tests are not commercially available. The most frequently employed serologic tools for assessing host response are the immunofluorescent detection of antibodies to VZV membrane antigens, the fluorescent antibody to membrane antigen (FAMA) test, immune adherence hemagglutination, and enzyme-linked immunosorbent assay (ELISA). The FAMA test and the ELISA appear to be most sensitive.

TREATMENT Varicella-Zoster Virus Infections

Medical management of chickenpox in the immunologically normal host is directed toward the prevention of avoidable complications. Obviously, good hygiene includes daily bathing and soaks. Secondary bacterial infection of the skin can be avoided by meticulous skin care, particularly with close cropping of fingernails. Pruritus can be decreased with topical dressings or the administration of antipruritic drugs. Tepid water baths and wet compresses are better than drying lotions for the relief of itching. Administration of aspirin to children with chickenpox should be avoided because of the association of aspirin derivatives with the development of Reye's syndrome. Acyclovir (800 mg by mouth five times daily), valacyclovir (1 g three times daily), or famciclovir (250 mg three times daily) for 5–7 days is recommended for adolescents and adults with chickenpox of ≥24 h duration. (Valacyclovir is licensed for use in children and adolescents. Famciclovir is recommended but not licensed for varicella.) Likewise, acyclovir therapy may be of benefit to children <12 years of age if initiated early in the disease (<24 h) at a dose of 20 mg/kg every 6 h. The advantages (i.e., pharmacokinetics) of the second-generation agents valacyclovir and famciclovir are described in Chap. 83.

Aluminum acetate soaks for the management of herpes zoster can be both soothing and cleansing. Patients with herpes zoster benefit from oral antiviral therapy, as evidenced by accelerated healing of lesions and resolution of zoster-associated pain with acyclovir, valacyclovir, or famciclovir. Acyclovir, now off patent, is administered at a dosage of 800 mg five times daily for 7–10 days. Famciclovir, the prodrug of penciclovir, is at least as effective as acyclovir and perhaps more so; the dose is 500 mg by mouth three times daily for 7 days. Valacyclovir, the prodrug of acyclovir that is now off patent, accelerates healing and resolution of zoster-associated pain more promptly than acyclovir. The dose is 1 g by mouth three times daily for 5–7 days. Compared with acyclovir, both famciclovir and valacyclovir offer the advantage of less frequent administration.

In severely immunocompromised hosts (e.g., transplant recipients, patients with lymphoproliferative malignancies), both chickenpox and herpes zoster (including disseminated disease) should be treated, at least at the outset, with IV acyclovir, which reduces the occurrence of visceral complications but has no effect on healing of skin lesions or pain. The dose is 10 mg/kg every 8 h for 7 days. For low-risk immunocompromised hosts, oral therapy with valacyclovir or famciclovir appears beneficial. If medically feasible, it is desirable to decrease immunosuppressive treatment concomitant with the administration of IV acyclovir.

Patients with varicella pneumonia often require ventilatory support. Persons with zoster ophthalmicus should be referred immediately to an ophthalmologist. Therapy for this condition consists of the administration of analgesics for severe pain and the use of atropine. Acyclovir, valacyclovir, and famciclovir all accelerate healing. Decisions about the use of glucocorticoids should be made by the ophthalmologist.

The management of acute neuritis and/or postherpetic neuralgia can be particularly difficult. In addition to the judicious use of analgesics, ranging from nonnarcotics to narcotic derivatives, drugs such as gabapentin, pregabalin, amitriptyline hydrochloride, lidocaine (patches), and fluphenazine hydrochloride are reportedly beneficial for pain relief. In one study, glucocorticoid therapy administered early in the course of localized herpes zoster significantly accelerated such quality-of-life improvements as a return to usual activity and termination of analgesic medications. The dose of prednisone administered orally was 60 mg/d on days 1–7, 30 mg/d on days 8–14, and 15 mg/d on days 15–21. This regimen is appropriate only for relatively healthy elderly persons with moderate or severe pain at presentation. Patients with osteoporosis, diabetes mellitus, glycosuria, or hypertension may not be appropriate candidates. Glucocorticoids should not be used without concomitant antiviral therapy.

PREVENTION

Three methods are used for the prevention of VZV infections. First, a live attenuated varicella vaccine (Oka) is recommended for all children >1 year of age (up to 12 years of age) who have not had chickenpox and for adults known to be seronegative for VZV. Two doses are recommended for all children: the first at 12–15 months of age and the second at ~4–6 years of age. VZV-seronegative persons >13 years of age should receive two doses of vaccine at least 1 month apart. The vaccine is both safe and efficacious. Breakthrough cases

are mild and may result in spread of the vaccine virus to susceptible contacts. The universal vaccination of children is resulting in a decreased incidence of chickenpox in sentinel communities. Furthermore, inactivation of the vaccine virus significantly decreases the occurrence of herpes zoster after hematopoietic stem-cell transplantation. In individuals >60 years of age, a VZV vaccine with 18 times the viral content of the Oka vaccine decreased the incidence of shingles by 51%, the burden of illness by 61%, and the incidence of postherpetic neuralgia by 66%. The Advisory Committee on Immunization Practices has therefore recommended that persons in this age group be offered this vaccine in order to reduce the frequency of shingles and the severity of postherpetic neuralgia.

A second approach is to administer varicella-zoster immune globulin (VZIG) to individuals who are susceptible, are at high risk for developing complications of varicella, and have had a significant exposure. This product should be given within 96 h (preferably within 72 h) of the exposure. Indications for administration of VZIG appear in **Table 85-1.** VZIG is available under an investigational new drug protocol from FFF Enterprises (800-843-7477).

Lastly, antiviral therapy can be given as prophylaxis to individuals at high risk who are ineligible for vaccine or who are beyond the 96-h window after direct contact. While the initial studies have used acyclovir, similar benefit can be anticipated with either valacyclovir or famciclovir. Therapy is instituted 7 days after intense exposure. At this time, the host is midway into the incubation period. This approach significantly decreases disease severity, if not totally preventing disease.

TABLE 85-1

RECOMMENDATIONS FOR VZIG ADMINISTRATION

Exposure Criteria

1. Exposure to person with chickenpox or zoster
   a. Household: residence in the same household
   b. Playmate: face-to-face indoor play
   c. Hospital
      Varicella: same 2- to 4-bed room or adjacent beds in large ward, face-to-face contact with infectious staff member or patient, visit by a person deemed contagious
      Zoster: intimate contact (e.g., touching or hugging) with a person deemed contagious
   d. Newborn infant: onset of varicella in the mother ≤5 days before delivery or ≤48 h after delivery; VZIG not indicated if the mother has zoster
2. Patient should receive VZIG as soon as possible but not >96 h after exposure

Candidates (Provided They Have Significant Exposure) Include:

1. Immunocompromised susceptible children without a history of varicella or varicella immunization
2. Susceptible pregnant women
3. Newborn infants whose mother had onset of chickenpox within 5 days before or within 48 h after delivery
4. Hospitalized premature infant (≥28 weeks of gestation) whose mother lacks a reliable history of chickenpox or serologic evidence of protection against varicella
5. Hospitalized premature infant (<28 weeks of gestation or ≤1000-g birth weight), regardless of maternal history of varicella or varicella-zoster virus serologic status

CHAPTER 86

EPSTEIN-BARR VIRUS INFECTIONS, INCLUDING INFECTIOUS MONONUCLEOSIS

Jeffrey I. Cohen

DEFINITION

Epstein-Barr virus (EBV) is the cause of heterophile-positive infectious mononucleosis (IM), which is characterized by fever, sore throat, lymphadenopathy, and atypical lymphocytosis. EBV is also associated with several human tumors, including nasopharyngeal carcinoma, Burkitt's lymphoma, Hodgkin's disease, and (in patients with immunodeficiencies) B cell lymphoma. The virus is a member of the family Herpesviridae.

The two types of EBV that are widely prevalent in nature are not distinguishable by conventional serologic tests.

EPIDEMIOLOGY

EBV infections occur worldwide. These infections are most common in early childhood, with a second peak during late adolescence. By adulthood, more than 90% of individuals have been infected and have antibodies to the virus. IM is usually a disease of young adults. In lower socioeconomic groups and in areas of the world with deficient standards of hygiene (e.g., developing regions), EBV tends to infect children at an early age, and IM is uncommon. In areas with higher standards of hygiene, infection with EBV is often delayed until adulthood, and IM is more prevalent.

EBV is spread by contact with oral secretions. The virus is frequently transmitted from asymptomatic adults to infants and among young adults by transfer of saliva during kissing. Transmission by less intimate contact is rare. EBV has been transmitted by blood transfusion and by bone marrow transplantation. More than 90% of asymptomatic seropositive individuals shed the virus in oropharyngeal secretions. Shedding is increased in immunocompromised patients and those with IM.

PATHOGENESIS

EBV is transmitted by salivary secretions. The virus infects the epithelium of the oropharynx and the salivary glands and is shed from these cells. While B cells may become infected after contact with epithelial cells, studies suggest that lymphocytes in the tonsillar crypts can be infected directly. The virus then spreads through the bloodstream. The proliferation and expansion of EBV-infected B cells along with reactive T cells during IM result in enlargement of lymphoid tissue. Polyclonal activation of B cells leads to the production of antibodies to host-cell and viral proteins. During the acute phase of IM, up to 1 in every 100 B cells in the peripheral blood is infected by EBV; after recovery, 1–50 in every 1 million B cells is infected. During IM, there is an inverted CD4+/CD8+ T cell ratio. The percentage of CD4+ T cells decreases, while there are large clonal expansions of CD8+ T cells; up to 40% of CD8+ T cells are directed against EBV antigens during acute infection. Memory B cells, not epithelial cells, are the reservoir for EBV in the body. When patients are treated with acyclovir, shedding of EBV from the oropharynx stops but the virus persists in B cells.

The EBV receptor (CD21) on the surface of B cells is also the receptor for the C3d component of complement. EBV infection of epithelial cells results in viral replication and production of virions. When B cells are infected by EBV in vitro, they become transformed and can proliferate indefinitely. During latent infection of B cells, only the EBV nuclear antigens (EBNAs), latent membrane proteins (LMPs), and small EBV RNAs are expressed in vitro. EBV-transformed B cells secrete immunoglobulin; only a small fraction of cells produce virus.

Cellular immunity is more important than humoral immunity in controlling EBV infection. In the initial phase of infection, suppressor T cells, natural killer cells, and nonspecific cytotoxic T cells are important in controlling the proliferation of EBV-infected B cells. Levels of markers of T cell activation and serum interferon (IFN) γ are elevated. Later in infection, human leukocyte antigen–restricted cytotoxic T cells that recognize EBNAs and LMPs and destroy EBV-infected cells are generated. Studies have shown that one of the late proteins expressed during EBV replication, *BCRF1*, is a homologue of interleukin 10 and can inhibit the production of IFN-γ by mononuclear cells in vitro.

If T cell immunity is compromised, EBV-infected B cells may begin to proliferate. When EBV is associated with lymphoma, virus-induced proliferation is but one step in a multistep process of neoplastic transformation. In many EBV-containing tumors, LMP-1 mimics members of the tumor necrosis factor receptor family (e.g., CD40), transmitting growth-proliferating signals.

CLINICAL MANIFESTATIONS

Signs and symptoms

Most EBV infections in infants and young children either are asymptomatic or present as mild pharyngitis with or without tonsillitis. In contrast, up to 75% of infections in adolescents present as IM. IM in the elderly presents relatively often as nonspecific symptoms, including prolonged fever, fatigue, myalgia, and malaise. In contrast, pharyngitis, lymphadenopathy, splenomegaly, and atypical lymphocytes are relatively rare in elderly patients.

The incubation period for IM in young adults is ~4–6 weeks. A prodrome of fatigue, malaise, and myalgia may last for 1–2 weeks before the onset of fever, sore throat, and lymphadenopathy. Fever is usually low-grade and is most common in the first 2 weeks of the illness; however, it may persist for >1 month. Common signs and symptoms are listed along with their frequencies in **Table 86-1.** Lymphadenopathy and pharyngitis are most prominent during the first 2 weeks of the illness, while splenomegaly is more prominent during the second and third weeks. Lymphadenopathy most often affects the posterior cervical nodes but may be generalized. Enlarged lymph nodes are frequently tender and symmetric but are not fixed in place. Pharyngitis, often the most prominent sign, can be accompanied by enlargement of the tonsils with an exudate resembling that of streptococcal pharyngitis. A morbilliform or papular rash, usually on the arms or trunk, develops in ~5% of cases **(Fig. 86-1)**. Most patients treated with ampicillin develop a macular rash;

TABLE 86-1

SIGNS AND SYMPTOMS OF INFECTIOUS MONONUCLEOSIS

MANIFESTATION	MEDIAN PERCENTAGE OF PATIENTS (RANGE)
Symptoms	
Sore throat	75 (50–87)
Malaise	47 (42–76)
Headache	38 (22–67)
Abdominal pain, nausea, or vomiting	17 (5–25)
Chills	10 (9–11)
Signs	
Lymphadenopathy	95 (83–100)
Fever	93 (60–100)
Pharyngitis or tonsillitis	82 (68–90)
Splenomegaly	51 (43–64)
Hepatomegaly	11 (6–15)
Rash	10 (0–25)
Periorbital edema	13 (2–34)
Palatal enanthem	7 (3–13)
Jaundice	5 (2–10)

this rash is not predictive of future adverse reactions to penicillins. Erythema nodosum and erythema multiforme have also been described. Most patients have symptoms for 2–4 weeks, but malaise and difficulty concentrating can persist for months.

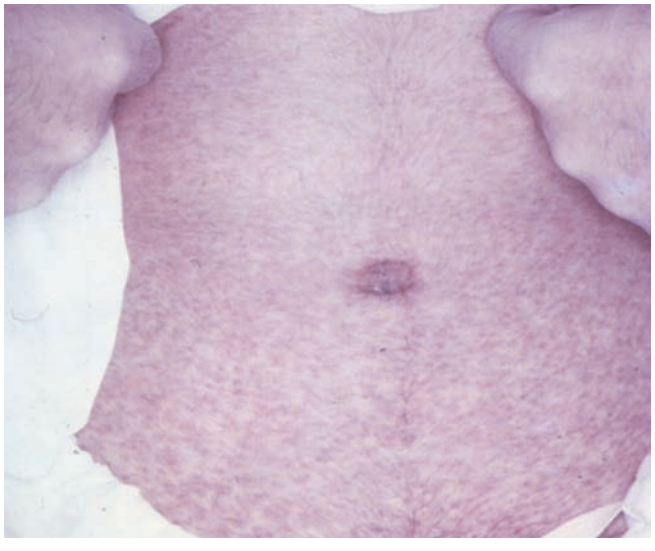


FIGURE 86-1
Rash in a patient with infectious mononucleosis due to Epstein-Barr virus. (*Courtesy of Maria Turner, MD; with permission.*)

Laboratory findings

The white blood cell count is usually elevated and peaks at 10,000–20,000/μL during the second or third week of illness. Lymphocytosis is usually demonstrable, with >10% atypical lymphocytes. The latter cells are enlarged lymphocytes that have abundant cytoplasm, vacuoles, and indentations of the cell membrane **(Fig. 86-2)**. CD8+ cells predominate among the atypical lymphocytes. Low-grade neutropenia and thrombocytopenia are common during the first month of illness. Liver function is abnormal in >90% of cases. Serum levels of aminotransferases and alkaline phosphatase are usually mildly elevated. The serum concentration of bilirubin is elevated in ~40% of cases.

Complications

Most cases of IM are self-limited. Deaths are very rare and most often are due to central nervous system (CNS) complications, splenic rupture, upper airway obstruction, or bacterial superinfection.

When CNS complications develop, they usually do so during the first 2 weeks of EBV infection; in some patients, especially children, they are the only clinical manifestations of IM. Heterophile antibodies and atypical lymphocytes may be absent. Meningitis and encephalitis are the most common neurologic abnormalities, and patients may present with headache, meningismus, or cerebellar ataxia. Acute hemiplegia and psychosis have also been described. The cerebrospinal fluid (CSF) contains mainly lymphocytes, with occasional atypical lymphocytes. Most cases resolve without neurologic sequelae. Acute EBV infection has also been associated with cranial nerve palsies (especially those involving cranial nerve VII), Guillain-Barré syndrome, acute transverse myelitis, and peripheral neuritis.

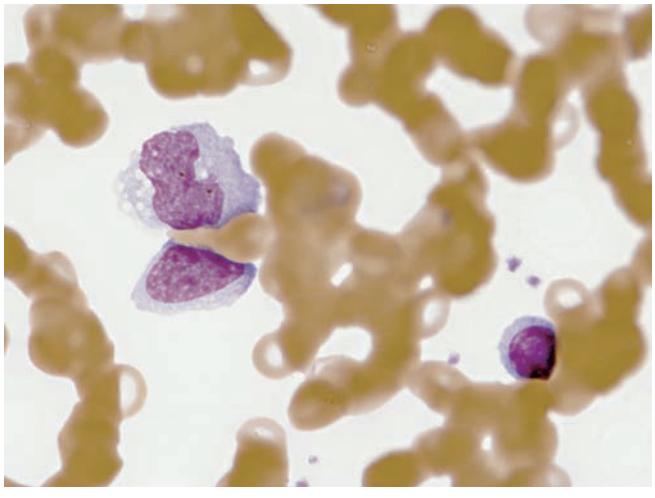


FIGURE 86-2
Atypical lymphocytes from a patient with infectious mononucleosis due to Epstein-Barr virus.

Autoimmune hemolytic anemia occurs in ~2% of cases during the first 2 weeks. In most cases, the anemia is Coombs-positive, with cold agglutinins directed against the red blood cell antigen. Most patients with hemolysis have mild anemia that lasts for 1–2 months, but some patients have severe disease with hemoglobinuria and jaundice. Nonspecific antibody responses may also include rheumatoid factor, antinuclear antibodies, anti–smooth muscle antibodies, antiplatelet antibodies, and cryoglobulins. IM has been associated with red-cell aplasia, severe granulocytopenia, thrombocytopenia, pancytopenia, and hemophagocytic lymphohistiocytosis. The spleen ruptures in <0.5% of cases. Splenic rupture is more common among male than female patients and may manifest as abdominal pain, referred shoulder pain, or hemodynamic compromise.

Hypertrophy of lymphoid tissue in the tonsils or adenoids can result in upper airway obstruction, as can inflammation and edema of the epiglottis, pharynx, or uvula. About 10% of patients with IM develop streptococcal pharyngitis after their initial sore throat resolves.

Other rare complications associated with acute EBV infection include hepatitis (which can be fulminant), myocarditis or pericarditis with electrocardiographic changes, pneumonia with pleural effusion, interstitial nephritis, genital ulcerations, and vasculitis.

EBV-associated diseases other than IM

EBV-associated lymphoproliferative disease has been described in patients with congenital or acquired immunodeficiency, including those with severe combined immunodeficiency, patients with AIDS, and recipients of bone marrow or organ transplants who are receiving immunosuppressive drugs (especially cyclosporine). Proliferating EBV-infected B cells infiltrate lymph nodes and multiple organs, and patients present with fever and lymphadenopathy or gastrointestinal symptoms. Pathologic studies show B cell hyperplasia or poly- or monoclonal lymphoma. X-linked lymphoproliferative disease (XLPD) is a recessive disorder of young boys who have a normal response to childhood infections but develop fatal lymphoproliferative disorders after infection with EBV. The protein associated with most cases of this syndrome (SAP) binds to a protein that mediates interactions of B and T cells. Most patients with this syndrome die of acute IM. Others develop hypogammaglobulinemia, malignant B cell lymphomas, aplastic anemia, or agranulocytosis. Disease resembling XLPD has also been associated with mutations in the XIAP or ITK proteins. Moreover, IM has proved fatal to some patients with no obvious preexisting immune abnormality.

Oral hairy leukoplakia **(Fig. 86-3)** is an early manifestation of infection with HIV in adults (Chap. 93). Most patients present with raised, white corrugated lesions on the tongue (and occasionally on the buccal mucosa) that contain EBV DNA. Children infected with HIV can develop lymphoid interstitial pneumonitis; EBV DNA is often found in lung tissue from these patients.

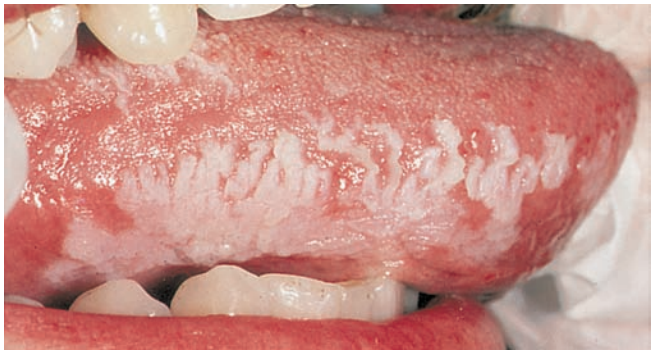


FIGURE 86-3
Oral hairy leukoplakia often presents as white plaques on the lateral surface of the tongue and is associated with Epstein-Barr virus infection.

Patients with chronic fatigue syndrome may have titers of antibody to EBV that are elevated but are not significantly different from those in healthy EBV-seropositive adults. While some patients have malaise and fatigue that persist for weeks or months after IM, persistent EBV infection is not a cause of chronic fatigue syndrome. Chronic active EBV infection is very rare and is distinct from chronic fatigue syndrome. The affected patients have an illness lasting >6 months, with elevated levels of EBV DNA in the blood, very high titers of antibody to EBV, and evidence of organ involvement, including hepatosplenomegaly, lymphadenopathy, and pneumonitis, uveitis, or neurologic disease.

EBV is associated with several malignancies. About 15% of cases of Burkitt's lymphoma in the United States and ~90% of those in Africa are associated with EBV. African patients with Burkitt's lymphoma have high levels of antibody to EBV, and their tumor tissue usually contains viral DNA. Malaria infection in Africa may impair cellular immunity to EBV and induce polyclonal B cell activation with an expansion of EBV-infected B cells. These changes may enhance the proliferation of B cells with elevated EBV DNA in the bloodstream, thereby increasing the likelihood of a *c-myc* translocation—the hallmark of Burkitt's lymphoma. EBV-containing Burkitt's lymphoma also occurs in patients with AIDS.

Anaplastic nasopharyngeal carcinoma is common in southern China and is uniformly associated with EBV; the affected tissues contain viral DNA and antigens. Patients with nasopharyngeal carcinoma often have elevated titers of antibody to EBV. High levels of EBV plasma DNA before treatment or detectable levels of EBV DNA after radiation therapy correlate with lower rates of overall survival and relapse-free survival among patients with nasopharyngeal carcinoma.

EBV has been associated with Hodgkin's disease, especially the mixed-cellularity type. Patients with Hodgkin's disease often have elevated titers of antibody to EBV. In about half of cases in the United States, viral DNA and antigens are found in Reed-Sternberg cells. The risk of EBV-positive Hodgkin's disease is significantly increased in young adults after EBV-seropositive IM. About 50%

of non-Hodgkin's lymphomas in patients with AIDS are EBV-positive.

EBV is present in B cells of lesions from patients with lymphomatoid granulomatosis. In some cases, EBV DNA has been detected in tumors from immunocompetent patients with angiocentric nasal NK/T cell lymphoma, T cell lymphoma, gastric carcinoma, and CNS lymphoma. Studies have demonstrated viral DNA in leiomyosarcomas from AIDS patients and in smooth-muscle tumors from organ transplant recipients. Virtually all CNS lymphomas in AIDS patients are associated with EBV. Studies have found that a history of IM and higher levels of antibodies to EBV before the onset of disease is more common in persons with multiple sclerosis than in the general population, and additional research on a possible causal relationship is needed.

DIAGNOSIS

Serologic testing

The heterophile test is used for the diagnosis of IM in children and adults **(Table 86-2)**. In the test for this antibody, human serum is absorbed with guinea pig kidney, and the heterophile titer is defined as the greatest serum dilution that agglutinates sheep, horse, or cow erythrocytes. The heterophile antibody does not interact with EBV proteins. A titer of ≥forty-fold is diagnostic of acute EBV infection in a patient who has symptoms compatible with IM and atypical lymphocytes. Tests for heterophile antibodies are positive in 40% of patients with IM during the first week of illness and in 80–90% during the third week. Therefore, repeated testing may be necessary, especially if the initial test is performed early. Tests usually remain positive for 3 months after the onset of illness, but heterophile antibodies can persist for up to 1 year. These antibodies usually are not detectable in children <5 years of age, in the elderly, or in patients presenting with symptoms not typical of IM. The commercially available monospot test for heterophile antibodies is somewhat more sensitive than the classic heterophile test. The monospot test is ~75% sensitive and ~90% specific compared with EBV-specific serologies. False-positive monospot results are more common among persons with connective tissue disease, lymphoma, viral hepatitis, and malaria.

EBV-specific antibody testing is used for patients with suspected acute EBV infection who lack heterophile antibodies and for patients with atypical infections (Table 86-2). Titers of IgM and IgG antibodies to viral capsid antigen (VCA) are elevated in the serum of more than 90% of patients at the onset of disease. IgM antibody to VCA is most useful for the diagnosis of acute IM because it is present at elevated titers only during the first 2–3 months of the disease; in contrast, IgG antibody to VCA is usually not useful for diagnosis of IM but is often used to assess past exposure to EBV because it persists for life. Seroconversion to EBNA positivity is also useful for the diagnosis of acute infection with EBV. Antibodies to EBNA become detectable relatively late (3–6 weeks after the onset of symptoms) in nearly all cases of acute EBV infection and persist for the lifetime of the patient. These antibodies may be lacking in immunodeficient patients and in those with chronic active EBV infection.

Titers of other antibodies may also be elevated in IM; however, these elevations are less useful for diagnosis. Antibodies to early antigens (EAs) are detectable 3–4 weeks after the onset of symptoms in patients with IM. About 70% of individuals with IM have EA-D antibodies during the illness; the presence of EA-D antibodies is especially likely in patients with relatively severe disease. These antibodies usually persist for only 3–6 months. Levels of EA-D antibodies are also elevated in patients with nasopharyngeal carcinoma or chronic active EBV infection. EA-R antibodies are only occasionally detected in patients with IM but are often found at elevated titers in patients with African Burkitt's lymphoma or chronic active EBV infection.

TABLE 86-2

SEROLOGIC FEATURES OF EBV-ASSOCIATED DISEASES

	RESULT IN INDICATED TEST					
		ANTI-VCA		ANTI-EA		
CONDITION	HETEROPHILE	IgM	IgG	EA-D	EA-R	ANTI-EBNA
Acute infectious mononucleosis	+	+	++	+	–	–
Convalescence	±	–	+	–	±	+
Past infection	–	–	+	–	–	+
Reactivation with immunodeficiency	–	–	++	+	+	±
Burkitt's lymphoma	–	–	+++	±	++	+
Nasopharyngeal carcinoma	–	–	+++	++	±	+

Abbreviations: EA, early antigen; EA-D antibody, antibody to early antigen in diffuse pattern in nucleus and cytoplasm of infected cells; EA-R antibody, antibody to early antigen restricted to the cytoplasm; EBNA, Epstein-Barr nuclear antigen; VCA, viral capsid antigen.
Source: Adapted from M Okano et al: Clin Microbiol Rev 1:300, 1988.

IgA antibodies to EBV antigens have proved useful for the identification of patients with nasopharyngeal carcinoma and of persons at high risk for the disease.

Other studies

Detection of EBV DNA, RNA, or proteins has been valuable in demonstrating the association of the virus with various malignancies. The polymerase chain reaction has been used to detect EBV DNA in the CSF of some AIDS patients with lymphomas and to monitor the amount of EBV DNA in the blood of patients with lymphoproliferative disease. Detection of high levels of EBV DNA in blood during the first few weeks of IM may be useful if serologic studies yield equivocal results. Culture of EBV from throat washings or blood is not helpful in the diagnosis of acute infection, since EBV commonly persists in the oropharynx and in B cells for the lifetime of the infected individual.

Differential diagnosis

Whereas ~90% of cases of IM are due to EBV, 5–10% of cases are due to cytomegalovirus (CMV). CMV is the most common cause of heterophile-negative mononucleosis; less common causes of IM and differences from IM due to EBV are shown in **Table 86-3.**

TREATMENT EBV-Associated Disease

Therapy for IM consists of supportive measures, with rest and analgesia. Excessive physical activity during the first month should be avoided to reduce the possibility of splenic rupture, which necessitates splenectomy. Glucocorticoid therapy is not indicated for uncomplicated IM and in fact may predispose to bacterial superinfection. Prednisone (40–60 mg/d for 2–3 days, with subsequent tapering of the dose over 1–2 weeks) has been used for the prevention of airway obstruction in patients with severe tonsillar hypertrophy, for autoimmune hemolytic anemia, for hemophagocytic lymphohistiocytosis, and for severe thrombocytopenia. Glucocorticoids have also been administered to a few selected patients with severe malaise and fever and to patients with severe CNS or cardiac disease.

Acyclovir has had no significant clinical impact on IM in controlled trials. In one study, the combination of acyclovir and prednisolone had no significant effect on the duration of symptoms of IM.

Acyclovir, at a dosage of 400–800 mg five times daily, has been effective for the treatment of oral hairy leukoplakia (despite common relapses). The posttransplantation EBV lymphoproliferative syndrome (Chap. 13) generally does not respond to antiviral therapy. When possible, therapy should be directed toward reduction of immunosuppression. Antibody to CD20 (rituximab)

TABLE 86-3
DIFFERENTIAL DIAGNOSIS OF INFECTIOUS MONONUCLEOSIS

	SIGN OR SYMPTOM				
ETIOLOGY	FEVER	ADENOPATHY	SORE THROAT	ATYPICAL LYMPHOCYTES	DIFFERENCES FROM EBV MONONUCLEOSIS
EBV	+	+	+	+	—
CMV	+	±	±	+	Older age at presentation, longer duration of fever
HIV	+	+	+	±	Diffuse rash, oral/genital ulcers, aseptic meningitis
Toxoplasmosis	+	+	±	±	Less splenomegaly, exposure to cats or raw meat
HHV-6	+	+	+	+	Older age at presentation
Streptococcal pharyngitis	+	+	+	–	No splenomegaly, less fatigue
Viral hepatitis	+	±	–	±	Higher aminotransferase levels
Rubella	+	+	±	±	Maculopapular rash, no splenomegaly
Lymphoma	+	+	+	+	Fixed, nontender lymph nodes
Drugs[a]	+	+	–	±	Occurs at any age

[a]Most commonly phenytoin, carbamazepine, sulfonamides, or minocycline. CMV, cytomegalovirus; EBV, Epstein-Barr virus; HHV, human herpesvirus.

has been effective in some cases. Infusions of donor lymphocytes are often effective for stem cell transplant recipients, although graft-versus-host disease can occur. Infusions of EBV-specific cytotoxic T cells have been used to prevent EBV lymphoproliferative disease in high-risk settings as well as to treat the disease. IFN-α administration, cytotoxic chemotherapy, and radiation therapy (especially for CNS lesions) have also been used. Infusion of autologous EBV-specific cytotoxic T lymphocytes has shown promise in small studies of patients with nasopharyngeal carcinoma and Hodgkin's disease. Treatment of several cases of XLPD with antibody to CD20 resulted in a successful outcome of what otherwise would probably have been fatal acute EBV infection.

PREVENTION

The isolation of patients with IM is unnecessary. A vaccine directed against the major EBV glycoprotein reduced the frequency of IM but did not affect the rate of asymptomatic infection.

CHAPTER 87

CYTOMEGALOVIRUS AND HUMAN HERPESVIRUS TYPES 6, 7, AND 8

Martin S. Hirsch

CYTOMEGALOVIRUS

DEFINITION

Cytomegalovirus (CMV), which was initially isolated from patients with congenital cytomegalic inclusion disease, is now recognized as an important pathogen in all age groups. In addition to inducing severe birth defects, CMV causes a wide spectrum of disorders in older children and adults, ranging from an asymptomatic subclinical infection to a mononucleosis syndrome in healthy individuals to disseminated disease in immunocompromised patients. Human CMV is one of several related species-specific viruses that cause similar diseases in various animals. All are associated with the production of characteristic enlarged cells—hence the name *cytomegalovirus*.

CMV, a β-herpesvirus, has double-strand DNA, four species of mRNA, a protein capsid, and a lipoprotein envelope. Like other herpesviruses, CMV demonstrates icosahedral symmetry, replicates in the cell nucleus, and can cause either a lytic and productive or a latent infection. CMV can be distinguished from other herpesviruses by certain biologic properties, such as host range and type of cytopathology. Viral replication is associated with the production of large intranuclear inclusions and smaller cytoplasmic inclusions. CMV appears to replicate in a variety of cell types in vivo; in tissue culture it grows preferentially in fibroblasts. Although there is little evidence that CMV is oncogenic in vivo, it does transform fibroblasts in rare instances, and genomic transforming fragments have been identified.

EPIDEMIOLOGY

CMV has a worldwide distribution. Of newborns in the United States, ~1% are infected with CMV; the percentages are higher in many less-developed countries. Communal living and poor personal hygiene facilitate early spread. Perinatal and early childhood infections are common. CMV may be present in breast milk, saliva, feces, and urine. Transmission has occurred among young children in day-care centers and has been traced from infected toddler to pregnant mother to developing fetus. When an infected child introduces CMV into a household, 50% of susceptible family members seroconvert within 6 months.

CMV is not readily spread by casual contact but rather requires repeated or prolonged intimate exposure for transmission. In late adolescence and young adulthood, CMV is often transmitted sexually, and asymptomatic

carriage in semen or cervical secretions is common. Antibody to CMV is present at detectable levels in a high proportion of sexually active men and women, who may harbor several strains simultaneously. Transfusion of whole blood or certain blood products containing viable leukocytes may transmit CMV, with a frequency of 0.14–10% per unit transfused.

Once infected, an individual generally carries CMV for life. The infection usually remains silent. However, CMV reactivation syndromes develop frequently when T lymphocyte–mediated immunity is compromised—for example, after organ transplantation, in association with lymphoid neoplasms and certain acquired immunodeficiencies (in particular, HIV infection; Chap. 93), or in critically ill patients on intensive care units. Most primary CMV infections in organ transplant recipients (Chap. 13) result from transmission in the graft itself. In CMV-seropositive transplant recipients, infection results from reactivation of latent virus or, less commonly, from reinfection by a new strain. CMV infection may also be associated with diseases as diverse as coronary artery stenosis and malignant gliomas, but these associations require further validation.

PATHOGENESIS

Congenital CMV infection can result from either primary or reactivation infection of the mother. However, clinical disease in the fetus or newborn is related almost exclusively to primary maternal infection **(Table 87-1)**. The factors determining the severity of congenital infection are unknown; a deficient capacity to produce precipitating antibodies and to mount T cell responses to CMV is associated with relatively severe disease.

Primary infection with CMV in late childhood or adulthood is often associated with a vigorous T lymphocyte response that may contribute to the development of a mononucleosis syndrome similar to that observed after infection with Epstein-Barr virus (Chap. 86). The hallmark of such infection is the appearance of atypical lymphocytes in the peripheral blood; these cells are predominantly activated CD8+ T lymphocytes. Polyclonal activation of B cells by CMV contributes to the development of rheumatoid factors and other autoantibodies during mononucleosis.

Once acquired, CMV persists indefinitely in host tissues. The sites of persistent infection probably include multiple cell types and various organs. Transmission via blood transfusion or organ transplantation is due to silent infections in these tissues. Autopsy studies suggest that salivary glands and bowel may be sites of latent infection.

If the host's T cell responses become compromised by disease or by iatrogenic immunosuppression, latent virus can be reactivated to cause a variety of syndromes. Chronic antigenic stimulation in the presence of immunosuppression (for example, after tissue transplantation) appears to be an ideal setting for CMV activation and CMV-induced disease. Certain particularly potent suppressants of T cell immunity (e.g., antithymocyte globulin) are associated with a high rate of clinical CMV syndromes, which may follow either primary or reactivation infection. CMV may itself contribute to further T lymphocyte hyporesponsiveness, which often precedes superinfection with other opportunistic pathogens, such as *Pneumocystis*. CMV and *Pneumocystis* are frequently found together in immunosuppressed patients with severe interstitial pneumonia.

TABLE 87-1

CMV DISEASE IN THE IMMUNOCOMPROMISED HOST

POPULATION	RISK FACTORS	PRINCIPAL SYNDROMES	TREATMENT	PREVENTION
Fetus	Primary maternal infection/early pregnancy	Cytomegalic inclusion disease	Ganciclovir for symptomatic neonates	Avoidance of exposure; possibly, maternal treatment with CMV immunoglobulin during pregnancy
Organ transplant recipient	Seropositivity of donor and/or recipient; immunosuppressive regimen; high degree of rejection	Febrile leukopenia; pneumonia; gastrointestinal disease	Ganciclovir or valganciclovir	Donor matching; prophylaxis or preemptive therapy with ganciclovir or valganciclovir
Bone marrow transplant recipient	Graft-vs.-host disease; older age of recipient; seropositive recipient; viremia	Pneumonia; gastrointestinal disease	Ganciclovir plus CMV immunoglobulin	Donor matching; prophylaxis or preemptive therapy with ganciclovir or valganciclovir
Person with AIDS	<100 CD4+ T cells/μL; CMV seropositivity	Retinitis; gastrointestinal disease; neurologic disease	Ganciclovir, valganciclovir, foscarnet, or cidofovir	Oral valganciclovir

PATHOLOGY

Cytomegalic cells in vivo (presumed to be infected epithelial cells) are two to four times larger than surrounding cells and often contain an 8- to 10-μm intranuclear inclusion that is eccentrically placed and is surrounded by a clear halo, producing an "owl's eye" appearance. Smaller granular cytoplasmic inclusions are demonstrated occasionally. Cytomegalic cells are found in a wide variety of organs, including the salivary gland, lung, liver, kidney, intestine, pancreas, adrenal gland, and central nervous system.

The cellular inflammatory response to infection consists of plasma cells, lymphocytes, and monocyte-macrophages. Granulomatous reactions occasionally develop, particularly in the liver. Immunopathologic reactions may contribute to CMV disease. Immune complexes have been detected in infected infants, sometimes in association with CMV-related glomerulopathies. Immune-complex glomerulopathy has also been observed in some CMV-infected patients after renal transplantation.

CLINICAL MANIFESTATIONS

Congenital CMV infection

Fetal infections range from inapparent to severe and disseminated. Cytomegalic inclusion disease develops in ~5% of infected fetuses and is seen almost exclusively in infants born to mothers who develop primary infections during pregnancy. Petechiae, hepatosplenomegaly, and jaundice are the most common presenting features (60–80% of cases). Microcephaly with or without cerebral calcifications, intrauterine growth retardation, and prematurity are reported in 30–50% of cases. Inguinal hernias and chorioretinitis are less common. Laboratory abnormalities include elevated alanine aminotransferase levels in serum, thrombocytopenia, conjugated hyperbilirubinemia, hemolysis, and elevated protein levels in cerebrospinal fluid. The prognosis for severely infected infants is poor; the mortality rate is 20–30%, and few survivors escape intellectual or hearing difficulties later in childhood. The differential diagnosis of cytomegalic inclusion disease in infants includes syphilis, rubella, toxoplasmosis, infection with herpes simplex virus or enterovirus, and bacterial sepsis.

Most congenital CMV infections are clinically inapparent at birth. Of asymptomatically infected infants, 5–25% develop significant psychomotor, hearing, ocular, or dental abnormalities over the next several years.

Perinatal CMV infection

The newborn may acquire CMV at delivery by passage through an infected birth canal or by postnatal contact with infected breast milk or other maternal secretions. Of infants who are breast-fed for >1 month by seropositive mothers, 40–60% become infected. Iatrogenic transmission can result from neonatal blood transfusion; screening of blood products before transfusion into low-birth-weight seronegative infants or seronegative pregnant women decreases risk.

The great majority of infants infected at or after delivery remain asymptomatic. However, protracted interstitial pneumonitis has been associated with perinatally acquired CMV infection, particularly in premature infants, and occasionally has been accompanied by infection with *Chlamydia trachomatis*, *Pneumocystis*, or *Ureaplasma urealyticum*. Poor weight gain, adenopathy, rash, hepatitis, anemia, and atypical lymphocytosis may also be found, and CMV excretion often persists for months or years.

CMV mononucleosis

The most common clinical manifestation of CMV infection in immunocompetent hosts beyond the neonatal period is a heterophile antibody–negative mononucleosis syndrome, which may develop spontaneously or follow transfusion of leukocyte-containing blood products. Although the syndrome occurs at all ages, it most often involves sexually active young adults. With incubation periods of 20–60 days, the illness generally lasts for 2–6 weeks. Prolonged high fevers, sometimes with chills, profound fatigue, and malaise, characterize this disorder. Myalgias, headache, and splenomegaly are common, but in CMV (as opposed to Epstein-Barr virus) mononucleosis, exudative pharyngitis, and cervical lymphadenopathy are rare. Occasional patients develop rubelliform rashes, often after exposure to ampicillin or certain other antibiotics. Less common are interstitial or segmental pneumonia, myocarditis, pleuritis, arthritis, and encephalitis. In rare cases, Guillain-Barré syndrome complicates CMV mononucleosis. The characteristic laboratory abnormality is relative lymphocytosis in peripheral blood, with >10% atypical lymphocytes. Total leukocyte counts may be low, normal, or markedly elevated. Although significant jaundice is uncommon, serum aminotransferase and alkaline phosphatase levels are often moderately elevated. Heterophile antibodies are absent; however, transient immunologic abnormalities are common and may include the presence of cryoglobulins, rheumatoid factors, cold agglutinins, and antinuclear antibodies. Hemolytic anemia, thrombocytopenia, and granulocytopenia complicate recovery in rare instances.

Most patients recover without sequelae, although postviral asthenia may persist for months. The excretion of CMV in urine, genital secretions, and/or saliva often continues for months or years. Rarely, CMV infection is fatal in immunocompetent hosts; survivors can have recurrent episodes of fever and malaise, sometimes associated with autonomic nervous system dysfunction (e.g., attacks of sweating or flushing).

CMV infection in the immunocompromised host

(Table 87-1) CMV appears to be the most common and important viral pathogen complicating organ transplantation (Chap. 13). In recipients of kidney, heart,

lung, and liver transplants, CMV induces a variety of syndromes, including fever and leukopenia, hepatitis, pneumonitis, esophagitis, gastritis, colitis, and retinitis. CMV disease may be an independent risk factor for both graft loss and death. The period of maximal risk is between 1 and 4 months after transplantation, although retinitis may be a later complication. Disease likelihood and viral replication levels generally are greater after primary infection than after reactivation. In addition, molecular studies indicate that seropositive transplant recipients are susceptible to reinfection with donor-derived, genotypically variant CMV, and such infection often results in disease. Reactivation infection, although common, is less likely than primary infection to be important clinically. The risk of clinical disease is related to various factors, such as degree of immunosuppression; use of antibodies to T cell receptors; lack of utilization of anti-CMV prophylaxis; and co-infection with other pathogens. The transplanted organ is particularly vulnerable as a target for CMV infection; thus, there is a tendency for CMV hepatitis to follow liver transplantation and for CMV pneumonitis to follow lung transplantation.

CMV pneumonia occurs in 15–20% of bone marrow transplant recipients; the case-fatality rate is 84–88%, although the risk of severe disease may be reduced by prophylaxis or preemptive therapy with antiviral drugs. The risk is greatest 5–13 weeks after transplantation, and identified risk factors include certain types of immunosuppressive therapy, acute graft-versus-host disease, older age, viremia, and pretransplantation seropositivity.

CMV is an important pathogen in patients with advanced HIV infection (Chap. 93), in whom it may cause retinitis or disseminated disease, particularly when peripheral-blood CD4+ T cell counts fall below 50–100/μL. As treatment for underlying HIV infection has improved, the incidence of serious CMV infections (e.g., retinitis) has decreased. However, during the first few weeks after institution of highly active antiretroviral therapy, acute flare-ups of CMV retinitis may occur secondary to an immune reconstitution inflammatory syndrome.

Syndromes produced by CMV in immunocompromised hosts often begin with prolonged fever, malaise, anorexia, fatigue, night sweats, and arthralgias or myalgias. Liver function abnormalities, leukopenia, thrombocytopenia, and atypical lymphocytosis may be observed during these episodes. The development of tachypnea, hypoxemia, and unproductive cough signals respiratory involvement. Radiologic examination of the lung often shows bilateral interstitial or reticulonodular infiltrates that begin in the periphery of the lower lobes and spread centrally and superiorly; localized segmental, nodular, or alveolar patterns are less common. The differential diagnosis includes *Pneumocystis* infection; other viral, bacterial, or fungal infections; pulmonary hemorrhage; and injury secondary to irradiation or to treatment with cytotoxic drugs.

Gastrointestinal CMV involvement may be localized or extensive and almost exclusively affects compromised hosts. Ulcers of the esophagus, stomach, small intestine, or colon may result in bleeding or perforation. CMV infection may lead to exacerbations of underlying ulcerative colitis. Hepatitis occurs frequently, particularly after liver transplantation, and acalculous cholecystitis and adrenalitis have been described.

CMV rarely causes meningoencephalitis in otherwise-healthy individuals. Two forms of CMV encephalitis are seen in patients with AIDS. One resembles HIV encephalitis and presents as progressive dementia; the other is a ventriculoencephalitis characterized by cranial-nerve deficits, nystagmus, disorientation, lethargy, and ventriculomegaly. In immunocompromised patients, CMV can also cause subacute progressive polyradiculopathy, which is often reversible if recognized and treated promptly.

CMV retinitis is an important cause of blindness in immunocompromised patients, particularly patients with advanced AIDS (Chap. 93). Early lesions consist of small, opaque, white areas of granular retinal necrosis that spread in a centrifugal manner and are later accompanied by hemorrhages, vessel sheathing, and retinal edema **(Fig. 87-1)**. CMV retinopathy must be distinguished from that due to other conditions, including toxoplasmosis, candidiasis, and herpes simplex virus infection.

Fatal CMV infections are often associated with persistent viremia and the involvement of multiple organ systems. Progressive pulmonary infiltrates, pancytopenia, hyperamylasemia, and hypotension are characteristic features that are frequently found in conjunction with a terminal bacterial, fungal, or protozoan superinfection. Extensive adrenal necrosis with CMV inclusions is often documented at autopsy, as is CMV involvement of many other organs.

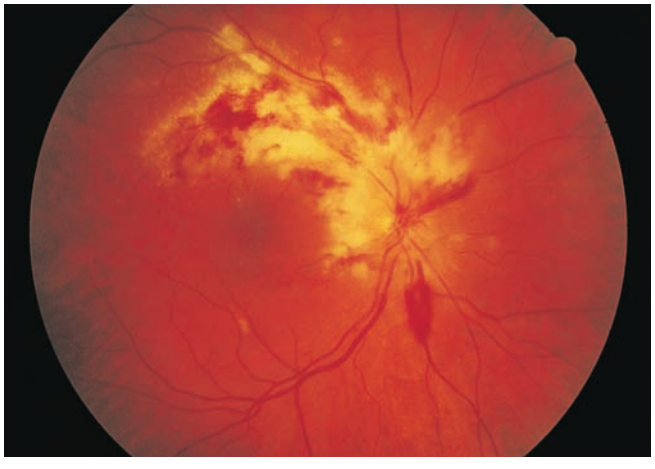


FIGURE 87-1
Cytomegalovirus infection in a patient with AIDS may appear as an arcuate zone of retinitis with hemorrhages and optic disk swelling. Often CMV is confined to the retinal periphery, beyond view of the direct ophthalmoscope.

DIAGNOSIS

The diagnosis of CMV infection usually cannot be made reliably on clinical grounds alone. Isolation of CMV or detection of its antigens or DNA in appropriate clinical specimens is the preferred approach. Virus excretion or viremia is readily detected by culture of appropriate specimens on human fibroblast monolayers. If CMV titers are high, as is common in congenital disseminated infection and in patients with AIDS, characteristic cytopathic effects may be detected within a few days. However, in some situations (e.g., CMV mononucleosis), viral titers are low, and cytopathic effects may take several weeks to appear. Many laboratories expedite diagnosis with an overnight tissue-culture method (shell vial assay) involving centrifugation and an immunocytochemical detection technique employing monoclonal antibodies to an immediate-early CMV antigen. Isolation of virus from urine or saliva does not, by itself, constitute proof of acute infection, since excretion from these sites may continue for months or years after illness. Detection of viremia is a better predictor of acute infection.

Detection of CMV antigens (pp65) in peripheral-blood leukocytes or of CMV DNA in blood or tissues may hasten diagnosis. Such assays may yield a positive result several days earlier than culture methods. The most sensitive way to detect CMV in blood or other fluids may be by amplifying CMV DNA by polymerase chain reaction (PCR). PCR detection of CMV DNA in blood may predict the risk for disease progression, particularly in immunocompromised hosts, and PCR detection of CMV DNA in cerebrospinal fluid is useful in the diagnosis of CMV encephalitis or polyradiculopathy. However, considerable variation among different assays and different laboratories has been observed.

A variety of serologic assays detect increases in titers of antibody to CMV antigens. An increased antibody level may not be detectable for up to 4 weeks after primary infection, and titers often remain high for years after infection. For this reason, single-sample antibody determinations are of no value in assessing the acuteness of infection. Detection of CMV-specific IgM is sometimes useful in the diagnosis of recent or active infection; however, circulating rheumatoid factors may result in occasional false-positive IgM tests.

TREATMENT Cytomegalovirus Infection

Several measures are useful for the prevention of CMV infection in high-risk patients. The use of blood from seronegative donors or of blood that has been frozen, thawed, and deglycerolized greatly decreases the rate of transfusion-associated transmission. Matching of organ or bone marrow transplants by CMV serology, with exclusive use of organs from seronegative donors in seronegative recipients, reduces rates of primary infection after transplantation. A CMV glycoprotein B vaccine reduced infections in a placebo-controlled trial among 464 CMV-seronegative women; this outcome raises the possibility that this experimental vaccine will reduce congenital infections, but further studies must validate this approach.

CMV immune or hyperimmune globulin has been reported (1) to reduce rates of CMV-associated syndromes and of fungal or parasitic superinfections among seronegative renal transplant recipients and (2) to prevent congenital CMV infection in infants of women with primary infection during pregnancy. Studies in bone marrow transplant recipients have produced conflicting results. Prophylactic acyclovir or valacyclovir may reduce rates of CMV infection and disease in certain seronegative renal transplant recipients, although neither drug is effective in the treatment of active CMV disease.

Ganciclovir is a guanosine derivative that has considerably more activity against CMV than its congener acyclovir. After intracellular conversion by a viral phosphotransferase encoded by CMV gene region UL97, ganciclovir triphosphate is a selective inhibitor of CMV DNA polymerase. Several clinical studies have indicated response rates of 70–90% among patients with AIDS who are given ganciclovir for the treatment of CMV retinitis or colitis. In severe infections (e.g., CMV pneumonia in bone marrow transplant recipients), ganciclovir is often combined with CMV immune globulin. Prophylactic or suppressive (preemptive) ganciclovir may be useful in high-risk bone marrow or organ transplant recipients (e.g., those who are CMV-seropositive before transplantation or who are CMV culture–positive afterward). In many patients with AIDS, persistently low CD4+ T cell counts, and CMV disease, clinical and virologic relapses occur promptly if treatment with ganciclovir is discontinued. Therefore, prolonged maintenance regimens are recommended for such patients. Resistance to ganciclovir is common among patients treated for >3 months and is usually related to mutations in the CMV UL97 gene.

Valganciclovir is an orally bioavailable prodrug that is rapidly metabolized to ganciclovir in intestinal tissues and the liver. Approximately 60–70% of an oral dose of valganciclovir is absorbed. An oral valganciclovir dose of 900 mg results in ganciclovir blood levels similar to those obtained with an IV ganciclovir dose of 5 mg/kg. Oral valganciclovir appears to be as effective as IV ganciclovir for both CMV induction and maintenance regimens. Furthermore, the adverse-event profiles and rates of resistance development for the two drugs are similar.

Ganciclovir or valganciclovir therapy for CMV retinitis consists of a 14- to 21-day induction course (5 mg/kg IV twice daily for ganciclovir or 900 mg twice daily for valganciclovir) followed by prolonged maintenance therapy. For parenteral maintenance, the ganciclovir dose is 5 mg/kg daily or 6 mg/kg 5 days per week; for oral maintenance, 900 mg of valganciclovir once daily is recommended. Peripheral-blood neutropenia develops in 16–29% of treated patients but may be ameliorated by granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor. Discontinuation of maintenance therapy should be considered in patients with AIDS who, while receiving antiretroviral

therapy, have a sustained (3- to 6-month) increase in CD4+ T cell counts to >100/μL.

For treatment of CMV retinitis, ganciclovir may also be administered via a slow-release pellet sutured into the eye. Although this intraocular device provides good local protection, contralateral eye disease and disseminated disease are not affected, and early retinal detachment is possible. A combination of intraocular and systemic therapy may be better than the intraocular implant alone.

Foscarnet (sodium phosphonoformate) inhibits CMV DNA polymerase. Because this agent does not require phosphorylation to be active, it is also effective against most ganciclovir-resistant isolates. Foscarnet is less well tolerated than ganciclovir and causes considerable toxicity, including renal dysfunction, hypomagnesemia, hypokalemia, hypocalcemia, genital ulcers, dysuria, nausea, and paresthesia. Moreover, foscarnet administration requires the use of an infusion pump and close clinical monitoring. With aggressive hydration and dose adjustments for renal dysfunction, the toxicity of foscarnet can be reduced. The use of foscarnet should be avoided when a saline load cannot be tolerated (e.g., in cardiomyopathy). The approved induction regimen is 60 mg/kg every 8 h for 2 weeks, although 90 mg/kg every 12 h is equally effective and no more toxic. Maintenance infusions should deliver 90–120 mg/kg once daily. No oral preparation is available. Foscarnet-resistant virus may emerge during extended therapy.

Cidofovir is a nucleotide analogue with a long intracellular half-life that allows intermittent IV administration. Induction regimens of 5 mg/kg weekly for 2 weeks are followed by maintenance regimens of 3–5 mg/kg every 2 weeks. Cidofovir can cause severe nephrotoxicity through dose-dependent proximal tubular cell injury; however, this adverse effect can be tempered somewhat by saline hydration and probenecid.

It is not clear whether universal prophylaxis or preemptive therapy is the preferable approach in CMV-seropositive immunocompromised hosts. Both ganciclovir and valganciclovir have been used successfully for prophylaxis and preemptive therapy in transplant recipients. For patients with advanced HIV infection (CD4+ T cell counts of <50/μL), some authorities have advocated prophylaxis with oral ganciclovir or valganciclovir. However, side effects, lack of proven benefit, possible induction of viral resistance, and high cost have precluded the wide acceptance of this practice. Preemptive ganciclovir or valganciclovir therapy based on detection of CMV viremia by either antigenemia or PCR techniques is under study.

HUMAN HERPESVIRUS TYPES 6, 7, AND 8

Human herpesvirus (HHV) type 6 was first isolated in 1986 from peripheral-blood leukocytes of six persons with various lymphoproliferative disorders. The virus has a worldwide distribution, and two genetically distinct variants (HHV-6A and HHV-6B) are now recognized. HHV-6 appears to be transmitted by saliva and possibly by genital secretions.

Infection with HHV-6 frequently occurs during infancy as maternal antibody wanes. The peak age of acquisition is 9–21 months; by 24 months, seropositivity rates approach 80%. Older siblings appear to serve as a source of transmission. Congenital infection may also occur, and ~1% of newborns are infected with HHV-6; placental infection with HHV-6 has been described. Most postnatally infected children develop symptoms (fever, fussiness, and diarrhea). A minority develop exanthem subitum (roseola infantum; see Fig. 11-5), a common illness characterized by fever with subsequent rash. In addition, ~10–20% of febrile seizures without rash during infancy are caused by HHV-6. After initial infection, HHV-6 persists in peripheral-blood mononuclear cells as well as in the central nervous system, salivary glands, and female genital tract.

In older age groups, HHV-6 has been associated with mononucleosis syndromes; focal encephalitis; and (in immunocompromised hosts) pneumonitis, syncytial giant-cell hepatitis, and disseminated disease. In transplant recipients, HHV-6 infection may be associated with similar syndromes and with graft dysfunction. Acute HHV-6-associated limbic encephalitis has been reported in transplant recipients and is characterized by memory loss, confusion, seizures, hyponatremia, and abnormal electroencephalographic and magnetic resonance imaging results. High plasma loads of HHV-6 DNA in stem cell transplant recipients are associated with allelic-mismatched donors, use of glucocorticoids, delayed monocyte and platelet engraftment, development of limbic encephalitis, and increased all-cause mortality rates. Like many other viruses, HHV-6 has been implicated in the pathogenesis of multiple sclerosis, although further study is needed to distinguish between association and etiology.

HHV-7 was isolated in 1990 from T lymphocytes from the peripheral blood of a healthy 26-year-old man. The virus is frequently acquired during childhood, albeit at a later age than HHV-6. HHV-7 is commonly present in saliva, which is presumed to be the principal source of infection; breast milk can also carry the virus. Viremia can be associated with either primary or reactivation infection. The most common clinical manifestations of childhood HHV-7 infections are fever and seizures. Some children present with respiratory or gastrointestinal signs and symptoms. An association has been made between HHV-7 and pityriasis rosea, but evidence is insufficient to indicate a causal relationship.

HHV-6, HHV-7, and CMV infections may cluster in transplant recipients, making it difficult to sort out the roles of the various agents in individual clinical syndromes. HHV-6 and HHV-7 appear to be susceptible to ganciclovir and foscarnet, although definitive evidence of clinical response is lacking.

Unique herpesvirus-like DNA sequences were reported during 1994 and 1995 in tissues derived from Kaposi's sarcoma (KS) and body cavity–based lymphoma occurring in patients with AIDS. The virus from which

these sequences were derived is designated HHV-8 or Kaposi's sarcoma–associated herpesvirus (KSHV). HHV-8, which infects B lymphocytes, macrophages, and both endothelial and epithelial cells, appears to be causally related not only to KS but also to a subgroup of AIDS-related B cell body cavity–based lymphomas (primary effusion lymphomas) and to multicentric Castleman's disease, a lymphoproliferative disorder of B cells. The association of HHV-8 with several other diseases has been reported but not confirmed.

Unlike other herpesvirus infections, HHV-8 infection is much more common in some geographic areas (e.g., central and southern Africa) than in others (North America, Asia, northern Europe). In high-prevalence areas, infection occurs in childhood, seropositivity is associated with having a seropositive mother or (to a lesser extent) older sibling, and HHV-8 may be transmitted in saliva. In low-prevalence areas, infections typically occur in adults, probably with sexual transmission. Concurrent epidemics of HIV-1 and HHV-8 infections among certain populations (e.g., men who have sex with men) in the late 1970s and early 1980s appear to have resulted in the frequent association of AIDS and KS. Transmission of HHV-8 may also be associated with organ transplantation, injection drug use, and blood transfusion; however, transmission via blood transfusion in the United States appears to be rare or nonexistent.

Primary HHV-8 infection in immunocompetent children may manifest as fever and maculopapular rash. Among individuals with intact immunity, chronic asymptomatic infection is the rule, and neoplastic disorders generally develop only after subsequent immunocompromise. Immunocompromised persons with primary infection may present with fever, splenomegaly, lymphoid hyperplasia, pancytopenia, or rapid-onset KS. Quantitative analysis of HHV-8 DNA suggests a predominance of latently infected cells in KS lesions and frequent lytic replication in multicentric Castleman's disease.

Effective antiretroviral therapy for HIV-infected individuals has led to a marked reduction in rates of KS among persons dually infected with HHV-8 and HIV in resource-rich areas. HHV-8 itself is susceptible in vitro to ganciclovir, foscarnet, and cidofovir. A small randomized, double-blind, placebo-controlled, crossover trial suggested that oral valganciclovir administered once daily reduced HHV-8 replication. However, clinical benefits of valganciclovir or other drugs in HHV-8 infection have not yet been demonstrated.

CHAPTER 88

MOLLUSCUM CONTAGIOSUM, MONKEYPOX, AND OTHER POXVIRUS INFECTIONS

Fred Wang

The poxvirus family includes a large number of related DNA viruses that infect various vertebrate hosts. The poxviruses responsible for infections in humans, along with the main manifestations of these infections, are listed in **Table 88-1**. Infections with orthopoxviruses—e.g., smallpox (variola major) virus (Chap. 7) or the zoonotic monkeypox virus—can result in systemic, potentially lethal human disease. Other poxvirus infections cause primarily localized skin disease in humans.

MOLLUSCUM CONTAGIOSUM

Molluscum contagiosum virus is an obligate human pathogen that causes distinctive proliferative skin lesions. These lesions measure 2–5 mm in diameter and are pearly, flesh-colored, and umbilicated, with a characteristic dimple at the center **(Fig. 88-1)**. A relative lack of inflammation and necrosis distinguishes these proliferative lesions from other poxvirus lesions. Lesions may be found—singly or in clusters—anywhere

TABLE 88-1

POXVIRUSES AND HUMAN INFECTIONS

GENUS	SPECIES	GEOGRAPHIC LOCATION	HOST RESERVOIR	HUMAN DISEASE
Orthopoxvirus	Variola[a]	Extinct	Humans	Smallpox, systemic
	Monkeypox	Africa	Rodents	Smallpox-like, systemic
	Cowpox	Europe	Rodents	Local pox lesion, occasionally systemic
	Buffalopox	Indian subcontinent	Water buffalo	Local pox lesion, mild illness
	Cantagalo and Araçatuba	South America	Cattle	Local pox lesion, mild illness
	Vaccinia	—	—	Smallpox vaccine
Molluscipoxvirus	Molluscum contagiosum	Worldwide	Humans	Multiple cutaneous lesions (molluscum contagiosum)
Parapoxvirus	Orf	Worldwide	Sheep, goats	Local pox lesions (contagious pustular dermatitis)
	Pseudocowpox (paravaccinia)	Worldwide	Cattle	Local pox lesions (milker's nodule)
	Bovine papular stomatitis	Worldwide	Cattle	Local pox lesions
	Deerpox	Deer herds	Deer	Local pox lesions
	Sealpox	Seal colonies	Seals	Local pox lesions
Yatapoxvirus	Tanapox	Africa	Monkeys	Local pox lesions

[a]See Chap. 7.

on the body except on the palms and soles and may be associated with an eczematous rash.

Molluscum contagiosum is highly prevalent in children and is the most common human disease resulting from poxvirus infection. Swimming pools are a common vector for transmission. Atopy and compromise of skin integrity increase the risk of infection. Genital lesions are more frequent in adults, to whom the virus may be transmitted by sexual contact. The incubation period ranges from2 weeks to 6 months, with an average of 2–7 weeks. In most cases, the disease is self-limited and regresses spontaneously after 3–4 months in immunocompetent hosts. There are no systemic complications, but skin lesions may persist for 3–5 years. Molluscum contagiosum can be associated with immunosuppression and is frequently seen among HIV-infected patients (Chap. 93). The disease can be more generalized, severe, and persistent in AIDS patients than in other groups. Moreover, molluscum contagiosum can be exacerbated in the immune reconstitution inflammatory syndrome (IRIS) associated with the initiation of antiretroviral therapy.

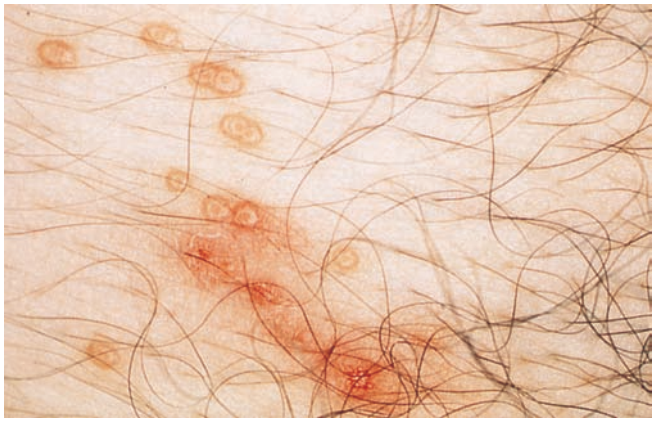


FIGURE 88-1

Molluscum contagiosum is a cutaneous poxvirus infection characterized by multiple umbilicated flesh-colored or hypopigmented papules.

The diagnosis of molluscum contagiosum is typically based on its clinical presentation and can be confirmed by histologic demonstration of the cytoplasmic eosinophilic inclusions (*molluscum bodies*) that are characteristic of poxvirus replication. Molluscum contagiosum virus cannot be propagated in vitro, but electron microscopy and molecular studies can be used for its identification.

There is no specific systemic treatment for molluscum contagiosum, but a variety of techniques for physical ablation have been used. Cidofovir displays in vitro activity against many poxviruses, and case reports suggest that parenteral or topical cidofovir may have some efficacy in the treatment of recalcitrant molluscum contagiosum in immunosuppressed hosts.

MONKEYPOX

Although monkeypox virus was named after the animal from which it was originally isolated, rodents are the primary viral reservoir.

Human infections with monkeypox virus typically occur in Africa when humans come into direct contact with infected animals. Human-to-human propagation of monkeypox infection is rare. Human disease is characterized by a systemic illness and vesicular rash similar to those of variola. The clinical presentation of monkeypox can be confused with that of the more common varicella-zoster virus infection (Chap. 85). Compared with the lesions of this herpesvirus infection, monkeypox lesions tend to be more uniform (i.e., in the same stage of development), diffuse, and peripheral in distribution. Lymphadenopathy is a prominent feature of monkeypox infection.

The first outbreak of human monkeypox infection in the Western Hemisphere occurred during 2003, when more than 70 cases were reported in the midwestern United States. The outbreak was linked to contact with pet prairie dogs that had become infected while being housed with rodents imported from Ghana. Patients presented most frequently with fever, rash, and lymphadenopathy ~12 days after exposure. Nine patients were hospitalized, but there were no deaths. Smallpox vaccination can provide cross-reactive immunity to monkeypox infection; studies of people exposed in the outbreak detected subclinical infection in a few vaccinated individuals—an observation suggesting the possibility of long-term vaccine protection. The risk of human disease from animal orthopoxvirus infections may increase as smallpox immunity wanes in the general population and the popularity of exotic animals as household pets grows.

OTHER ZOONOTIC POXVIRUS INFECTIONS

Cowpox and buffalopox are rare zoonotic infections characterized by cutaneous poxlike lesions and mild systemic illness. Outbreaks of similar poxlike lesions among cattle and farm workers in Brazil have been due to Cantagalo and Araçatuba viruses, which are virtually identical to vaccinia virus and may have become established in cattle during smallpox vaccination programs.

Parapoxviruses are widely scattered among animal species, but only a few are known to cause human disease via direct contact with infected animals. Parapoxviruses are antigenically distinct from orthopoxviruses and share no cross-immunity. *Tanapox* virus belongs to a separate, antigenically distinct genus and usually causes a single nodular lesion on the exposed area after contact with infected monkeys.

CHAPTER 89

PARVOVIRUS INFECTIONS

Kevin E. Brown

Parvoviruses, members of the family Parvoviridae, are small (diameter, ~22 nm), nonenveloped, icosahedral-shaped viruses with a linear single-strand DNA genome of ~5000 nucleotides. These viruses are dependent on either rapidly dividing host cells or helper viruses for replication. At least four groups of parvoviruses infect humans: parvovirus B19 (B19V), dependoviruses (adeno-associated viruses; AAVs), PARV4/5 virus, and human bocaviruses (HBoVs). Human dependoviruses are nonpathogenic and will not be considered further in this chapter.

PARVOVIRUS B19

DEFINITION

B19V is the type member of the genus *Erythrovirus*. On the basis of viral sequence, B19V is divided into three genotypes (designated 1, 2, and 3), but only a single B19V antigenic type has been described. Genotype 1 is predominant in most parts of the world; genotype 2 is rarely associated with active infection; and genotype 3 appears to predominate in parts of western Africa.

EPIDEMIOLOGY

B19V exclusively infects humans, and infection is endemic in virtually all parts of the world. Transmission occurs predominantly via the respiratory route and is followed by the onset of rash and arthralgia. By the age of 15 years, ~ 50% of children have detectable IgG; this figure rises to >90% among the elderly. In pregnant women, the estimated annual seroconversion rate is ~1%. Within households, secondary infection rates approach 50%.

Detection of high-titer B19V in blood is not unusual (see "Pathogenesis," next). Transmission can occur as a result of transfusion, most commonly of pooled components. To reduce the risk of transmission, plasma pools are screened by nucleic acid amplification technology, and high-titer pools are discarded. B19V is resistant to both heat and solvent-detergent inactivation.

PATHOGENESIS

B19V replicates primarily in erythroid progenitors. This specificity is due in part to the limited tissue distribution of the primary B19V receptor, blood group P antigen (globoside). Infection leads to high-titer viremia, with $>10^{12}$ virus particles (or IU)/mL detectable in the blood at the apex **(Fig. 89-1)**, and virus-induced cytotoxicity results in cessation of red cell production. In immunocompetent individuals, viremia and arrest of erythropoiesis are transient and resolve as the IgM and IgG antibody response is mounted. In individuals with normal erythropoiesis, there is only a minimal drop in hemoglobin levels; however, in those with increased erythropoiesis (especially with hemolytic anemia), this cessation of red cell production can induce a transient crisis with severe anemia (Fig. 89-1). Similarly, if an individual (or, after maternal infection, a fetus) does not mount a neutralizing antibody response and halt the lytic infection, erythroid production is compromised and chronic anemia develops (Fig. 89-1).

The immune-mediated phase of illness, which begins 2–3 weeks after infection as the IgM response peaks, manifests as the rash of fifth disease together with arthralgia and/or frank arthritis. Low-level B19V DNA can be detected by polymerase chain reaction (PCR) in blood and tissues for months to years after acute infection. The B19V receptor is found in a variety of other cells and tissues, including megakaryocytes, endothelial cells, placenta, myocardium, and liver. Infection of these tissues by B19V

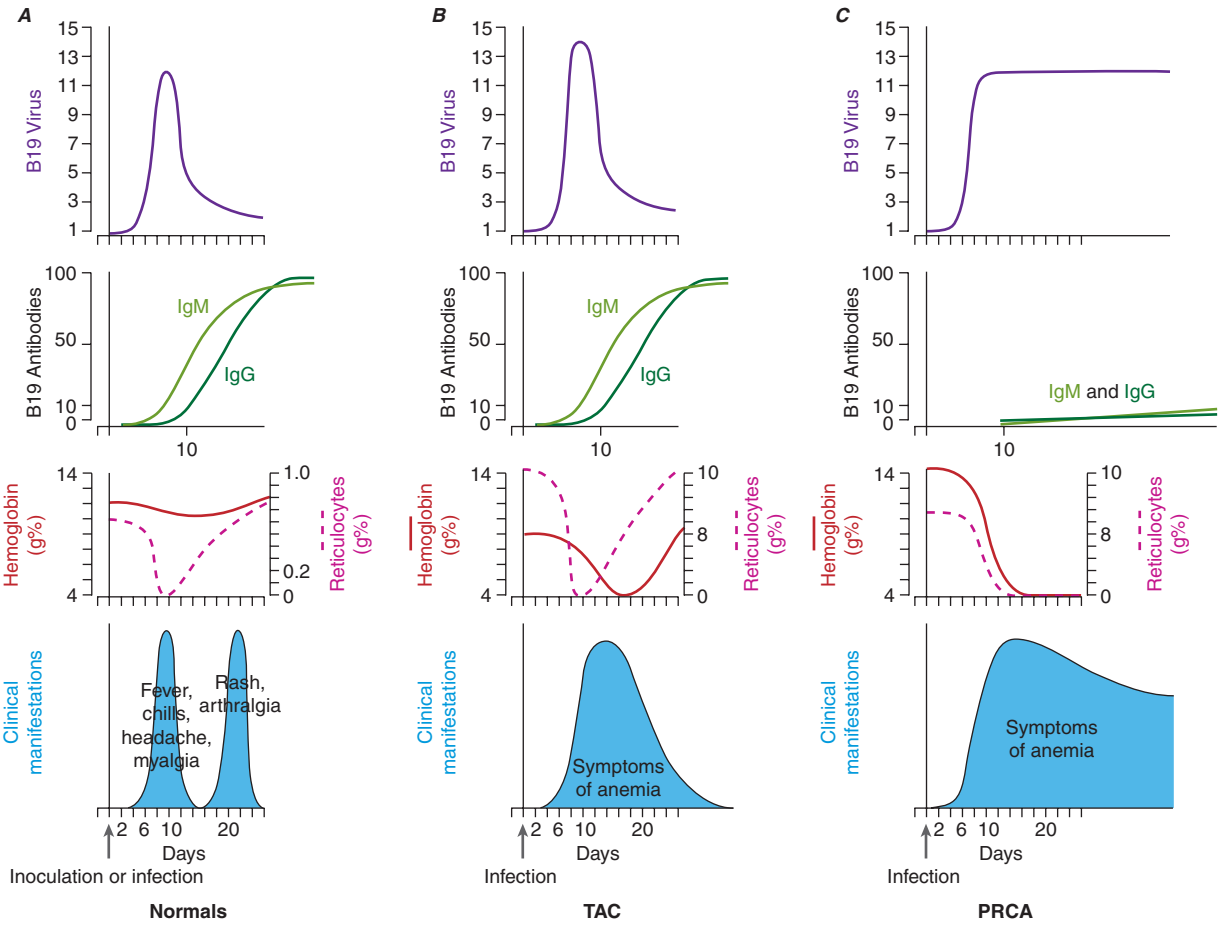


FIGURE 89-1

Schematic of the time course of parvovirus B19V infection in (***A***) normals (erythema infectiosum), (***B***) transient aplastic crisis (TAC), and (***C***) chronic anemia/pure red-cell aplasia (PRCA). (*Reprinted with permission from NS Young, KE Brown: N Engl J Med 350:586, 2004. © 2004 Massachusetts Medical Society. All rights reserved.*)

may be responsible for some of the more unusual presentations of the infection. Rare individuals who lack P antigen are naturally resistant to B19V infection.

CLINICAL MANIFESTATIONS

Erythema infectiosum

Most B19V infections are asymptomatic or are associated with only a mild nonspecific illness. The main manifestation of symptomatic B19V infection is erythema infectiosum, also known as *fifth disease* (Fig. 11-1) or *slapped-cheek disease* **(Fig. 89-2)**. Infection begins with a minor febrile prodrome ~7–10 days after exposure, and the classic facial rash develops several days later; after 2–3 days, the erythematous macular rash may spread to the extremities in a lacy reticular pattern. However, its intensity and distribution vary, and B19V-induced rash is difficult to distinguish from other viral exanthems. Adults typically do not exhibit the "slapped-cheek" phenomenon but present with arthralgia, with or without the macular rash.

Polyarthropathy syndrome

Although uncommon among children, arthropathy occurs in ~50% of adults and is more common among women than among men. The distribution of the affected joints is often symmetrical, with arthralgia affecting the small joints of the hands and occasionally the ankles, knees, and wrists. Resolution usually occurs within a few weeks, but recurring symptoms can continue for months. The illness may mimic rheumatoid arthritis, and rheumatoid factor can often be detected in serum. B19V infection may trigger rheumatoid disease in some patients and has been associated with juvenile idiopathic arthritis.

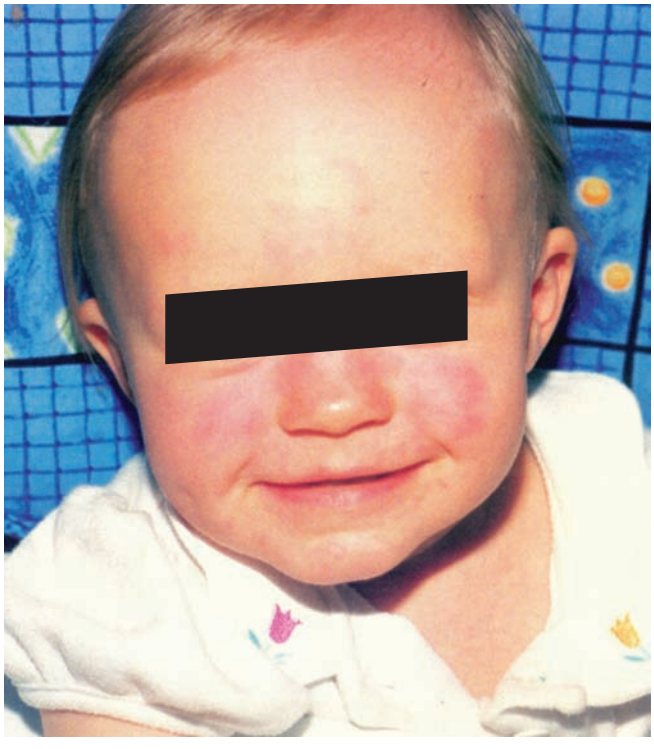


FIGURE 89-2
Young child with erythema infectiosum, or fifth disease, showing typical "slapped-cheek" appearance.

Transient aplastic crisis

Asymptomatic transient reticulocytopenia occurs in most individuals with B19V infection. However, in patients who depend on continual rapid production of red cells, infection can cause transient aplastic crisis (TAC). Affected individuals include those with hemolytic disorders, hemoglobinopathies, red cell enzymopathies, and autoimmune hemolytic anemias. Patients present with symptoms of severe anemia (sometimes life-threatening) and a low reticulocyte count, and bone marrow examination reveals an absence of erythroid precursors and characteristic giant pronormoblasts. As its name indicates, the illness is transient, and anemia resolves with the cessation of cytopathic infection in the erythroid progenitors.

Pure red-cell aplasia/chronic anemia

Chronic B19V infection has been reported in a wide range of immunosuppressed patients, including those with congenital immunodeficiency, AIDS (Chap. 93), lymphoproliferative disorders (especially acute lymphocytic leukemia), and transplantation (Chap. 13). Patients have persistent anemia with reticulocytopenia, absent or low levels of B19V IgG, high titers of B19V DNA in serum, and—in many cases—scattered giant pronormoblasts in bone marrow. Rarely, nonerythroid hematologic lineages are also affected. Transient neutropenia, lymphopenia, and thrombocytopenia (including idiopathic thrombocytopenic purpura) have been observed. B19V occasionally causes a hemophagocytic syndrome.

A recent study in Papua New Guinea, where malaria is endemic, suggested that B19V infection plays a major role in the development of severe anemia. Further studies must determine whether B19V infection contributes to severe anemia in other malarial regions.

Hydrops fetalis

B19V infection during pregnancy can lead to hydrops fetalis and/or fetal loss. The risk of transplacental fetal infection is ~30%, and the risk of fetal loss (predominantly early in the second trimester) is ~9%. The risk of congenital infection is <1%. Although B19V does not appear to be teratogenic, anecdotal cases of eye damage and central nervous system (CNS) abnormalities have been reported. Cases of congenital anemia have also been described. B19V probably causes 10–20% of all cases of nonimmune hydrops.

Unusual manifestations

B19V infection may rarely cause hepatitis, vasculitis, myocarditis, glomerulosclerosis, or meningitis. A variety of other cardiac manifestations, CNS diseases, and

TABLE 89-1

DISEASES ASSOCIATED WITH HUMAN PARVOVIRUS B19 INFECTION AND METHODS OF DIAGNOSIS

DISEASE	HOST(S)	IgM	IgG	PCR	QUANTITATIVE PCR
Fifth disease	Healthy children	Positive	Positive	Positive	$>10^3$ IU/mL
Polyarthropathy syndrome	Healthy adults (more often women)	Positive within 3 months of onset	Positive	Positive	$>10^3$ IU/mL
Transient aplastic crisis	Patients with increased erythropoiesis	Negative/positive	Negative/positive	Positive	Often $>10^{12}$ IU/mL, but rapidly decreases
Persistent anemia/pure red-cell aplasia	Immunodeficient or immunocompetent patients	Negative/weakly positive	Negative/weakly positive	Positive	Often $>10^{12}$ IU/mL, but should be $>10^6$ in the absence of treatment
Hydrops fetalis/congenital anemia	Fetus (<20 weeks)	Negative/positive	Positive	Positive amniotic fluid or tissue	n/a

Abbreviations: IU, international units (1 IU equals ~1 genome); n/a, not applicable; PCR, polymerase chain reaction.

autoimmune infections have also been reported. However, B19V DNA can be detected by PCR for years in many tissues; this finding is of no known clinical significance, but its interpretation may cause confusion regarding B19V disease association.

DIAGNOSIS

Diagnosis of B19V infection in immunocompetent individuals is generally based on detection of B19V IgM antibodies (Table 89-1). IgM can be detected at the time of rash in erythema infectiosum and by the third day of TAC in patients with hematologic disorders; these antibodies remain detectable for ~3 months. B19V IgG is detectable by the seventh day of illness and persists throughout life. Detection of B19V DNA should be used for the diagnosis of early TAC or chronic anemia. Although B19V levels fall rapidly with the development of the immune response, DNA can be detectable by PCR for months or even years after infection, even in healthy individuals; therefore, quantitative PCR should be used. In acute infection at the height of viremia, $>10^{12}$ B19V DNA IU/mL of serum can be detected; however, titers fall rapidly within 2 days. Patients with aplastic crisis or B19V-induced chronic anemia generally have $>10^5$ B19V DNA IU/mL.

TREATMENT Parvovirus B19 Infection

No antiviral drug effective against B19V is available, and treatment of B19V infection often targets symptoms only. TAC precipitated by B19V infection frequently necessitates symptom-based treatment with blood transfusions. In patients receiving chemotherapy, temporary cessation of treatment may result in an immune response and resolution. If this approach is unsuccessful or not applicable, commercial immune globulin (IVIg; Gammagard, Sandoglobulin) from healthy blood donors can cure or ameliorate persistent B19V infection in immunosuppressed patients. Generally, the dose used is 400 mg/kg daily for 5–10 days. Like patients with TAC, immunosuppressed patients with persistent B19V infection should be considered infectious. Administration of IVIg is not beneficial for erythema infectiosum or B19V-associated polyarthropathy. Intrauterine blood transfusion can prevent fetal loss in some cases of fetal hydrops.

PREVENTION

No vaccine has been approved for the prevention of B19V infection. A vaccine based on virus-like particles expressed in insect cells is under development; the results of phase 1 trials were promising.

PARV4/5

DEFINITION

The PARV4 viral sequence was initially detected in a patient with an acute viral syndrome. Similar sequences, including the related PARV5 sequence, have been detected in pooled plasma collections. The DNA sequence of PARV4/5 is distinctly different from that of all other parvoviruses, and this virus cannot be classified within the current genera of Parvoviridae.

EPIDEMIOLOGY

Parv4 DNA is commonly found in plasma pools but at lower titers than those of B19V found before plasma pool screening. The higher levels of Parv4 DNA and IgG antibody in tissues (bone marrow and lymphoid tissue)

and sera from IV drug users than in the corresponding specimens from control patients suggest that the virus is transmitted predominantly by parenteral means.

CLINICAL MANIFESTATIONS

Parv4/5 infection has not been associated with any clinical disease to date.

HUMAN BOCAVIRUSES

DEFINITION

Animal bocaviruses are associated with mild respiratory symptoms and enteritis in young animals. HBoV was originally identified in the respiratory tract of young children with lower respiratory tract infections. More recently, HBoV and the related viruses HBoV2 and HBoV3 have all been identified in human fecal samples.

EPIDEMIOLOGY

Seroepidemiologic studies with HBoV virus-like particles suggest that human bocavirus infection is common. Worldwide, most individuals are infected before the age of 5 years.

CLINICAL MANIFESTATIONS

Although HBoV DNA is commonly found in respiratory secretions from children with acute respiratory infection, the role of this finding in pathogenesis is unknown, and HBoV sequences are often found in the presence of other pathogens. However, increasing evidence indicates that the virus is associated with wheezing in young children. The role of human bocaviruses in childhood gastroenteritis remains to be established.

CHAPTER 90

HUMAN PAPILLOMAVIRUS INFECTIONS

Richard C. Reichman

DEFINITION

Human papillomaviruses (HPVs) selectively infect the epithelium of skin and mucous membranes. These infections may be asymptomatic, produce warts, or be associated with a variety of both benign and malignant neoplasias.

ETIOLOGIC AGENT

Papillomaviruses constitute the *Papillomavirus* genus of the family Papillomaviridae. They are nonenveloped, measure 50–55 nm in diameter, have icosahedral capsids composed of 72 capsomeres, and contain a double-strand circular DNA genome of ~7900 base pairs. The genomic organization of all papillomaviruses is similar and consists of an early (E) region, a late (L) region, and a noncoding upstream regulatory region (URR). Oncogenic HPV types can immortalize human keratinocytes, and this activity has been mapped to products of early genes E6 and E7. E6 protein facilitates the degradation of the p53 tumor-suppressor protein, and E7 protein binds the retinoblastoma gene product and related proteins. The E1 and E2 proteins modulate viral DNA replication and regulate gene expression. The L1 gene codes for the major capsid protein, which makes up 80% of the virion mass. L2 codes for a minor capsid protein. Type-specific conformational antigenic determinants are located on the virion surface. Papillomavirus types are distinguished from one another by the degree of nucleic acid sequence homology. Distinct types share <90% of their DNA sequences in L1. More than 100 HPV types are recognized, and individual types are associated with specific clinical manifestations. For example, HPV-1 causes plantar warts, HPV-6 causes anogenital warts, and HPV-16 infection can produce cervical dysplasia and invasive cervical cancer. HPVs are species-specific and have not been propagated in routine tissue culture or in common experimental animals. However, some HPV types have been propagated in organotypic culture systems, and some have been produced in human tissues implanted in immunodeficient mice.

EPIDEMIOLOGY

There are few good studies of the incidence or prevalence of human warts in well-defined populations. Common warts (*verruca vulgaris*) are found in as many as 25% of some groups and are most prevalent among young children. Plantar warts (*verruca plantaris*) are also widely prevalent; they occur most often among adolescents and young adults. Anogenital warts (*condyloma acuminatum*) represent one of the most common sexually transmitted diseases in the United States. HPV infection of the uterine cervix produces the squamous cell abnormalities most frequently detected on Papanicolaou smears.

Most anogenital HPV infections are transmitted through direct contact with infectious lesions. However, lesion characteristics that are associated with transmission, including appearance, have not been defined, and individuals without obvious disease may transmit infection. Close personal contact is also assumed to play a role in the transmission of most cutaneous warts; the importance of fomites in this setting is not clear. Minor trauma at the site of inoculation may facilitate transmission. Recurrent respiratory papillomatosis in young children is an uncommon disease that is acquired from the infected maternal genital tract. In adults, orogenital sexual contact may transmit the disease.

A large body of epidemiologic and biologic data has established that some HPV infections cause cervical cancer. For example, >95% of cervical cancers contain HPV DNA of oncogenic (high-risk) types, such as 16, 18, 31, 33, and 45. HPV DNA is also present in the precursor lesions of cervical cancer (cervical intraepithelial neoplasias). Such lesions containing DNA of oncogenic types are more likely to progress than those associated with low-risk HPV types, such as 6 and 11. HPV DNA is transcribed in tumor tissues, and many epidemiologic studies have confirmed a strong relationship between HPV infection (with or without cofactors) and the development of cervical cancer. Definitive proof of the causative role of high-risk HPV types in the pathogenesis of high-grade cervical dysplasia has been provided by the results of recently conducted trials of HPV vaccines. However, it is important to realize that most cervical HPV infections, including those caused by high-risk types, are self-limited. Infection with high-risk HPV types has also been associated with squamous cell carcinomas and dysplasias of the penis, anus, vagina, and vulva. HPV infection may play a role in squamous cell carcinomas of the head and neck. In patients with *epidermodysplasia verruciformis* (see "Clinical Manifestations," next), squamous cell cancers develop frequently at sites infected with specific HPV types, including 5 and 8.

CLINICAL MANIFESTATIONS

The clinical manifestations of HPV infection depend on the location of lesions and the type of virus. Common warts usually occur on the hands as flesh-colored to brown, exophytic, and hyperkeratotic papules. Plantar warts may be quite painful; they can be differentiated from calluses by paring of the surface to reveal thrombosed capillaries. Flat warts (*verruca plana*) are most common among children and occur on the face, neck, chest, and flexor surfaces of the forearms and legs.

Anogenital warts develop on the skin and mucosal surfaces of external genitalia and perianal areas **(Fig. 90-1)**. Among circumcised men, warts are most commonly found on the penile shaft. Lesions frequently occur at the urethral meatus and may extend proximally. Receptive anal intercourse predisposes both men and women to the development of perianal warts, but such lesions occasionally develop without such a history. In women, warts appear first at the posterior introitus and on the adjacent labia. They then spread to other parts of the vulva and commonly involve the vagina and cervix. In both sexes, external warts suggest the presence of internal lesions; however, internal lesions may be present without external warts, particularly in women. The differential diagnosis of anogenital warts includes condylomata lata of secondary syphilis, molluscum contagiosum, hirsutoid papillomatosis (pearly penile papules), fibroepitheliomas, and a variety of benign and malignant mucocutaneous neoplasms. Respiratory papillomatosis in young children, which may be life-threatening, presents as hoarseness, stridor, or respiratory distress. The disease in adults is usually milder.

Immunosuppressed patients, particularly those undergoing organ transplantation, often develop pityriasis versicolor–like lesions, from which DNA of several HPV types has been extracted. Occasionally, such lesions appear to undergo malignant transformation. Patients infected with HIV are often infected with uncommon HPV types, frequently have severe clinical manifestations of HPV infection, and are at high risk for cervical and anal dysplasia as well as for invasive cancer.

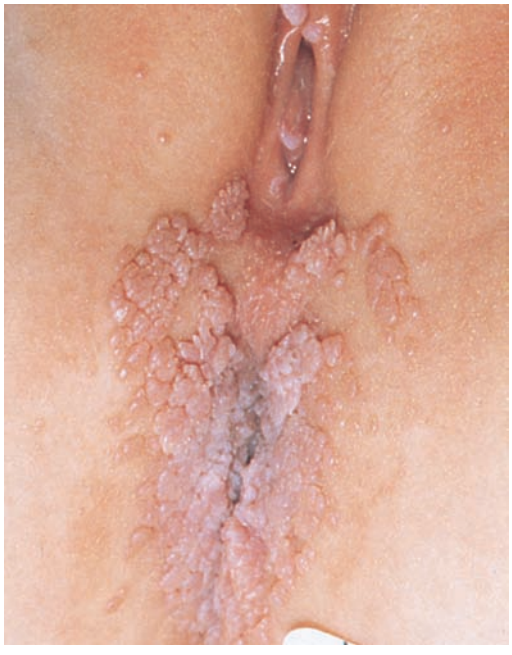


FIGURE 90-1
Anogenital warts are lesions produced by human papillomavirus and in this patient are seen as multiple verrucous papules coalescing into plaques.

HPV disease in patients with HIV infection may be associated with multiple HPV types, is difficult to treat, and often recurs (Chap. 93).

Epidermodysplasia verruciformis is a rare autosomal recessive disease characterized by an inability to control HPV infection. Patients are often infected with unique HPV types (i.e., types that affect only this group) and frequently develop cutaneous squamous cell malignancies, particularly in sun-exposed areas. The lesions resemble flat warts or macules similar to those of pityriasis versicolor.

The complications of warts include itching and occasionally bleeding. In rare cases, warts become secondarily infected with bacteria or fungi. Large masses of warts may cause mechanical problems, such as obstruction of the birth canal or the urinary tract. Dysplasias of the uterine cervix are generally asymptomatic until frank carcinoma develops. Patients with anogenital HPV disease may develop serious psychological symptoms due to anxiety and depression over this condition.

PATHOGENESIS

The incubation period of HPV disease is usually 3–4 months (range, 1 month to 2 years). All types of squamous epithelium can be infected by HPV, and the gross and histologic appearances of individual lesions vary with the site of infection and the type of virus. The replication of HPV begins with infection of basal cells. As cellular differentiation proceeds, HPV DNA replicates and is transcribed. Ultimately, virions are assembled in the nucleus and released when keratinocytes are shed. This process is associated with proliferation of all epidermal layers except the basal layer and produces acanthosis, parakeratosis, and hyperkeratosis. Koilocytes—large round cells with pyknotic nuclei—appear in the granular layer. Histologically normal epithelium may contain HPV DNA, and residual DNA after treatment can be associated with recurrent disease.

Episomal HPV DNA is present in the nuclei of infected cells in benign lesions caused by HPV. However, in severe dysplasias and cancers, HPV DNA is generally integrated, with disruption of the E1/E2 open reading frames. This disruption leads to upregulation of E6 and E7 and subsequent interference with cellular tumor-suppressor proteins. Expression of E6 and E7 proteins of oncogenic HPV types is necessary for the development and maintenance of the transformed state in both cervical cancers and cell lines derived from these tumors.

Host defense responses to HPV infection remain incompletely understood. However, several studies of recently developed HPV vaccines have demonstrated that production of high titers of type-specific neutralizing antibodies by vaccinated individuals is associated with type-specific protection from HPV infection and disease. Because patients with defects in cell-mediated immune responses (including transplant recipients and patients with HIV infection) frequently develop severe HPV disease, such responses are probably important for the control of established virus replication and disease. Histologic studies demonstrating an epidermal lymphomonocytic infiltrate in resolving warts suggest that local immunity may be of particular importance in the resolution of disease. HPV infection also elicits a detectable serologic response in many patients. Using HPV virus-like particles (VLPs) as antigens, type-specific antibodies can be found in sera of about two-thirds of patients with anogenital infection. Antibodies to E-region proteins, most notably E7, have been detected among patients with cervical carcinoma.

DIAGNOSIS

Most warts that are visible to the naked eye can be diagnosed correctly by history and physical examination alone. The use of a colposcope is invaluable in assessing vaginal and cervical lesions and is helpful in the diagnosis of oral and cutaneous HPV disease as well. Application of 3–5% solutions of acetic acid may aid in the visualization of lesions, although the sensitivity and specificity of this procedure are unknown. Papanicolaou smears prepared from cervical or anal scrapings often show cytologic evidence of HPV infection. Persistent or atypical lesions should be biopsied and examined by routine histologic methods. The most sensitive and specific methods of virologic diagnosis use techniques such as the polymerase chain reaction or the hybrid capture assay to detect HPV nucleic acids and to identify specific virus types. Such tests may be useful in the diagnosis and management of cervical HPV disease, although their utility may vary according to the prevalence of disease and the availability of traditional cytologic and histologic testing. Serologic techniques to diagnose HPV infection are not helpful in individual cases and are not widely available.

TREATMENT Human Papillomavirus Infections

(Table 90-1) Decisions regarding the initiation of therapy should be made with the recognition that currently available modes of treatment are not completely effective and some have significant side effects. In addition, treatment may be expensive, and many HPV lesions resolve spontaneously. Frequently used therapies include cryosurgery, application of caustic agents, electrodesiccation, surgical excision, and ablation with a laser. Topical antimetabolites such as 5-fluorouracil have also been used. Both failure and recurrence have been well documented with all of these methods of treatment. Cryosurgery is the initial treatment of choice for condyloma acuminatum. Topically applied podophyllum preparations as well as podofilox may also be used. Various interferon preparations have been employed with modest success in the treatment of respiratory papillomatosis and condyloma acuminatum. A topically applied interferon inducer, imiquimod, is also of benefit in the treatment of condyloma acuminatum. The diagnosis and management of anogenital dysplasias and of internal anogenital warts require special skills and resources, and patients with such lesions should be referred to a qualified specialist.

TABLE 90-1

TREATMENT OF EXTERNAL, EXOPHYTIC ANOGENITAL WARTS

I. Administered by provider
   A. Cryotherapy with liquid nitrogen or cryoprobe weekly
   B. Podophyllin resin, 10–25% weekly for up to 4 weeks
   C. Trichloroacetic acid or bichloroacetic acid, 80–90% weekly
   D. Surgical excision
   E. Other regimens
      1. Intralesionally administered interferon
      2. Laser surgery
II. Administered by patient
   A. Podofilox, 0.5% solution or gel twice daily for 3 days, followed by 4 days without therapy. This cycle may be repeated four times.
   B. Imiquimod, 5% cream 3 times per week for up to 16 weeks

Source: Modified from Centers for Disease Control and Prevention: MMWR Recomm Rep 55(RR-11):1, 2006 *(www.cdc.gov/mmwr/preview/mmwrhtml/rr5511a1/htm?)*.

PREVENTION

Recently developed HPV VLP vaccines dramatically reduce rates of infection and disease produced by the HPV types in the vaccines. These products are directed against virus types that cause anogenital tract disease and are derived from expression of the major capsid protein (L1) gene in tissue culture. When expressed using appropriate vectors and tissue culture systems, L1 self-assembles into a VLP that cannot be distinguished morphologically or antigenically from its wild-type counterpart **(Fig. 90-2)** but that contains no viral nucleic acid. To date, one quadrivalent product (Gardasil, Merck) containing HPV types 6, 11, 16, and 18 and one bivalent product (Cervarix, GlaxoSmithKline) containing HPV types 16 and 18 have been licensed in the United States. HPV types 6 and 11 cause 90% of anogenital warts, whereas types 16 and 18 are responsible for 70% of cervical cancers. Both vaccines are highly immunogenic, as measured by serum antibody titers after vaccination. Vaccine efficacy has varied according to the immunologic and virologic characteristics of study populations at baseline and according to the endpoints evaluated. Among study participants who are shown at baseline not to be infected with a specific virus type contained in the vaccine and who adhere to the study protocol, rates of vaccine efficacy regularly exceed 90%, as measured by both infection and disease caused by that specific virus type. Study participants who are already infected at baseline with a specific virus type contained in the vaccine do not benefit from vaccination against that type but may benefit from vaccination against other virus types contained in the vaccine preparation. Thus available HPV vaccines have potent prophylactic effects but no therapeutic effects. The Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention has recommended that HPV vaccination be routinely offered to girls and young women 9–26 years of age. The quadrivalent vaccine has also been licensed in the United States for use in males; the ACIP has stated that this product may be used to prevent anogenital warts in boys and young men 9–26 years of age. Because 30% of cervical cancers are caused by HPV types not contained in the vaccines, no changes in cervical cancer screening programs are currently recommended. Barrier methods of contraception may also be helpful in preventing transmission of condyloma acuminatum and other anogenital HPV-associated diseases. Methods to prevent other HPV infections are limited to avoidance of contact with infectious lesions.

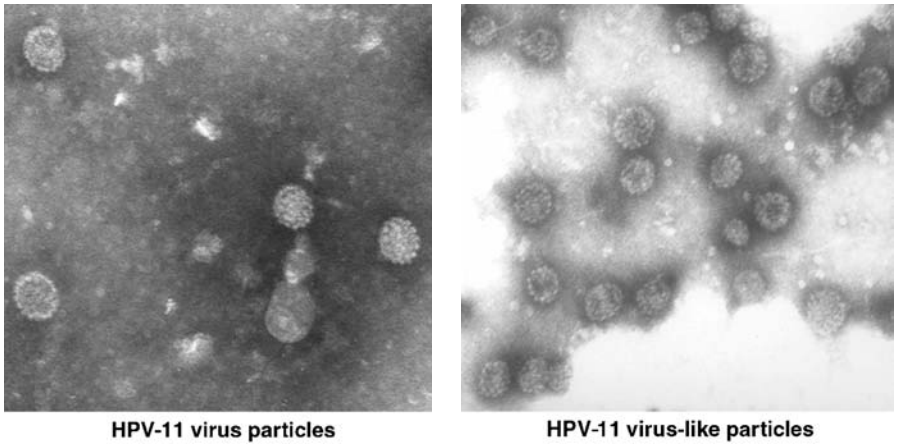


FIGURE 90-2

HPV-11 virus-like particles produced in insect cells (***right***) are morphologically and antigenically indistinguishable from wild-type HPV-11 particles (***left***). (*Images courtesy of Drs. William Bonnez and Robert C. Rose; with permission.*)

CHAPTER 91

COMMON VIRAL RESPIRATORY INFECTIONS

Raphael Dolin

GENERAL CONSIDERATIONS

Acute viral respiratory illnesses are among the most common of human diseases, accounting for one-half or more of all acute illnesses. The incidence of acute respiratory disease in the United States is 3–5.6 cases per person per year. The rates are highest among children <1 year old (6.1–8.3 cases per year) and remain high until age 6, when a progressive decrease begins. Adults have 3–4 cases per person per year. Morbidity from acute respiratory illnesses accounts for 30–50% of time lost from work by adults and for 60–80% of time lost from school by children. The use of antibacterial agents to treat viral respiratory infections represents a major source of abuse of that category of drugs.

It has been estimated that two-thirds to three-fourths of cases of acute respiratory illnesses are caused by viruses. More than 200 antigenically distinct viruses from 10 genera have been reported to cause acute respiratory illness, and it is likely that additional agents will be described in the future. The vast majority of these viral infections involve the upper respiratory tract, but lower respiratory tract disease can also develop, particularly in younger age groups, in the elderly, and in certain epidemiologic settings.

The illnesses caused by respiratory viruses traditionally have been divided into multiple distinct syndromes, such as the "common cold," pharyngitis, croup (laryngotracheobronchitis), tracheitis, bronchiolitis, bronchitis, and pneumonia. Each of these general categories of illness has a certain epidemiologic and clinical profile; for example, croup occurs exclusively in very young children and has a characteristic clinical course. Some types of respiratory illness are more likely to be associated with certain viruses (e.g., the common cold with rhinoviruses), while others occupy characteristic epidemiologic niches (e.g., adenovirus infections in military recruits). The syndromes most commonly associated with infections with the major respiratory virus groups are summarized in **Table 91-1**. Most respiratory viruses clearly have the potential to cause more than one type of respiratory illness, and features of several types of illness may be found in the same patient. Moreover, the clinical illnesses induced by these viruses are rarely sufficiently distinctive to permit an etiologic diagnosis on clinical grounds alone, although the epidemiologic setting increases the likelihood that one group of viruses rather than another is involved. In general, laboratory methods must be relied on to establish a specific viral diagnosis.

This chapter reviews viral infections caused by six of the major groups of respiratory viruses: rhinoviruses, coronaviruses, respiratory syncytial viruses, metapneumoviruses, parainfluenza viruses, and adenoviruses. The extraordinary outbreaks of lower respiratory tract disease associated with coronaviruses (severe acute respiratory syndrome, or SARS) in 2002–2003 are also discussed. Influenza viruses, which are a major cause of death as well as morbidity, are reviewed in Chap. 92. Herpesviruses, which occasionally cause pharyngitis and which also cause lower respiratory tract disease in immunosuppressed patients, are reviewed in Chap. 84. Enteroviruses, which account for occasional respiratory illnesses during the summer months, are reviewed in Chap. 97.

RHINOVIRUS INFECTIONS

ETIOLOGIC AGENT

Rhinoviruses are members of the Picornaviridae family, small (15- to 30-nm) nonenveloped viruses that contain a single-stranded RNA genome and have been divided into three genetic species: HRV-A, HRV-B, and HRV-C. In contrast to other members of the picornavirus family, such as enteroviruses, rhinoviruses are acid-labile and are almost completely inactivated at pH ≤ 3. Rhinoviruses grow preferentially at 33°–34°C (the temperature of the human nasal passages) rather than at 37°C (the temperature of the lower respiratory tract). Of the 102 recognized serotypes of rhinovirus, 91 use intercellular adhesion molecule 1 (ICAM-1) as a cellular receptor and constitute the "major" receptor group, 10 use the low-density lipoprotein receptor (LDLR) and constitute the "minor" receptor group, and 1 uses decay-accelerating factor.

TABLE 91-1

ILLNESSES ASSOCIATED WITH RESPIRATORY VIRUSES

	FREQUENCY OF RESPIRATORY SYNDROMES		
VIRUS	**MOST FREQUENT**	**OCCASIONAL**	**INFREQUENT**
Rhinoviruses	Common cold	Exacerbation of chronic bronchitis and asthma	Pneumonia in children
Coronaviruses[a]	Common cold	Exacerbation of chronic bronchitis and asthma	Pneumonia and bronchiolitis
Human respiratory syncytial virus	Pneumonia and bronchiolitis in young children	Common cold in adults	Pneumonia in elderly and immunosuppressed patients
Parainfluenza viruses	Croup and lower respiratory tract disease in young children	Pharyngitis and common cold	Tracheobronchitis in adults; lower respiratory tract disease in immunosuppressed patients
Adenoviruses	Common cold and pharyngitis in children	Outbreaks of acute respiratory disease in military recruits[b]	Pneumonia in children; lower respiratory tract and disseminated disease in immunosuppressed patients
Influenza A viruses	Influenza[c]	Pneumonia and excess mortality in high-risk patients	Pneumonia in healthy individuals
Influenza B viruses	Influenza[c]	Rhinitis or pharyngitis alone	Pneumonia
Enteroviruses	Acute undifferentiated febrile illnesses[d]	Rhinitis or pharyngitis alone	Pneumonia
Herpes simplex viruses	Gingivostomatitis in children; pharyngotonsillitis in adults	Tracheitis and pneumonia in immunocompromised patients	Disseminated infection in immunocompromised patients
Human metapneumoviruses	Upper and lower respiratory tract disease in children	Upper respiratory tract illness in adults	Pneumonia in elderly and immunosuppressed patients

[a]SARS-associated coronavirus (SARS-CoV) caused epidemics of pneumonia from November 2002 to July 2003 (see text).
[b]Serotypes 4 and 7.
[c]Fever, cough, myalgia, malaise.
[d]May or may not have a respiratory component.

EPIDEMIOLOGY

Rhinoviruses are a prominent cause of the common cold and have been detected in up to 50% of common cold–like illnesses by tissue culture and polymerase chain reaction (PCR) techniques. Overall rates of rhinovirus infection are higher among infants and young children and decrease with increasing age. Rhinovirus infections occur throughout the year, with seasonal peaks in early fall and spring in temperate climates. These infections are most often introduced into families by preschool or grade-school children <6 years old. Of initial illnesses in family settings, 25–70% are followed by secondary cases, with the highest attack rates among the youngest siblings at home. Attack rates also increase with family size.

Rhinoviruses appear to spread through direct contact with infected secretions, usually respiratory droplets. In some studies of volunteers, transmission was most efficient by hand-to-hand contact, with subsequent self-inoculation of the conjunctival or nasal mucosa. Other studies demonstrated transmission by large- or small-particle aerosol. Virus can be recovered from plastic surfaces inoculated 1–3 h previously; this observation suggests that environmental surfaces contribute to transmission. In studies of married couples in which neither partner had detectable serum antibody, transmission was associated with prolonged contact (≥122 h) during a 7-day period. Transmission was infrequent unless (1) virus was recoverable from the donor's hands and nasal mucosa, (2) at least 1000 $TCID_{50}$ of virus was present in nasal washes from the donor, and (3) the donor was at least moderately symptomatic with the "cold." Despite anecdotal observations, exposure to cold temperatures, fatigue, and sleep deprivation have not been associated with increased rates of rhinovirus-induced illness in volunteers, although some studies have suggested that psychologically defined "stress" may contribute to development of symptoms.

Infection with rhinoviruses is worldwide in distribution. By adulthood, nearly all individuals have neutralizing antibodies to multiple serotypes, although the prevalence of antibody to any one serotype varies widely. Multiple serotypes circulate simultaneously, and generally no single serotype or group of serotypes has been more prevalent than the others.

PATHOGENESIS

Rhinoviruses infect cells through attachment to specific cellular receptors; as mentioned earlier, most serotypes attach to ICAM-1, while a few use LDLR. Relatively limited information is available on the histopathology and pathogenesis of acute rhinovirus infections in humans. Examination of biopsy specimens obtained during experimentally induced and naturally occurring illness indicates that the nasal mucosa is edematous, is often hyperemic, and—during acute illness—is covered by a mucoid discharge. There is a mild infiltrate with inflammatory cells, including neutrophils, lymphocytes, plasma cells, and eosinophils. Mucus-secreting glands in the submucosa appear hyperactive; the nasal turbinates are engorged, a condition that may lead to obstruction of nearby openings of sinus cavities. Several mediators—e.g., bradykinin; lysylbradykinin; prostaglandins; histamine; interleukins 1β, 6, and 8; and tumor necrosis factor α—have been linked to the development of signs and symptoms in rhinovirus-induced colds.

The incubation period for rhinovirus illness is short, generally 1–2 days. Virus shedding coincides with the onset of illness or may begin shortly before symptoms develop. The mechanisms of immunity to rhinovirus infection are not well worked out. In some studies, the presence of homotypic antibody has been associated with significantly reduced rates of subsequent infection and illness, but data conflict regarding the relative importance of serum and local antibody in protection from rhinovirus infection.

CLINICAL MANIFESTATIONS

The most common clinical manifestations of rhinovirus infections are those of the common cold. Illness usually begins with rhinorrhea and sneezing accompanied by nasal congestion. The throat is frequently sore, and in some cases sore throat is the initial complaint. Systemic signs and symptoms, such as malaise and headache, are mild or absent, and fever is unusual. Illness generally lasts for 4–9 days and resolves spontaneously without sequelae. In children, bronchitis, bronchiolitis, and bronchopneumonia have been reported; nevertheless, it appears that rhinoviruses are not major causes of lower respiratory tract disease in children. Rhinoviruses may cause exacerbations of asthma and chronic pulmonary disease in adults. The vast majority of rhinovirus infections resolve without sequelae, but complications related to obstruction of the eustachian tubes or sinus ostia, including otitis media or acute sinusitis, can develop. In immunosuppressed patients, particularly bone marrow transplant recipients, severe and even fatal pneumonias have been associated with rhinovirus infections.

DIAGNOSIS

Although rhinoviruses are the most frequently recognized cause of the common cold, similar illnesses are caused by a variety of other viruses, and a specific viral etiologic diagnosis cannot be made on clinical grounds alone. Rather, rhinovirus infection is diagnosed by isolation of the virus from nasal washes or nasal secretions in tissue culture. In practice, this procedure is rarely undertaken because of the benign, self-limited nature of the illness. In most settings, detection of rhinovirus RNA by PCR is more sensitive than that by tissue culture; however, PCR for rhinoviruses is largely a research procedure. Given the many serotypes of rhinovirus, diagnosis by serum antibody tests is currently impractical. Likewise, common laboratory tests, such as white blood cell count and erythrocyte sedimentation rate, are not helpful.

TREATMENT **Rhinovirus Infections**

Because rhinovirus infections are generally mild and self-limited, treatment is not usually necessary. Therapy in the form of first-generation antihistamines and nonsteroidal anti-inflammatory drugs may be beneficial in patients with particularly pronounced symptoms, and an oral decongestant may be added if nasal obstruction is particularly troublesome. Reduction of activity is prudent in instances of significant discomfort or fatigability. Antibacterial agents should be used only if bacterial complications such as otitis media or sinusitis develop. Specific antiviral therapy is not available.

PREVENTION

Intranasal application of interferon sprays has been effective in the prophylaxis of rhinovirus infections but is also associated with local irritation of the nasal mucosa. Studies of prevention of rhinovirus infection by blocking of ICAM-1 or by drug binding to parts of the viral capsid (pleconaril) have yielded mixed results. Experimental vaccines to certain rhinovirus serotypes have been generated, but their usefulness is questionable because of the myriad serotypes and the uncertainty about mechanisms of immunity. Thorough hand washing, environmental decontamination, and protection against autoinoculation may help to reduce rates of transmission of infection.

CORONAVIRUS INFECTIONS

ETIOLOGIC AGENT

Coronaviruses are pleomorphic, single-stranded RNA viruses that measure 100–160 nm in diameter. The name derives from the crownlike appearance produced by the club-shaped projections that stud the viral envelope. Coronaviruses infect a wide variety of animal species and have been divided into three antigenic and genetic groups. Before the emergence of the coronavirus associated with SARS (SARS-CoV), coronaviruses recognized as causes of infection in humans fell into groups 1 and 2, which include human isolates

HCoV-229E and HCoV-OC43, respectively. SARS-CoV was at first believed to represent a novel group but now is considered to be a distantly related member of group 2. The SARS-CoV strains that have been fully sequenced have shown only minimal variation.

In general, human coronaviruses have been difficult to cultivate in vitro, and some strains grow only in human tracheal organ cultures rather than in tissue culture. SARS-CoV is an exception whose ready growth in African green monkey kidney (Vero E6) cells greatly facilitates its study.

EPIDEMIOLOGY

Generally, human coronavirus infections are present throughout the world. Seroprevalence studies of strains HCoV-229E and HCoV-OC43 have demonstrated that serum antibodies are acquired early in life and increase in prevalence with advancing age, so that >80% of adult populations have antibodies as measured by enzyme-linked immunosorbent assay (ELISA). Overall, coronaviruses account for 10–35% of common colds, depending on the season. Coronavirus infections appear to be particularly prevalent in late fall, winter, and early spring—times when rhinovirus infections are less common.

An extraordinary outbreak of the coronavirus-associated illness known as SARS occurred in 2002–2003. The outbreak apparently began in southern China and eventually resulted in 8096 recognized cases in 28 countries in Asia, Europe, and North and South America; ~90% of cases occurred in China and Hong Kong. The natural reservoir of SARS-CoV appeared to be the horseshoe bat, and the outbreak may have originated from human contact with infected semidomesticated animals such as the palm civet. In most cases, however, the infection was transmitted from human to human. Case-fatality rates varied among outbreaks, with an overall figure of ~9.5%. The disease appeared to be somewhat milder in cases in the United States and was clearly less severe among children. The outbreak ceased in 2003; 17 cases were detected in 2004, mostly in laboratory-associated settings, and no cases were reported in 2005–2009.

The mechanisms of transmission of SARS are incompletely understood. Clusters of cases suggest that spread may occur by both large and small aerosols and perhaps by the fecal-oral route as well. The outbreak of illness in a large apartment complex in Hong Kong suggested that environmental sources, such as sewage or water, may also play a role in transmission. Some ill individuals ("super-spreaders") appeared to be hyperinfectious and were capable of transmitting infection to 10–40 contacts, although most infections resulted in spread either to no one or to three or fewer individuals.

PATHOGENESIS

Coronaviruses that cause the common cold (e.g., strains HCoV-229E and HCoV-OC43) infect ciliated epithelial cells in the nasopharynx via the aminopeptidase N receptor (group 1) or a sialic acid receptor (group 2). Viral replication leads to damage of ciliated cells and induction of chemokines and interleukins, with consequent common-cold symptoms similar to those induced by rhinoviruses.

SARS-CoV infects cells of the respiratory tract via the angiotensin-converting enzyme 2 receptor. The result is a systemic illness in which virus is also found in the bloodstream, in the urine, and (for up to 2 months) in the stool. Virus persists in the respiratory tract for 2–3 weeks, and titers peak ~10 days after the onset of systemic illness. Pulmonary pathology consists of hyaline membrane formation, desquamation of pneumocytes in alveolar spaces, and an interstitial infiltrate made up of lymphocytes and mononuclear cells. Giant cells are frequently seen, and coronavirus particles have been detected in type II pneumocytes. Elevated levels of proinflammatory cytokines and chemokines have been detected in sera from patients with SARS.

CLINICAL MANIFESTATIONS

After an incubation period that generally lasts 2–7 days (range, 1–14 days), SARS usually begins as a systemic illness marked by the onset of fever, which is often accompanied by malaise, headache, and myalgias and is followed in 1–2 days by a nonproductive cough and dyspnea. Approximately 25% of patients have diarrhea. Chest x-rays can show a variety of infiltrates, including patchy areas of consolidation—most frequently in peripheral and lower lung fields—or interstitial infiltrates, which can progress to diffuse involvement.

In severe cases, respiratory function may worsen during the second week of illness and progress to frank adult respiratory distress syndrome accompanied by multiorgan dysfunction. Risk factors for severe disease include an age of >50 years and comorbidities such as cardiovascular disease, diabetes, or hepatitis. Illness in pregnant women may be particularly severe, but SARS-CoV infection appears to be milder in children than in adults.

The clinical features of common colds caused by human coronaviruses are similar to those of illness caused by rhinoviruses. In studies of volunteers, the mean incubation period of colds induced by coronaviruses (3 days) is somewhat longer than that of llness caused by rhinoviruses, and the duration of llness is somewhat shorter (mean, 6–7 days). In some studies, the amount of nasal discharge was greater in colds induced by coronaviruses than in those induced by rhinoviruses. Coronaviruses other than SARS-CoV have been recovered occasionally from infants with pneumonia and from military recruits with lower respiratory tract disease and have been associated with worsening of chronic bronchitis. Two novel coronaviruses, HCoV-NL63 (group 1) and HCoV-HKU1 (group 2), have been isolated from patients hospitalized with acute respiratory illness. Their overall role as causes of human respiratory disease remains to be determined.

LABORATORY FINDINGS AND DIAGNOSIS

Laboratory abnormalities in SARS include lymphopenia, which is present in ~50% of cases and which mostly affects CD4+ T cells but also involves CD8+ T cells and natural killer cells. Total white blood cell counts are normal or slightly low, and thrombocytopenia may develop as the illness progresses. Elevated serum levels of aminotransferases, creatine kinase, and lactate dehydrogenase have been reported.

A rapid diagnosis of SARS-CoV infection can be made by reverse-transcription PCR (RT-PCR) of respiratory tract samples and plasma early in illness and of urine and stool later on. SARS-CoV can also be grown from respiratory tract samples by inoculation into Vero E6 tissue culture cells, in which a cytopathic effect is seen within days. RT-PCR appears to be more sensitive than tissue culture, but only around one-third of cases are positive by PCR at initial presentation. Serum antibodies can be detected by ELISA or immunofluorescence, and nearly all patients develop detectable serum antibodies within 28 days after the onset of illness.

Laboratory diagnosis of coronavirus-induced colds is rarely required. Coronaviruses that cause those illnesses are frequently difficult to cultivate in vitro but can be detected in clinical samples by ELISA or immunofluorescence assays or by RT-PCR for viral RNA. These research procedures can be used to detect coronaviruses in unusual clinical settings.

TREATMENT Coronavirus Infections

There is no specific therapy of established efficacy for SARS. Although ribavirin has frequently been used, it has little if any activity against SARS-CoV in vitro, and no beneficial effect on the course of illness has been demonstrated. Because of suggestions that immunopathology may contribute to the disease, glucocorticoids have also been widely used, but their benefit, if any, is likewise unestablished. Supportive care to maintain pulmonary and other organ-system functions remains the mainstay of therapy.

The approach to the treatment of common colds caused by coronaviruses is similar to that discussed earlier for rhinovirus-induced illnesses.

PREVENTION

The recognition of SARS led to a worldwide mobilization of public health resources to apply infection control practices to contain the disease. Case definitions were established, travel advisories were proposed, and quarantines were imposed in certain locales. As of this writing, no additional cases of SARS have been reported since 2004. However, it remains unknown whether the disappearance of cases is a result of control measures, whether it is part of a seasonal or otherwise unexplained epidemiologic pattern of SARS, or when or whether SARS might reemerge. The U.S. Centers for Disease Control and Prevention and the World Health Organization maintain recommendations for surveillance and assessment of potential cases of SARS (*www.cdc.gov/ncidod/sars/*). The frequent transmission of the disease to health care workers makes it mandatory that strict infection-control practices be employed by health care facilities to prevent airborne, droplet, and contact transmission from any suspected cases of SARS. Health care workers who enter areas in which patients with SARS may be present should don gowns, gloves, and eye and respiratory protective equipment (e.g., an N95 filtering facepiece respirator certified by the National Institute for Occupational Safety and Health).

Vaccines have been developed against several animal coronaviruses but not against known human coronaviruses. The emergence of SARS-CoV has stimulated interest in the development of vaccines against such agents.

HUMAN RESPIRATORY SYNCYTIAL VIRUS INFECTIONS

ETIOLOGIC AGENT

Human respiratory syncytial virus (HRSV) is a member of the Paramyxoviridae family (genus *Pneumovirus*). An enveloped virus ~150–350 nm in diameter, HRSV is so named because its replication in vitro leads to the fusion of neighboring cells into large multinucleated syncytia. The single-stranded RNA genome codes for 11 virus-specific proteins. Viral RNA is contained in a helical nucleocapsid surrounded by a lipid envelope bearing two glycoproteins: the G protein, by which the virus attaches to cells, and the F (fusion) protein, which facilitates entry of the virus into the cell by fusing host and viral membranes. HRSV is considered to be of a single antigenic type, but two distinct subgroups (A and B) and multiple subtypes within each subgroup have now been described. Antigenic diversity is reflected by differences in the G protein, while the F protein is highly conserved. Both antigenic groups can circulate simultaneously in outbreaks, although there are typically alternating patterns in which one subgroup predominates over 1- to 2-year periods.

EPIDEMIOLOGY

HRSV is a major respiratory pathogen of young children and the foremost cause of lower respiratory disease in infants. Infection with HRSV is seen throughout the world in annual epidemics that occur in late fall, winter, or spring and last up to 5 months. The virus is rarely encountered during the summer. Rates of illness are highest among infants 1–6 months of age, peaking at 2–3 months of age. The attack rates among susceptible infants and children are extraordinarily high, approaching 100% in settings such as day-care centers where large numbers of susceptible infants are present.

By age 2, virtually all children will have been infected with HRSV. HRSV accounts for 20–25% of hospital admissions of young infants and children for pneumonia and for up to 75% of cases of bronchiolitis in this age group. It has been estimated that more than half of infants who are at risk will become infected during an HRSV epidemic.

In older children and adults, reinfection with HRSV is frequent but disease is milder than in infancy. A common cold–like syndrome is the illness most commonly associated with HRSV infection in adults. Severe lower respiratory tract disease with pneumonitis can occur in elderly (often institutionalized) adults and in patients with immunocompromising disorders or treatment, including recipients of stem cell and solid-organ transplants. HRSV is also an important nosocomial pathogen; during an outbreak, it can infect pediatric patients and up to 25–50% of the staff on pediatric wards. The spread of HRSV among families is efficient: up to 40% of siblings may become infected when the virus is introduced into the family setting.

HRSV is transmitted primarily by close contact with contaminated fingers or fomites and by self-inoculation of the conjunctiva or anterior nares. Virus may also be spread by coarse aerosols produced by coughing or sneezing, but it is inefficiently spread by fine-particle aerosols. The incubation period is ~4–6 days, and virus shedding may last for ≥2 weeks in children and for shorter periods in adults. In immunosuppressed patients, shedding can continue for weeks.

PATHOGENESIS

Little is known about the histopathology of minor HRSV infection. Severe bronchiolitis or pneumonia is characterized by necrosis of the bronchiolar epithelium and a peribronchiolar infiltrate of lymphocytes and mononuclear cells. Interalveolar thickening and filling of alveolar spaces with fluid can also be found. The correlates of protective immunity to HRSV are incompletely understood. Because reinfection occurs frequently and is often associated with illness, the immunity that develops after single episodes of infection clearly is not complete or long-lasting. However, the cumulative effect of multiple reinfections is to temper subsequent disease and to provide some temporary measure of protection against infection. Studies of experimentally induced disease in healthy volunteers indicate that the presence of nasal IgA neutralizing antibody correlates more closely with protection than does the presence of serum antibody. Studies in infants, however, suggest that maternally acquired antibody provides some protection from lower respiratory tract disease, although illness can be severe even in infants who have moderate levels of maternally derived serum antibody. The relatively severe disease observed in immunosuppressed patients and experimental animal models indicates that cell-mediated immunity is an important mechanism of host defense against HRSV. Evidence suggests that major histocompatibility class I–restricted cytotoxic T cells may be particularly important in this regard.

CLINICAL MANIFESTATIONS

HRSV infection leads to a wide spectrum of respiratory illnesses. In infants, 25–40% of infections result in lower respiratory tract involvement, including pneumonia, bronchiolitis, and tracheobronchitis. In this age group, illness begins most frequently with rhinorrhea, low-grade fever, and mild systemic symptoms, often accompanied by cough and wheezing. Most patients recover gradually over 1–2 weeks. In more severe illness, tachypnea and dyspnea develop, and eventually frank hypoxia, cyanosis, and apnea can ensue. Physical examination may reveal diffuse wheezing, rhonchi, and rales. Chest radiography shows hyperexpansion, peribronchial thickening, and variable infiltrates ranging from diffuse interstitial infiltrates to segmental or lobar consolidation. Illness may be particularly severe in children born prematurely and in those with congenital cardiac disease, bronchopulmonary dysplasia, nephrotic syndrome, or immunosuppression. One study documented a 37% mortality rate among infants with HRSV pneumonia and congenital cardiac disease.

In adults, the most common symptoms of HRSV infection are those of the common cold, with rhinorrhea, sore throat, and cough. Illness is occasionally associated with moderate systemic symptoms such as malaise, headache, and fever. HRSV has also been reported to cause lower respiratory tract disease with fever in adults, including severe pneumonia in the elderly—particularly in nursing-home residents, among whom its impact can rival that of influenza. HRSV pneumonia can be a significant cause of morbidity and death among patients undergoing stem cell and solid-organ transplantation, in whom case-fatality rates of 20–80% have been reported. Sinusitis, otitis media, and worsening of chronic obstructive and reactive airway disease have also been associated with HRSV infection.

LABORATORY FINDINGS AND DIAGNOSIS

The diagnosis of HRSV infection can be suspected on the basis of a suggestive epidemiologic setting—that is, severe illness among infants during an outbreak of HRSV in the community. Infections in older children and adults cannot be differentiated with certainty from those caused by other respiratory viruses. The specific diagnosis is established by detection of HRSV in respiratory secretions, such as sputum, throat swabs, or nasopharyngeal washes. Virus can be isolated in tissue culture, but this method has been largely supplanted by rapid viral diagnostic techniques consisting of immunofluorescence or ELISA of nasopharyngeal washes, aspirates, and (less satisfactorily) nasopharyngeal swabs. With specimens from children, these techniques have sensitivities and specificities of 80–95%; they are somewhat less sensitive with specimens from adults. RT-PCR detection techniques have shown even higher rates of sensitivity and specificity, particularly in adults. Serologic diagnosis may be made by comparison of acute- and convalescent-phase serum specimens by ELISA or by neutralization or complement-fixation tests. These tests may be useful in older children and adults but are less sensitive in children <4 months of age.

TREATMENT **Human Respiratory Syncytial Virus Infections**

Treatment of upper respiratory tract HRSV infection is aimed primarily at the alleviation of symptoms and is similar to that for other viral infections of the upper respiratory tract. For lower respiratory tract infections, respiratory therapy, including hydration, suctioning of secretions, and administration of humidified oxygen and antibronchospastic agents, is given as needed. In severe hypoxia, intubation and ventilatory assistance may be required. Studies of infants with HRSV infection who were given aerosolized ribavirin, a nucleoside analogue active in vitro against HRSV, demonstrated a modest beneficial effect on the resolution of lower respiratory tract illness, including alleviation of blood-gas abnormalities, in some studies. The American Academy of Pediatrics recommends that treatment with aerosolized ribavirin "may be considered" for infants who are severely ill or who are at high risk for complications of HRSV infection; included are premature infants and those with bronchopulmonary dysplasia, congenital heart disease, or immunosuppression. The efficacy of ribavirin against HRSV pneumonia in older children and adults, including those with immunosuppression, has not been established. No benefit has been found in the treatment of HRSV pneumonia with standard immunoglobulin; immunoglobulin with high titers of antibody to HRSV (RSVIg), which is no longer available; or chimeric mouse-human monoclonal IgG antibody to HRSV (palivizumab). Combined therapy with aerosolized ribavirin and palivizumab is being evaluated in immunosuppressed patients with HRSV pneumonia.

PREVENTION

Monthly administration of RSVIg (no longer available) or palivizumab has been approved as prophylaxis against HRSV for children <2 years of age who have bronchopulmonary dysplasia or cyanotic heart disease or who were born prematurely. Considerable interest exists in the development of vaccines against HRSV. Inactivated whole-virus vaccines have been ineffective; in one study, they actually potentiated disease in infants. Other approaches include immunization with purified F and G surface glycoproteins of HRSV or generation of stable, live attenuated virus vaccines. In settings such as pediatric wards where rates of transmission are high, barrier methods for the protection of hands and conjunctivae may be useful in reducing the spread of virus.

HUMAN METAPNEUMOVIRUS INFECTIONS

ETIOLOGIC AGENT

Human metapneumovirus (HMPV) is a viral respiratory pathogen that has been assigned to the Paramyxoviridae family (genus *Metapneumovirus*). Its morphology and genomic organization are similar to those of avian metapneumoviruses, which are recognized respiratory pathogens of turkeys. HMPV particles may be spherical, filamentous, or pleomorphic in shape and measure 150–600 nm in diameter. Particles contain 15-nm projections from the surface that are similar in appearance to those of other Paramyxoviridae. The single-stranded RNA genome codes for nine proteins that, except for the absence of nonstructural proteins, generally correspond to those of HRSV. HMPV is of only one antigenic type; two closely related genotypes (A and B), four subgroups, and two sublineages have been described.

EPIDEMIOLOGY

HMPV infections are worldwide in distribution, are most frequent during the winter, and occur early in life, so that serum antibodies to the virus are present in nearly all children by the age of 5. HMPV infections have been detected in older age groups, including elderly adults, and in both immunocompetent and immunosuppressed hosts. This virus accounts for 1–5% of childhood upper respiratory tract infections and for 10–15% of respiratory tract illnesses requiring hospitalization of children. In addition, HMPV causes 2–4% of acute respiratory illnesses in ambulatory adults and elderly patients. HMPV has been detected in a few cases of SARS, but its role (if any) in these illnesses has not been established.

CLINICAL MANIFESTATIONS

The spectrum of clinical illnesses associated with HMPV is similar to that associated with HRSV and includes both upper and lower respiratory tract illnesses, such as bronchiolitis, croup, and pneumonia. Reinfection with HMPV is common among older children and adults and has manifestations ranging from subclinical infections to common cold syndromes and occasionally pneumonia, which is seen primarily in elderly patients and those with cardiopulmonary diseases. Serious HMPV infections occur in immunocompromised patients, including those with neoplasia and hematopoietic stem cell transplants.

DIAGNOSIS

HMPV can be detected in nasal aspirates and respiratory secretions by immunofluorescence, by PCR, or by growth in rhesus monkey kidney (LLC-MK2) tissue cultures. A serologic diagnosis can be made by ELISA, which uses HMPV-infected tissue culture lysates as sources of antigens.

TREATMENT **Human Metapneumovirus Infections**

Treatment for HMPV infections is primarily supportive and symptom-based. Ribavirin is active against HMPV in vitro, but its efficacy in vivo is unknown.

PREVENTION

Vaccines against HMPV are in the early stages of development.

PARAINFLUENZA VIRUS INFECTIONS

ETIOLOGIC AGENT

Parainfluenza viruses belong to the Paramyxoviridae family (genera *Respirovirus* and *Rubulavirus*). They are 150–200 nm in diameter, are enveloped, and contain a single-stranded RNA genome. The envelope is studded with two glycoproteins: one possesses both hemagglutinin and neuraminidase activity, and the other contains fusion activity. The viral RNA genome is enclosed in a helical nucleocapsid and codes for six structural and several accessory proteins. All five serotypes of parainfluenza virus (1, 2, 3, 4A, and 4B) share certain antigens with other members of the Paramyxoviridae family, including mumps and Newcastle disease viruses.

EPIDEMIOLOGY

Parainfluenza viruses are distributed throughout the world; infection with serotypes 4A and 4B has been reported less widely, probably because these types are more difficult than the other three to grow in tissue culture. Infection is acquired in early childhood; by 5 years of age, most children have antibodies to serotypes 1, 2, and 3. Types 1 and 2 cause epidemics during the fall, often occurring in an alternate-year pattern. Type 3 infection has been detected during all seasons of the year, but epidemics have occurred annually in the spring.

The contribution of parainfluenza infections to respiratory disease varies with both the location and the year. In studies conducted in the United States, parainfluenza virus infections have accounted for 4.3–22% of respiratory illnesses in children. In adults, parainfluenza infections are generally mild and account for <10% of respiratory illnesses. The major importance of parainfluenza viruses is as a cause of respiratory illness in young children, in whom they rank second only to HRSV as causes of lower respiratory tract illness. Parainfluenza virus type 1 is the most frequent cause of croup (laryngotracheobronchitis) in children, while serotype 2 causes similar, although generally less severe, disease. Type 3 is an important cause of bronchiolitis and pneumonia in infants, while illnesses associated with types 4A and 4B have generally been mild. Unlike types 1 and 2, type 3 frequently causes illness during the first month of life, when passively acquired maternal antibody is still present. Parainfluenza viruses are spread through infected respiratory secretions, primarily by person-to-person contact and/or by large droplets. The incubation period has varied from 3 to 6 days in experimental infections but may be somewhat shorter for naturally occurring disease in children.

PATHOGENESIS

Immunity to parainfluenza viruses is incompletely understood, but evidence suggests that immunity to infections with serotypes 1 and 2 is mediated by local IgA antibodies in the respiratory tract. Passively acquired serum neutralizing antibodies also confer some protection against infection with types 1, 2, and (to a lesser degree) 3. Studies in experimental animal models and in immunosuppressed patients suggest that T cell–mediated immunity may also be important in parainfluenza virus infections.

CLINICAL MANIFESTATIONS

Parainfluenza virus infections occur most frequently among children, in whom initial infection with serotype 1, 2, or 3 is associated with an acute febrile illness in 50–80% of cases. Children may present with coryza, sore throat, hoarseness, and cough that may or may not be croupy. In severe croup, fever persists, with worsening coryza and sore throat. A brassy or barking cough may progress to frank stridor. Most children recover over the next 1 or 2 days, although progressive airway obstruction and hypoxia ensue occasionally. If bronchiolitis or pneumonia develops, progressive cough accompanied by wheezing, tachypnea, and intercostal retractions may occur. In this setting, sputum production increases modestly. Physical examination shows nasopharyngeal discharge and oropharyngeal injection, along with rhonchi, wheezes, or coarse breath sounds. Chest x-rays can show air trapping and occasionally interstitial infiltrates.

In older children and adults, parainfluenza infections tend to be milder, presenting most frequently as a common cold or as hoarseness, with or without cough. Lower respiratory tract involvement in older children and adults is uncommon, but tracheobronchitis in adults has been reported. Severe, prolonged, and even fatal parainfluenza infection has been reported in children and adults with severe immunosuppression, including hematopoietic stem cell and solid-organ transplant recipients.

LABORATORY FINDINGS AND DIAGNOSIS

The clinical syndromes caused by parainfluenza viruses (with the possible exception of croup in young children) are not sufficiently distinctive to be diagnosed on clinical grounds alone. A specific diagnosis is established by detection of virus in respiratory tract secretions, throat swabs, or nasopharyngeal washings. Viral growth in tissue culture is detected either by hemagglutination or by a cytopathic effect. Rapid viral diagnosis may be made by identification of parainfluenza antigens in exfoliated cells from the respiratory tract with immunofluorescence or ELISA, although these techniques appear to be less sensitive than tissue culture. Highly specific and sensitive PCR assays have also been developed. Serologic diagnosis can be established by hemagglutination inhibition, complement-fixation, or neutralization tests of acute- and convalescent-phase specimens.

However, since frequent heterotypic responses occur among the parainfluenza serotypes, the serotype causing illness often cannot be identified by serologic techniques alone.

Acute epiglottitis caused by *Haemophilus influenzae* type b must be differentiated from viral croup. Influenza A virus is also a common cause of croup during epidemic periods.

TREATMENT **Parainfluenza Virus Infections**

For upper respiratory tract illness, symptoms can be treated as discussed for other viral respiratory tract illnesses. If complications such as sinusitis, otitis, or superimposed bacterial bronchitis develop, appropriate antibacterial antibiotics should be administered. Mild cases of croup should be treated with bed rest and moist air generated by vaporizers. More severe cases require hospitalization and close observation for the development of respiratory distress. If acute respiratory distress develops, humidified oxygen and intermittent racemic epinephrine are usually administered. Aerosolized or systemically administered glucocorticoids are beneficial; the latter have a more profound effect. No specific antiviral therapy is available, although ribavirin is active against parainfluenza viruses in vitro and anecdotal reports describe its use clinically, particularly in immunosuppressed patients.

PREVENTION

Vaccines against parainfluenza viruses are under development.

ADENOVIRUS INFECTIONS

ETIOLOGIC AGENT

Adenoviruses are complex DNA viruses that measure 70–80 nm in diameter. Human adenoviruses belong to the genus *Mastadenovirus*, which includes 51 serotypes. Adenoviruses have a characteristic morphology consisting of an icosahedral shell composed of 20 equilateral triangular faces and 12 vertices. The protein coat (capsid) consists of hexon subunits with group-specific and type-specific antigenic determinants and penton subunits at each vertex primarily containing group-specific antigens. A fiber with a knob at the end projects from each penton; this fiber contains type-specific and some group-specific antigens. Human adenoviruses have been divided into six subgroups (A through F) on the basis of the homology of DNA genomes and other properties. The adenovirus genome is a linear double-stranded DNA that codes for structural and nonstructural polypeptides. The replicative cycle of adenovirus may result either in lytic infection of cells or in the establishment of a latent infection (primarily involving lymphoid cells). Some adenovirus types can induce oncogenic transformation, and tumor formation has been observed in rodents; however, despite intensive investigation, adenoviruses have not been associated with tumors in humans.

EPIDEMIOLOGY

Adenovirus infections most frequently affect infants and children. Infections occur throughout the year but are most common from fall to spring. Adenoviruses account for ~10% of acute respiratory infections in children but for <2% of respiratory illnesses in civilian adults. Nearly 100% of adults have serum antibody to multiple serotypes—a finding indicating that infection is common in childhood. Types 1, 2, 3, and 5 are the most common isolates from children. Certain adenovirus serotypes—particularly 4 and 7 but also 3, 14, and 21—are associated with outbreaks of acute respiratory disease in military recruits in winter and spring. Adenovirus infection can be transmitted by inhalation of aerosolized virus, by inoculation of virus into conjunctival sacs, and probably by the fecal-oral route as well. Type-specific antibody generally develops after infection and is associated with protection, albeit incomplete, against infection with the same serotype.

CLINICAL MANIFESTATIONS

In children, adenoviruses cause a variety of clinical syndromes. The most common is an acute upper respiratory tract infection, with prominent rhinitis. On occasion, lower respiratory tract disease, including bronchiolitis and pneumonia, also develops. Adenoviruses, particularly types 3 and 7, cause pharyngoconjunctival fever, a characteristic acute febrile illness of children that occurs in outbreaks, most often in summer camps. The syndrome is marked by bilateral conjunctivitis in which the bulbar and palpebral conjunctivae have a granular appearance. Low-grade fever is frequently present for the first 3–5 days, and rhinitis, sore throat, and cervical adenopathy develop. The illness generally lasts for 1–2 weeks and resolves spontaneously. Febrile pharyngitis without conjunctivitis has also been associated with adenovirus infection. Adenoviruses have been isolated from cases of whooping cough with or without *Bordetella pertussis*; the significance of adenovirus in that disease is unknown.

In adults, the most frequently reported illness has been acute respiratory disease caused by adenovirus types 4 and 7 in military recruits. This illness is marked by a prominent sore throat and the gradual onset of fever, which often reaches 39°C (102.2°F) on the second or third day of illness. Cough is almost always present, and coryza and regional lymphadenopathy are frequently seen. Physical examination may show pharyngeal edema, injection, and tonsillar enlargement with little or no exudate. If pneumonia has developed, auscultation and x-ray of the chest may indicate areas of patchy infiltration.

Adenoviruses have been associated with a number of non–respiratory tract diseases, including acute diarrheal

illness caused by types 40 and 41 in young children and hemorrhagic cystitis caused by types 11 and 21. Epidemic keratoconjunctivitis, caused most frequently by types 8, 19, and 37, has been associated with contaminated common sources such as ophthalmic solutions and roller towels. Adenoviruses have also been implicated in disseminated disease and pneumonia in immunosuppressed patients, including recipients of solid-organ or hematopoietic stem cell transplants. In hematopoietic stem cell transplant recipients, adenovirus infections have been manifested as pneumonia, hepatitis, nephritis, colitis, encephalitis, and hemorrhagic cystitis. In solid-organ transplant recipients, adenovirus infection may involve the organ transplanted (e.g., hepatitis in liver transplants, nephritis in renal transplants) but can disseminate to other organs as well. In patients with AIDS, high-numbered and intermediate adenovirus serotypes have been isolated, usually in the setting of low CD4+ T cell counts, but their isolation often has not been clearly linked to disease manifestations. Adenovirus nucleic acids have been detected in myocardial cells from patients with "idiopathic" myocardiopathies, and adenoviruses have been suggested as causative agents in some cases.

LABORATORY FINDINGS AND DIAGNOSIS

Adenovirus infection should be suspected in the epidemiologic setting of acute respiratory disease in military recruits and in certain of the clinical syndromes (such as pharyngoconjunctival fever or epidemic keratoconjunctivitis) in which outbreaks of characteristic illnesses occur. In most cases, however, illnesses caused by adenovirus infection cannot be differentiated from those caused by a number of other viral respiratory agents and *Mycoplasma pneumoniae*. A definitive diagnosis of adenovirus infection is established by detection of the virus in tissue culture (as evidenced by cytopathic changes) and by specific identification with immunofluorescence or other immunologic techniques. Rapid viral diagnosis can be established by immunofluorescence or ELISA of nasopharyngeal aspirates, conjunctival or respiratory secretions, urine, or stool. Highly sensitive and specific PCR assays and nucleic acid hybridization are also available. Adenovirus types 40 and 41, which have been associated with diarrheal disease in children, require special tissue-culture cells for isolation, and these serotypes are most commonly detected by direct ELISA of stool. Serum antibody rises can be demonstrated by complement-fixation or neutralization tests, ELISA, radioimmunoassay, or (for those adenoviruses that hemagglutinate red cells) hemagglutination inhibition tests.

TREATMENT Adenovirus Infections

Only symptom-based treatment and supportive therapy are available for adenovirus infections, and clinically useful antiviral therapy has not been established. Ribavirin and cidofovir are active in vitro against certain adenoviruses. Retrospective studies and anecdotes describe the use of these agents in disseminated adenovirus infections, but definitive efficacy data from controlled studies are not available.

PREVENTION

Live vaccines have been developed against adenovirus types 4 and 7 and have been used to control illness among military recruits. These vaccines consist of live, unattenuated virus administered in enteric-coated capsules. Infection of the gastrointestinal tract with types 4 and 7 does not cause disease but stimulates local and systemic antibodies that are protective against subsequent acute respiratory disease due to those serotypes. This vaccine has not been produced since 1999, and outbreaks of acute respiratory illness caused by adenovirus types 4 and 7 have again emerged among military recruits. Therefore, a program to redevelop type 4 and 7 vaccines is under way. Adenoviruses are also being studied as live-virus vectors for the delivery of vaccine antigens and for gene therapy.

CHAPTER 92

INFLUENZA

Raphael Dolin

DEFINITION

Influenza is an acute respiratory illness caused by infection with influenza viruses. The illness affects the upper and/or lower respiratory tract and is often accompanied by systemic signs and symptoms such as fever, headache, myalgia, and weakness. Outbreaks of illness of variable extent and severity occur nearly every year. Such outbreaks result in significant morbidity rates in the general population and in increased mortality rates among certain high-risk patients, mainly as a result of pulmonary complications.

ETIOLOGIC AGENT

Influenza viruses are members of the Orthomyxoviridae family, of which influenza A, B, and C viruses constitute three separate genera. The designation of influenza viruses as type A, B, or C is based on antigenic characteristics of the nucleoprotein (NP) and matrix (M) protein antigens. Influenza A viruses are further subdivided (subtyped) on the basis of the surface hemagglutinin (H) and neuraminidase (N) antigens (see later); individual strains are designated according to the site of origin, isolate number, year of isolation, and subtype—for example, influenza A/California/07/2009 (H1N1). Influenza A has 16 distinct H subtypes and 9 distinct N subtypes, of which only H1, H2, H3, N1, and N2 have been associated with epidemics of disease in humans. Influenza B and C viruses are similarly designated, but H and N antigens from these viruses do not receive subtype designations, since intratypic variations in influenza B antigens are less extensive than those in influenza A viruses and may not occur with influenza C virus.

Influenza A and B viruses are major human pathogens and the most extensively studied of the Orthomyxoviridae. Type A and type B viruses are morphologically similar. The virions are irregularly shaped spherical particles, measure 80–120 nm in diameter, and have a lipid envelope from the surface of which the H and N glycoproteins project (Fig. 92-1). The hemagglutinin is the site by which the virus binds to sialic acid cell receptors, whereas the neuraminidase degrades the receptor and plays a role in the release of the virus from infected cells after replication has taken place. Influenza viruses enter cells by receptor-mediated endocytosis, forming a virus-containing endosome. The viral hemagglutinin mediates fusion of the endosomal membrane with the virus envelope, and viral nucleocapsids are subsequently released into the cytoplasm. Immune responses to the H antigen are the major determinants of protection against infection with influenza virus, while those to the N antigen limit viral spread and contribute to reduction of the infection. The lipid envelope of influenza A virus also contains the M proteins M1 and M2, which are involved in stabilization of the lipid envelope and in virus assembly. The virion also contains the NP antigen, which is associated with the viral genome, as well as three polymerase (P) proteins that are essential for transcription and synthesis of viral RNA. Two nonstructural proteins function as an interferon antagonist and posttranscriptional regulator (NS1) and a nuclear export factor (NS2 or NEP).

The genomes of influenza A and B viruses consist of eight single-strand RNA segments, which code for the structural and nonstructural proteins. Because the genome is segmented, the opportunity for gene reassortment during infection is high; reassortment often occurs during infection of cells with more than one influenza A virus.

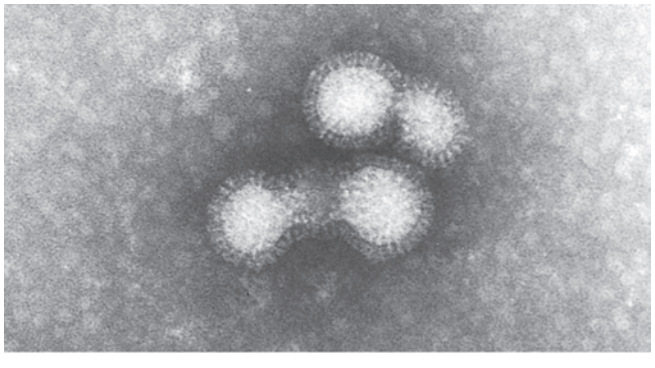


FIGURE 92-1
An electron micrograph of influenza A virus (×40,000).

TABLE 92-1

EMERGENCE OF ANTIGENIC SUBTYPES OF INFLUENZA A VIRUS ASSOCIATED WITH PANDEMIC OR EPIDEMIC DISEASE

YEARS	SUBTYPE	EXTENT OF OUTBREAK
1889–1890	H2N8[a]	Severe pandemic
1900–1903	H3N8[a]	?Moderate epidemic
1918–1919	H1N1[b] (formerly HswN1)	Severe pandemic
1933–1935	H1N1[b] (formerly H0N1)	Mild epidemic
1946–1947	H1N1	Mild epidemic
1957–1958	H2N2	Severe pandemic
1968–1969	H3N2	Moderate pandemic
1977–1978[c]	H1N1	Mild pandemic
2009–2010[d]	H1N1	Pandemic

[a]As determined by retrospective serologic survey of individuals alive during those years ("seroarchaeology").
[b]Hemagglutinins formerly designated as Hsw and H0 are now classified as variants of H1.
[c]From this time until 2008–2009, viruses of the H1N1 and H3N2 subtypes circulated either in alternating years or concurrently.
[d]Novel influenza A/H1N1 emerged to cause this pandemic.

EPIDEMIOLOGY

Influenza outbreaks are recorded virtually every year, although their extent and severity vary widely. Localized outbreaks take place at variable intervals, usually every 1–3 years. Global pandemics have occurred at variable intervals, but much less frequently than interpandemic outbreaks **(Table 92-1)**. The most recent pandemic emerged in March of 2009 and was caused by an influenza A/H1N1 virus that rapidly spread worldwide over the next several months.

Influenza A virus

Antigenic variation and influenza outbreaks and pandemics

The most extensive and severe outbreaks of influenza are caused by influenza A viruses, in part because of the remarkable propensity of the H and N antigens of these viruses to undergo periodic antigenic variation. Major antigenic variations, called *antigenic shifts*, are seen only with influenza A viruses and may be associated with pandemics. Minor variations are called *antigenic drifts*. Antigenic variation may involve the hemagglutinin alone or both the hemagglutinin and the neuraminidase. An example of an antigenic shift involving both the hemagglutinin and the neuraminidase is that of 1957, when the predominant influenza A virus subtype shifted from H1N1 to H2N2; this shift resulted in a severe pandemic, with an estimated 70,000 excess deaths (i.e., deaths in excess of the number expected without an influenza epidemic) in the United States alone. In 1968, an antigenic shift involving only the hemagglutinin occurred (H2N2 to H3N2); the subsequent pandemic was less severe than that of 1957. In 1977, an H1N1 virus emerged and caused a pandemic that primarily affected younger individuals (i.e., those born after 1957). As can be seen in Table 92-1, H1N1 viruses circulated from 1918 to 1956; thus, individuals born prior to 1957 would be expected to have some degree of immunity to H1N1 viruses. The pandemic of 2009–2010 was caused by an A/H1N1 virus against which little immunity was present in the general population, although approximately one-third of individuals born before 1950 had some apparent immunity to related H1N1 strains.

During most outbreaks of influenza A, a single subtype has circulated at a time. However, since 1977, H1N1 and H3N2 viruses have circulated simultaneously, resulting in outbreaks of varying severity. In some outbreaks, influenza B viruses have also circulated simultaneously with influenza A viruses. In 2009–2010, the pandemic A/H1N1 virus appeared to circulate nearly exclusively.

Avian influenza A viruses

In 1997, human cases of influenza caused by avian influenza viruses (A/H5N1) were detected in Hong Kong during an extensive outbreak of influenza in poultry. Between that time and February 2010, 478 cases of avian influenza in humans were reported in Asia and the Middle East. Nearly all of these cases were associated with contact with infected poultry. Efficient person-to-person transmission has not been observed to date. Mortality rates have been high (60%), and clinical manifestations have differed somewhat from those associated with "typical" outbreaks of influenza (see later). Transmission of avian influenza A/H7N7 viruses from infected poultry to humans has been observed, including outbreaks in the Netherlands, which resulted predominantly in cases of conjunctivitis and some respiratory illnesses. Infection with avian A/H9N2 viruses along with mild respiratory illness has been reported in children in Hong Kong. Because of the absence of widespread immunity to the H5, H7, and H9 viruses, concern persists that avian-to-human transmission might also contribute to the emergence of pandemic strains.

The origin of actual pandemic influenza A virus strains has been partially elucidated with molecular virologic techniques. It appears that the pandemic strains of 1957 and 1968 resulted from a genetic reassortment between human viruses and avian viruses with novel surface glycoproteins (H2N2, H3). The pandemic A/H1N1 virus of 2009–2010 was a quadruple reassortant among swine influenza viruses that circulated in North America and Eurasia, an avian virus, and a human influenza virus. The influenza A/H1N1 virus responsible for the most severe pandemic of modern times (1918–1919) appears to have represented an adaptation of an avian virus to efficient infection of humans.

Features of pandemic and interpandemic influenza A

Pandemics provide the most dramatic evidence of the impact of influenza A. However, illnesses occurring between pandemics (interpandemic disease) also account for extensive mortality and morbidity rates, albeit over a longer period. In the United States, influenza was associated with at least 19,000 excess deaths per season in 1976–1990 and with 36,000 excess deaths per season in 1990–1999. On average, there were 226,000 influenza-associated hospitalizations per year in this country in 1979–2001.

Influenza A viruses that circulate between pandemics demonstrate antigenic drifts in the H antigen. These antigenic drifts result from point mutations involving the RNA segment that codes for the hemagglutinin, which occur most frequently in five hypervariable regions. Epidemiologically significant strains—that is, those with the potential to cause widespread outbreaks—exhibit changes in amino acids in at least two of the major antigenic sites in the hemagglutinin molecule. Since two point mutations are unlikely to occur simultaneously, it is believed that antigenic drifts result from point mutations occurring sequentially during the spread of virus from person to person. Antigenic drifts have been reported nearly annually since 1977 for H1N1 viruses and since 1968 for H3N2 viruses.

Interpandemic influenza A outbreaks usually begin abruptly, peak over a 2- to 3-week period, generally last for 2–3 months, and often subside almost as rapidly as they began. In contrast, pandemic influenza may begin with rapid transmission at multiple locations, have high attack rates, and extend beyond the usual seasonality, with multiple waves of attack before or after the main outbreak. In interpandemic outbreaks, the first indication of influenza activity is an increase in the number of children with febrile respiratory illnesses who present for medical attention. This increase is followed by increases in rates of influenza-like illnesses among adults and eventually by an increase in hospital admissions for patients with pneumonia, worsening of congestive heart failure, and exacerbations of chronic pulmonary disease. Rates of absence from work and school also rise at this time. An increase in the number of deaths caused by pneumonia and influenza is generally a late observation in an outbreak. Attack rates have been highly variable from outbreak to outbreak in interpandemic influenza but most commonly are in the range of 10–20% of the general population.

While pandemic influenza may occur throughout the year, interpandemic influenza occurs almost exclusively during the winter months in the temperate zones of the Northern and Southern hemispheres. In those locations, it is highly unusual to detect influenza A virus at other times, although rises in serum antibody titer or even outbreaks have been noted rarely during warm-weather months. In contrast, influenza virus infections occur throughout the year in the tropics. Where or how influenza A viruses persist between outbreaks in temperate zones is unknown. It is possible that the viruses are maintained in the human population on a worldwide basis by person-to-person transmission and that large population clusters support a low level of interepidemic transmission. Alternatively, human strains may persist in animal reservoirs. Convincing evidence to support either explanation is not available. In the modern era, rapid transportation may contribute to the transmission of viruses among widespread geographic locales.

The factors that result in the inception and termination of outbreaks of influenza A are incompletely understood. A major determinant of the extent and severity of an outbreak is the level of immunity in the population at risk. With the emergence of an antigenically novel influenza virus to which little or no immunity is present in a community, extensive outbreaks may occur. When the absence of immunity is worldwide, epidemic disease may spread around the globe, resulting in a pandemic. Such pandemic waves can continue for several years, until immunity in the population reaches a high level. In the years following pandemic influenza, antigenic drifts among influenza viruses result in outbreaks of variable severity in populations with high levels of immunity to the pandemic strain that circulated earlier. This situation persists until another antigenically novel pandemic strain emerges. On the other hand, outbreaks sometimes end despite the persistence of a large pool of susceptible individuals in the population. It has been suggested that certain influenza A viruses may be intrinsically less virulent and cause less severe disease than other variants, even in immunologically virgin subjects. If so, then other (undefined) factors besides the level of preexisting immunity must play a role in the epidemiology of influenza.

Influenza B and C viruses

Influenza B virus causes outbreaks that are generally less extensive and are associated with less severe disease than those caused by influenza A virus. The hemagglutinin and neuraminidase of influenza B virus undergo less frequent and less extensive variation than those of influenza A viruses; this characteristic may account, in part, for the lesser extent of disease. Influenza B outbreaks are seen most frequently in schools and military camps, although outbreaks in institutions in which elderly individuals reside have also been noted on occasion. The most serious complication of influenza B virus infection is Reye's syndrome.

In contrast to influenza A and B viruses, influenza C virus appears to be a relatively minor cause of disease in humans. It has been associated with common cold–like symptoms and occasionally with lower respiratory tract illness. The widespread prevalence of serum antibody to this virus indicates that asymptomatic infection may be common.

Influenza-associated morbidity and mortality rates

The morbidity and mortality rates caused by influenza outbreaks continue to be substantial. Most individuals who die in this setting have underlying diseases that

TABLE 92-2

PERSONS AT HIGHER RISK FOR COMPLICATIONS OF INFLUENZA
Children from birth to 4 years old
Pregnant women
Persons ≥65 years old
Children and adolescents (6 months to 18 years old) who are receiving long-term aspirin therapy and therefore may be at risk for developing Reye's syndrome after influenza
Adults and children who have chronic disorders of the pulmonary or cardiovascular system, including asthma
Adults and children who have chronic metabolic diseases (including diabetes mellitus), renal dysfunction, hemoglobinopathies, or immunodeficiency (including immunodeficiency caused by medications or by HIV)
Adults and children who have any condition that can compromise respiratory function or compromise the handling of respiratory secretions or can increase the risk of aspiration
Residents of nursing homes and other chronic-care facilities that house persons of any age who have chronic medical conditions

place them at high risk for complications of influenza (Table 92-2). Excess annual hospitalizations for groups of adults and children with high-risk medical conditions ranged from 40 to 1900 per 100,000 during outbreaks of influenza in 1973–2004. The most prominent high-risk conditions are chronic cardiac and pulmonary diseases and old age. Mortality rates among individuals with chronic metabolic or renal diseases or certain immunosuppressive diseases have also been elevated, albeit lower than those among patients with chronic cardiopulmonary diseases. In the pandemic of 2009–2010, increased risk for severe disease was noted in children from birth to 4 years of age and in pregnant women. The morbidity rate attributable to influenza in the general population is considerable. It is estimated that interpandemic outbreaks of influenza currently incur annual economic costs of more than $87 billion in the United States. For pandemics, it is estimated that annual economic costs would range from $89.7 to $209.4 billion for attack rates of 15–35%.

PATHOGENESIS AND IMMUNITY

The initial event in influenza is infection of the respiratory epithelium with influenza virus acquired from respiratory secretions of acutely infected individuals. In all likelihood, the virus is transmitted via aerosols generated by coughs and sneezes, although hand-to-hand contact, other personal contact, and even fomite transmission may take place. Experimental evidence suggests that infection by a small-particle aerosol (particle diameter, <10 μm) is more efficient than that by larger droplets. Initially, viral infection involves the ciliated columnar epithelial cells, but it may also involve other respiratory tract cells, including alveolar cells, mucous gland cells, and macrophages. In infected cells, virus replicates within 4–6 h, after which infectious virus is released to infect adjacent or nearby cells. In this way, infection spreads from a few foci to a large number of respiratory cells over several hours. In experimentally induced infection, the incubation period of illness has ranged from 18 to 72 h, depending on the size of the viral inoculum. Histopathologic study reveals degenerative changes, including granulation, vacuolization, swelling, and pyknotic nuclei, in infected ciliated cells. The cells eventually become necrotic and desquamate; in some areas, previously columnar epithelium is replaced by flattened and metaplastic epithelial cells. The severity of illness is correlated with the quantity of virus shed in secretions; thus, the degree of viral replication itself may be an important factor in pathogenesis. Despite the frequent development of systemic signs and symptoms such as fever, headache, and myalgias, influenza virus has only rarely been detected in extrapulmonary sites (including the bloodstream). Evidence suggests that the pathogenesis of systemic symptoms in influenza may be related to the induction of certain cytokines, particularly tumor necrosis factor α, interferon α, interleukin 6, and interleukin 8, in respiratory secretions and in the bloodstream.

The host response to influenza infections involves a complex interplay of humoral antibody, local antibody, cell-mediated immunity, interferon, and other host defenses. Serum antibody responses, which can be detected by the second week after primary infection, are measured by a variety of techniques: hemagglutination inhibition (HI), complement fixation (CF), neutralization, enzyme-linked immunosorbent assay (ELISA), and antineuraminidase antibody assay. Antibodies to the hemagglutinin appear to be the most important mediators of immunity; in several studies, HI titers of ≥40 have been associated with protection from infection. Secretory antibodies produced in the respiratory tract are predominantly of the IgA class and also play a major role in protection against infection. Secretory antibody neutralization titers of ≥4 have also been associated with protection. A variety of cell-mediated immune responses, both antigen-specific and antigen-nonspecific, can be detected early after infection and depend on the prior immune status of the host. These responses include T cell proliferative, T cell cytotoxic, and natural killer cell activity. In humans, CD8+ human leukocyte antigen class I–restricted cytotoxic T lymphocytes (CTLs) are directed at conserved regions of internal proteins (NP, M, and P) as well as at the surface proteins H and N. Interferons can be detected in respiratory secretions shortly after the shedding of virus has begun, and rises in interferon titers coincide with decreases in virus shedding.

The host defense factors responsible for cessation of virus shedding and resolution of illness have not been defined specifically. Virus shedding generally stops within 2–5 days after symptoms first appear, at a time when serum and local antibody responses often are not detectable by conventional techniques (although

antibody rises may be detected earlier by use of highly sensitive techniques, particularly in individuals with previous immunity to the virus). It has been suggested that interferon, cell-mediated immune responses, and/or nonspecific inflammatory responses all contribute to the resolution of illness. CTL responses may be particularly important in this regard.

CLINICAL MANIFESTATIONS

Influenza has most frequently been described as an illness characterized by the abrupt onset of systemic symptoms, such as headache, feverishness, chills, myalgia, and malaise, as well as accompanying respiratory tract signs, particularly cough and sore throat. In many cases, the onset is so abrupt that patients can recall the precise time they became ill. However, the spectrum of clinical presentations is wide, ranging from a mild, afebrile respiratory illness similar to the common cold (with either a gradual or an abrupt onset) to severe prostration with relatively few respiratory signs and symptoms. In most of the cases that come to a physician's attention, the patient has a fever, with temperatures of 38°–41°C (100.4°–105.8°F). A rapid temperature rise within the first 24 h of illness is generally followed by gradual defervescence over 2–3 days, although, on occasion, fever may last as long as 1 week. Patients report a feverish feeling and chilliness, but true rigors are rare. Headache, either generalized or frontal, is often particularly troublesome. Myalgias may involve any part of the body but are most common in the legs and lumbosacral area. Arthralgias may also develop.

Respiratory symptoms often become more prominent as systemic symptoms subside. Many patients have a sore throat or persistent cough, which may last for ≥1 week and which is often accompanied by substernal discomfort. Ocular signs and symptoms include pain on motion of the eyes, photophobia, and burning of the eyes.

Physical findings are usually minimal in uncomplicated influenza. Early in the illness, the patient appears flushed and the skin is hot and dry, although diaphoresis and mottled extremities are sometimes evident, particularly in older patients. Examination of the pharynx may yield surprisingly unremarkable results despite a severe sore throat, but injection of the mucous membranes and postnasal discharge are apparent in some cases. Mild cervical lymphadenopathy may be noted, especially in younger individuals. The results of chest examination are largely negative in uncomplicated influenza, although rhonchi, wheezes, and scattered rales have been reported with variable frequency in different outbreaks. Frank dyspnea, hyperpnea, cyanosis, diffuse rales, and signs of consolidation are indicative of pulmonary complications. Patients with apparently uncomplicated influenza have been reported to have a variety of mild ventilatory defects and increased alveolar-capillary diffusion gradients; thus, subclinical pulmonary involvement may be more common than is appreciated.

In uncomplicated influenza, the acute illness generally resolves over 2–5 days, and most patients have largely recovered in 1 week, although cough may persist 1–2 weeks longer. In a significant minority (particularly the elderly), however, symptoms of weakness or lassitude (postinfluenza asthenia) may persist for several weeks and may prove troublesome for persons who wish to resume their full level of activity promptly. The pathogenetic basis for this asthenia is unknown, although pulmonary function abnormalities may persist for several weeks after uncomplicated influenza.

COMPLICATIONS

Complications of influenza (Table 92-2) occur most frequently in patients >65 years old and in those with certain chronic disorders, including cardiac or pulmonary diseases, diabetes mellitus, hemoglobinopathies, renal dysfunction, and immunosuppression. Pregnancy in the second or third trimester predisposes to complications with influenza. Children <5 years old (especially infants) are also at high risk for complications.

Pulmonary complications

Pneumonia

The most significant complication of influenza is pneumonia: "primary" influenza viral pneumonia, secondary bacterial pneumonia, or mixed viral and bacterial pneumonia.

Primary influenza viral pneumonia

Primary influenza viral pneumonia is the least common but most severe of the pneumonic complications. It presents as acute influenza that does not resolve but instead progresses relentlessly, with persistent fever, dyspnea, and eventual cyanosis. Sputum production is generally scanty, but the sputum can contain blood. Few physical signs may be evident early in the illness. In more advanced cases, diffuse rales may be noted, and chest x-ray findings consistent with diffuse interstitial infiltrates and/or acute respiratory distress syndrome may be present. In such cases, arterial blood-gas determinations show marked hypoxia. Viral cultures of respiratory secretions and lung parenchyma, especially if samples are taken early in illness, yield high titers of virus. In fatal cases of primary viral pneumonia, histopathologic examination reveals a marked inflammatory reaction in the alveolar septa, with edema and infiltration by lymphocytes, macrophages, occasional plasma cells, and variable numbers of neutrophils. Fibrin thrombi in alveolar capillaries, along with necrosis and hemorrhage, have also been noted. Eosinophilic hyaline membranes can be found lining alveoli and alveolar ducts.

Primary influenza viral pneumonia has a predilection for individuals with cardiac disease, particularly those with mitral stenosis, but has also been reported in otherwise-healthy young adults as well as in older individuals with chronic pulmonary disorders. In some pandemics of influenza (notably those of 1918 and 1957),

pregnancy increased the risk of primary influenza pneumonia. Subsequent epidemics of influenza have been associated with increased rates of hospitalization among pregnant women, which were also noted in the pandemic of 2009–2010.

Secondary bacterial pneumonia

Secondary bacterial pneumonia follows acute influenza. Improvement of the patient's condition over 2–3 days is followed by a reappearance of fever along with clinical signs and symptoms of bacterial pneumonia, including cough, production of purulent sputum, and physical and x-ray signs of consolidation. The most common bacterial pathogens in this setting are *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Haemophilus influenzae*—organisms that can colonize the nasopharynx and that cause infection in the wake of changes in bronchopulmonary defenses. The etiology can often be determined by Gram's staining and culture of an appropriately obtained sputum specimen. Secondary bacterial pneumonia occurs most frequently in high-risk individuals with chronic pulmonary and cardiac disease and in elderly individuals. Patients with secondary bacterial pneumonia often respond to antibiotic therapy when it is instituted promptly.

Mixed viral and bacterial pneumonia

Perhaps the most common pneumonic complications during outbreaks of influenza have mixed features of viral and bacterial pneumonia. Patients may experience a gradual progression of their acute illness or may show transient improvement followed by clinical exacerbation, with eventual manifestation of the clinical features of bacterial pneumonia. Sputum cultures may contain both influenza A virus and one of the bacterial pathogens described earlier. Patchy infiltrates or areas of consolidation may be detected by physical examination and chest x-ray. Patients with mixed viral and bacterial pneumonia generally have less widespread involvement of the lung than those with primary viral pneumonia, and their bacterial infections may respond to appropriate antibacterial drugs. Mixed viral and bacterial pneumonia occurs primarily in patients with chronic cardiovascular and pulmonary diseases.

Other pulmonary complications

Other pulmonary complications associated with influenza include worsening of chronic obstructive pulmonary disease and exacerbation of chronic bronchitis and asthma. In children, influenza infection may present as croup. Sinusitis as well as otitis media (the latter occurring particularly often in children) may also be associated with influenza.

Extrapulmonary complications

In addition to the pulmonary complications of influenza, a number of extrapulmonary complications may occur. These include *Reye's syndrome*, a serious complication in children that is associated with influenza B and to a lesser extent with influenza A virus infection as well as with varicella-zoster virus infection. An epidemiologic association between Reye's syndrome and aspirin therapy for the antecedent viral infection has been noted, and the syndrome's incidence has decreased markedly with widespread warnings regarding aspirin use by children with acute viral respiratory infections.

Myositis, rhabdomyolysis, and myoglobinuria are occasional complications of influenza infection. Although myalgias are exceedingly common in influenza, true myositis is rare. Patients with acute myositis have exquisite tenderness of the affected muscles, most commonly in the legs, and may not be able to tolerate even the slightest pressure, such as the touch of bedsheets. In the most severe cases, there is frank swelling and bogginess of muscles. Serum levels of creatine phosphokinase and aldolase are markedly elevated, and an occasional patient develops renal failure from myoglobinuria. The pathogenesis of influenza-associated myositis is also unclear, although the presence of influenza virus in affected muscles has been reported.

Myocarditis and pericarditis were reported in association with influenza virus infection during the 1918–1919 pandemic; these reports were based largely on histopathologic findings, and these complications have been reported only infrequently since that time. Electrocardiographic changes during acute influenza are common among patients who have cardiac disease but have been ascribed most often to exacerbations of the underlying cardiac disease rather than to direct involvement of the myocardium with influenza virus.

Central nervous system (CNS) diseases, including encephalitis, transverse myelitis, and Guillain-Barré syndrome, have been reported during influenza. The etiologic relationship of influenza virus to such CNS illnesses remains uncertain. Toxic shock syndrome associated with *S. aureus* or group A streptococcal infection following acute influenza infection has also been reported (Chaps. 38 and 39).

In addition to complications involving the specific organ systems described earlier, influenza outbreaks include a number of cases in which elderly and other high-risk individuals develop influenza and subsequently experience a gradual deterioration of underlying cardiovascular, pulmonary, or renal function—changes that occasionally are irreversible and lead to death. These deaths contribute to the overall excess mortality rate associated with influenza A outbreaks.

Complications of avian influenza

Cases of influenza caused by avian A/H5N1 virus are reportedly associated with high rates of pneumonia (>50%) and extrapulmonary manifestations such as diarrhea and CNS involvement. Deaths have been associated with multisystem dysfunction, including cardiac and renal failure.

LABORATORY FINDINGS AND DIAGNOSIS

During acute influenza, virus may be detected in throat swabs, nasopharyngeal swabs or washes, or sputum. The virus can be isolated by use of tissue culture—or,

less commonly, chick embryos—within 48–72 h after inoculation. Most commonly, the laboratory diagnosis is established with rapid tests that detect viral antigens by means of immunologic or enzymatic techniques. The tests are relatively specific but are of variable sensitivity depending on the technique and the virus to be detected. Some rapid tests can distinguish between influenza A and B viruses, but detection of differences in hemagglutinin subtypes requires additional subtype-specific immunologic techniques. The most sensitive and specific in vitro test for influenza virus is reverse-transcriptase polymerase chain reaction; this test proved particularly important in detecting the 2009–2010 pandemic A/H1N1 viruses, for which some rapid antigen detection tests were poorly sensitive. Serologic methods for diagnosis require comparison of antibody titers in sera obtained during the acute illness with those in sera obtained 10–14 days after the onset of illness and are useful primarily in retrospect. Fourfold or greater titer rises as detected by HI or CF or significant rises as measured by ELISA are diagnostic of acute infection. Other laboratory tests generally are not helpful in the specific diagnosis of influenza virus infection. Leukocyte counts are variable, frequently being low early in illness and normal or slightly elevated later. Severe leukopenia has been described in overwhelming viral or bacterial infection, while leukocytosis with >15,000 cells/μL raises the suspicion of secondary bacterial infection.

DIFFERENTIAL DIAGNOSIS

During a community-wide outbreak, a clinical diagnosis of influenza can be made with a high degree of certainty in patients who present to a physician's office with the typical febrile respiratory illness described earlier. In the absence of an outbreak (i.e., in sporadic or isolated cases), influenza may be difficult to differentiate on clinical grounds alone from an acute respiratory illness caused by any of a variety of respiratory viruses or by *Mycoplasma pneumoniae*. Severe streptococcal pharyngitis or early bacterial pneumonia may mimic acute influenza, although bacterial pneumonias generally do not run a self-limited course. Purulent sputum in which a bacterial pathogen can be detected by Gram's staining is an important diagnostic feature in bacterial pneumonia.

TREATMENT Influenza

Specific antiviral therapy is available for influenza (Table 92-3): the neuraminidase inhibitors zanamivir, oseltamivir, and peramivir for both influenza A and influenza B and the adamantane agents amantadine and rimantadine for influenza A (Chap. 83). A 5-day course of oseltamivir or zanamivir reduces the duration of signs and symptoms of uncomplicated

TABLE 92-3

ANTIVIRAL MEDICATIONS FOR TREATMENT AND PROPHYLAXIS OF INFLUENZA

	AGE GROUP (YEARS)		
ANTIVIRAL DRUG	**CHILDREN (≤12)**	**13–64**	**≥65**
Oseltamivir			
Treatment, influenza A and B	Age 1–12, dose varies by weight[a]	75 mg PO bid	75 mg PO bid
Prophylaxis, influenza A and B	Age 1–12, dose varies by weight[b]	75 PO qd	75 mg PO qd
Zanamivir			
Treatment, influenza A and B	Age 7–12, 10 mg bid by inhalation	10 mg bid by inhalation	10 mg bid by inhalation
Prophylaxis, influenza A and B	Age 5–12, 10 mg qd by inhalation	10 mg qd by inhalation	10 mg qd by inhalation
Amantadine[c]			
Treatment, influenza A	Age 1–9, 5 mg/kg in 2 divided doses, up to 150 mg/d	Age ≥10, 100 mg PO bid	≤100 mg/d
Prophylaxis, influenza A	Age 1–9, 5 mg/kg in 2 divided doses, up to 150 mg/d	Age ≥10, 100 mg PO bid	≤100 mg/d
Rimantadine[c]			
Treatment, influenza A	Not approved	100 mg PO bid	100–200 mg/d
Prophylaxis, influenza A	Age 1–9, 5 mg/kg in 2 divided doses, up to 150 mg/d	Age ≥10, 100 mg PO bid	100–200 mg/d

[a]<15 kg: 30 mg bid; >15–23 kg: 45 mg bid; >23–40 kg: 60 mg bid; >40 kg: 75 mg bid. For children <1 year of age, see *www.cdc.gov/h1n1flu/recommendations.htm*.

[b]<15 kg: 30 mg qd; >15–23 kg: 45 mg qd; >23–40 kg: 60 mg qd; >40 kg: 75 mg qd. For children <1 year of age, see *www.cdc.gov/h1n1flu/recommendations.htm*.

[c]Amantadine and rimantadine are not currently recommended (2009–2010) because of widespread resistance in influenza A viruses. Their use may be reconsidered if viral susceptibility is reestablished.

influenza by 1–1.5 days if treatment is started within 2 days of the onset of illness. Zanamivir may exacerbate bronchospasm in asthmatic patients, and oseltamivir has been associated with nausea and vomiting, whose frequency can be reduced by administration of the drug with food. Oseltamivir has also been associated with neuropsychiatric side effects in children. Peramivir, an investigational neuraminidase inhibitor that can be administered intravenously, is being evaluated in clinical trials, as is an intravenous form of zanamivir. Access to these medications can be sought through the FDA's Emergency Investigational New Drug (E-IND) application procedures.

Amantadine or rimantadine treatment of illness caused by sensitive strains of influenza A virus similarly reduces the duration of symptoms of uncomplicated influenza by ~50% if begun within 48 h of onset of illness. Five to 10% of amantadine recipients experience mild CNS side effects, primarily jitteriness, anxiety, insomnia, or difficulty concentrating. These side effects disappear promptly upon cessation of therapy. Rimantadine appears to be equally efficacious and is associated with less frequent CNS side effects than is amantadine. In adults, the usual dose of amantadine or rimantadine is 200 mg/d for 3–7 days. Since both drugs are excreted via the kidney, the dose should be reduced to ≤100 mg/d in elderly patients and in patients with renal insufficiency.

The epidemiologic patterns of resistance to the influenza antiviral drugs are crucial elements in agent selection. Since 2005–2006, the vast majority of A/H3N2 viruses, including >90% of U.S. isolates, have been resistant to the adamantanes but have remained sensitive to neuraminidase inhibitors. In contrast, the seasonal A/H1N1 viruses that circulated in 2008–2009 remained sensitive to the adamantanes but were resistant to oseltamivir (although still sensitive to zanamivir). The pandemic A/H1N1 viruses that circulated in 2009–2010 were resistant to the adamantanes but sensitive to zanamivir and usually to oseltamivir; a few oseltamivir-resistant isolates were identified. Up-to-date information on patterns of resistance to influenza antiviral drugs is available through *www.cdc.gov/flu*.

Ribavirin is a nucleoside analogue with activity against influenza A and B viruses in vitro. It has been reported to be variably effective against influenza when administered as an aerosol but ineffective when administered orally. Its efficacy in the treatment of influenza A or B has not been established.

The therapeutic efficacy of antiviral compounds in influenza has been demonstrated primarily in studies of young adults with uncomplicated disease. The effectiveness of these drugs in the treatment or prevention of complications of influenza is unclear. Pooled analyses of observational investigations and some efficacy studies have suggested that treatment with oseltamivir may reduce the frequency of lower respiratory complications and hospitalization. Therapy for primary influenza pneumonia is directed at maintaining oxygenation and is most appropriately undertaken in an intensive care unit, with aggressive respiratory and hemodynamic support as needed.

Antibacterial drugs should be reserved for the treatment of bacterial complications of acute influenza, such as secondary bacterial pneumonia. The choice of antibiotics should be guided by Gram's staining and culture of appropriate specimens of respiratory secretions, such as sputum. If the etiology of a case of bacterial pneumonia is unclear from an examination of respiratory secretions, empirical antibiotics effective against the most common bacterial pathogens in this setting (*S. pneumoniae*, *S. aureus*, and *H. influenzae*) should be selected (Chaps. 37, 38, and 50).

For uncomplicated influenza in individuals at low risk for complications, symptom-based rather than antiviral therapy may be considered. Acetaminophen or nonsteroidal anti-inflammatory agents can be used for relief of headache, myalgia, and fever, but salicylates should be avoided in children <18 years of age because of the possible association with Reye's syndrome. Since cough is ordinarily self-limited, treatment with cough suppressants generally is not indicated; codeine-containing compounds may be employed if the cough is particularly troublesome. Patients should be advised to rest and maintain hydration during acute illness and to return to full activity only gradually after illness has resolved, especially if it has been severe.

PROPHYLAXIS

The major public health measure for prevention of influenza is vaccination. Both inactivated (killed) and live attenuated vaccines are available and are generated from influenza A and B virus isolates that circulated in the previous influenza seasons and are anticipated to circulate in the upcoming season. For inactivated vaccines, 50–80% protection against influenza is expected if the vaccine virus and the currently circulating viruses are closely related. Available inactivated vaccines have been highly purified and are associated with few reactions. Up to 5% of individuals experience low-grade fever and mild systemic symptoms 8–24 h after vaccination, and up to one-third develop mild redness or tenderness at the vaccination site. Since the vaccine used in the United States and many other countries is produced in eggs, individuals with true hypersensitivity to egg products either should be desensitized or should not be vaccinated. Although the 1976 swine influenza vaccine appears to have been associated with an increased frequency of Guillain-Barré syndrome, influenza vaccines administered since 1976 generally have not been. Possible exceptions were noted during the 1992–1993 and 1993–1994 influenza seasons, when there may have been an excess risk of Guillain-Barré syndrome of slightly more than 1 case per million vaccine recipients. However, the overall health risk following influenza outweighs the potential risk associated with vaccination.

A live attenuated influenza vaccine administered by intranasal spray is available. The vaccine is generated by reassortment between currently circulating strains

of influenza A and B virus and a cold-adapted, attenuated master strain. The cold-adapted vaccine is well tolerated and highly efficacious (>90% protective) in young children; in one study, it provided protection against a circulating influenza virus that had drifted antigenically away from the vaccine strain. Live attenuated vaccine is approved for use in healthy nonpregnant persons 2–49 years of age.

Historically, the U.S. Public Health Service has recommended influenza vaccination for certain groups at high risk for complications of influenza on the basis of age or underlying disease or for their close contacts (Table 92-2). While such individuals will continue to be the focus of vaccination programs, the recommendations have been progressively expanded. In 2009–2010, immunization of all children 6 months to 18 years of age was recommended; for 2010–2011, recommendations are for immunization of the entire population above the age of 6 months, including adults. This expanded recommendation reflects increased recognition of previously unappreciated risk factors, including obesity, postpartum conditions, and racial or ethnic influences, as well as an appreciation that more widespread use of vaccine is required for influenza control. Inactivated vaccines may be administered safely to immunocompromised patients. Influenza vaccination is not associated with exacerbations of chronic nervous-system diseases such as multiple sclerosis. Vaccine should be administered early in the autumn before influenza outbreaks occur and should then be given annually to maintain immunity against the most current influenza virus strains.

Although antiviral drugs provide chemoprophylaxis against influenza, their use for that purpose has been limited because of concern about current patterns and further development of resistance. Chemoprophylaxis with oseltamivir or zanamivir has been 84–89% efficacious against influenza A and B (Table 92-3). Chemoprophylaxis with amantadine or rimantadine is no longer recommended because of widespread resistance to these drugs. In earlier studies with sensitive viruses, prophylaxis with amantadine or rimantadine (100–200 mg/d) was 70–100% effective against illness associated with influenza A.

Chemoprophylaxis for healthy persons after community exposure generally is not recommended but may be considered for individuals at high risk of complications who have had close contact with an acutely ill person with influenza. During an outbreak, antiviral chemoprophylaxis can be administered simultaneously with inactivated vaccine, since the drugs do not interfere with an immune response to the vaccine. However, concurrent administration of chemoprophylaxis and live attenuated vaccine may interfere with the immune response to the latter. Antiviral drugs should not be administered until at least 2 weeks after administration of live vaccine, and administration of live vaccine should not begin until at least 48 h after antiviral drug administration has been stopped. Chemoprophylaxis may also be considered to control nosocomial outbreaks of influenza. For that purpose, prophylaxis should be instituted promptly when influenza activity is detected and must be continued daily for the duration of the outbreak.

CHAPTER 93

HUMAN IMMUNODEFICIENCY VIRUS DISEASE: AIDS AND RELATED DISORDERS

Anthony S. Fauci ■ H. Clifford Lane

AIDS was first recognized in the United States in the summer of 1981, when the U.S. Centers for Disease Control and Prevention (CDC) reported the unexplained occurrence of *Pneumocystis jiroveci* (formerly *P. carinii*) pneumonia in five previously healthy homosexual men in Los Angeles and of Kaposi's sarcoma (KS) with or without *P. jiroveci* pneumonia in 26 previously healthy homosexual men in New York and Los Angeles. The disease was soon recognized in male and female injection drug users; in hemophiliacs and blood transfusion recipients; among female sexual partners of men with AIDS; and among infants born to mothers with AIDS or with a history of injection drug use. In 1983, human immunodeficiency virus (HIV) was isolated from a patient with lymphadenopathy, and by 1984 it was demonstrated clearly to be the causative agent of AIDS. In 1985, a sensitive enzyme-linked immunosorbent assay (ELISA) was developed; this led to an appreciation of the scope and evolution of the HIV epidemic at first in the United States and other developed nations and ultimately among developing nations throughout the world (see "HIV Infection and AIDS Worldwide" later in the chapter). The staggering worldwide evolution of the HIV pandemic has been matched by an explosion of information in the areas of HIV virology, pathogenesis (both immunologic and virologic), treatment of HIV disease, treatment and prophylaxis of the opportunistic diseases associated with HIV infection, prevention of infection, and vaccine development. The information flow related to HIV disease is enormous and continues to expand, and it has become almost impossible for the health care generalist to stay abreast of the literature. The purpose of this chapter is to present the most current information available on the scope of the epidemic; on its pathogenesis, treatment, and prevention; and on prospects for vaccine development. Above all, the aim is to provide a solid scientific basis and practical clinical guidelines for a state-of-the-art approach to the HIV-infected patient.

DEFINITION

The current CDC classification system for HIV-infected adolescents and adults categorizes persons on the basis of clinical conditions associated with HIV infection and CD4+ T lymphocyte counts. The system is based on three ranges of CD4+ T lymphocyte counts and three clinical categories and is represented by a matrix of nine mutually exclusive categories **(Tables 93-1 and 93-2)**. Using this system, any HIV-infected individual with a CD4+ T cell count of <200/μL has AIDS by definition, regardless of the presence of symptoms or opportunistic diseases (Table 93-1). Once individuals have had a clinical condition in category B, their disease classification cannot be reverted back to category A, even if the condition resolves; the same holds true for category C in relation to category B.

The definition of AIDS is indeed complex and comprehensive and was established not for the practical care of patients, but for surveillance purposes. Thus, the clinician should not focus on whether the patient fulfills the strict definition of AIDS but should view HIV disease

TABLE 93-1

1993 REVISED CLASSIFICATION SYSTEM FOR HIV INFECTION AND EXPANDED AIDS SURVEILLANCE CASE DEFINITION FOR ADOLESCENTS AND ADULTS

	CLINICAL CATEGORIES		
CD4+ T CELL CATEGORIES	A ASYMPTOMATIC, ACUTE (PRIMARY) HIV OR PGL	B SYMPTOMATIC, NOT A OR C CONDITIONS	C AIDS-INDICATOR CONDITIONS
>500/μL	A1	B1	C1
200–499/μL	A2	B2	C2
<200/μL	A3	B3	C3

Abbreviations: PGL, progressive generalized lymphadenopathy.
Source: MMWR 42(No. RR-17), December 18, 1992.

TABLE 93-2

CLINICAL CATEGORIES OF HIV INFECTION

Category A: Consists of one or more of the conditions listed below in an adolescent or adult (>13 years) with documented HIV infection. Conditions listed in categories B and C must not have occurred.
- Asymptomatic HIV infection
- Persistent generalized lymphadenopathy
- Acute (primary) HIV infection with accompanying illness or history of acute HIV infection

Category B: Consists of symptomatic conditions in an HIV-infected adolescent or adult that are not included among conditions listed in clinical category C and that meet at least one of the following criteria: (1) The conditions are attributed to HIV infection or are indicative of a defect in cell-mediated immunity; or (2) the conditions are considered by physicians to have a clinical course or to require management that is complicated by HIV infection. Examples include, but are not limited to, the following:
- Bacillary angiomatosis
- Candidiasis, oropharyngeal (thrush)
- Candidiasis, vulvovaginal; persistent, frequent, or poorly responsive to therapy
- Cervical dysplasia (moderate or severe)/cervical carcinoma in situ
- Constitutional symptoms, such as fever (38.5°C) or diarrhea lasting >1 month
- Hairy leukoplakia, oral
- Herpes zoster (shingles), involving at least two distinct episodes or more than one dermatome
- Idiopathic thrombocytopenic purpura
- Listeriosis
- Pelvic inflammatory disease, particularly if complicated by tuboovarian abscess
- Peripheral neuropathy

Category C: Conditions listed in the AIDS surveillance case definition
- Candidiasis of bronchi, trachea, or lungs
- Candidiasis, esophageal
- Cervical cancer, invasive[a]
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (>1 month's duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes)
- Cytomegalovirus retinitis (with loss of vision)
- Encephalopathy, HIV-related
- Herpes simplex: chronic ulcer(s) (>1 month's duration); or bronchitis, pneumonia, or esophagitis
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (>1 month's duration)
- Kaposi's sarcoma
- Lymphoma, Burkitt's (or equivalent term)
- Lymphoma, primary, of brain
- *Mycobacterium avium* complex or *M. kansasii*, disseminated or extrapulmonary
- *Mycobacterium tuberculosis*, any site (pulmonary[a] or extrapulmonary)
- *Mycobacterium*, other species or unidentified species, disseminated or extrapulmonary
- *Pneumocystis jiroveci* pneumonia
- Pneumonia, recurrent[a]
- Progressive multifocal leukoencephalopathy
- *Salmonella* septicemia, recurrent
- Toxoplasmosis of brain
- Wasting syndrome due to HIV

[a]Added in the 1993 expansion of the AIDS surveillance case definition.
Source: MMWR 42(No. RR-17), December 18, 1992.

as a spectrum ranging from primary infection, with or without the acute syndrome, to the asymptomatic stage, to advanced stages associated with opportunistic diseases (see "Pathophysiology and Pathogenesis," later in the chapter).

ETIOLOGIC AGENT

HIV is the etiologic agent of AIDS; it belongs to the family of human retroviruses (Retroviridae) and the subfamily of lentiviruses. Nononcogenic lentiviruses cause disease in other animal species, including sheep, horses, goats, cattle, cats, and monkeys. The four retroviruses known to cause human disease belong to two distinct groups: the human T lymphotropic viruses (HTLV)-I and HTLV-II, which are transforming retroviruses; and the human immunodeficiency viruses, HIV-1 and HIV-2, which cause cytopathic effects either directly or indirectly. The most common cause of HIV disease throughout the world, and certainly in the United States, is HIV-1,

which comprises several subtypes with different geographic distributions (see "Molecular Heterogeneity of HIV-1," later). HIV-2 was first identified in 1986 in West African patients and was originally confined to West Africa. However, a number of cases that generally can be traced to West Africa or to sexual contacts with West Africans have been identified throughout the world. The currently defined groups of HIV-1 (M, N, O, P) and the HIV-2 groups A through G each are likely derived from a separate transfer to humans from a nonhuman primate reservoir. HIV-1 viruses likely came from chimpanzees and/or gorillas, and HIV-2 from sooty mangabeys. The AIDS pandemic is primarily caused by the HIV-1 M group viruses. Although HIV-1 group O and HIV-2 viruses have been found in numerous countries, including those in the developed world, they have caused much more localized epidemics. The taxonomic relationship between primate lentiviruses is shown in **Fig. 93-1**.

MORPHOLOGY OF HIV

Electron microscopy shows that the HIV virion is an icosahedral structure **(Fig. 93-2)** containing numerous external spikes formed by the two major envelope proteins, the external gp120 and the transmembrane gp41. The virion buds from the surface of the infected cell and incorporates a variety of host proteins, including major histocompatibility complex (MHC) class I and II antigens, into its lipid bilayer. The structure of HIV-1 is schematically diagrammed in Fig. 93-2*B*.

REPLICATION CYCLE OF HIV

HIV is an RNA virus whose hallmark is the reverse transcription of its genomic RNA to DNA by the enzyme *reverse transcriptase*. The replication cycle of HIV begins with the high-affinity binding of the gp120 protein via a portion of its V1 region near the N terminus

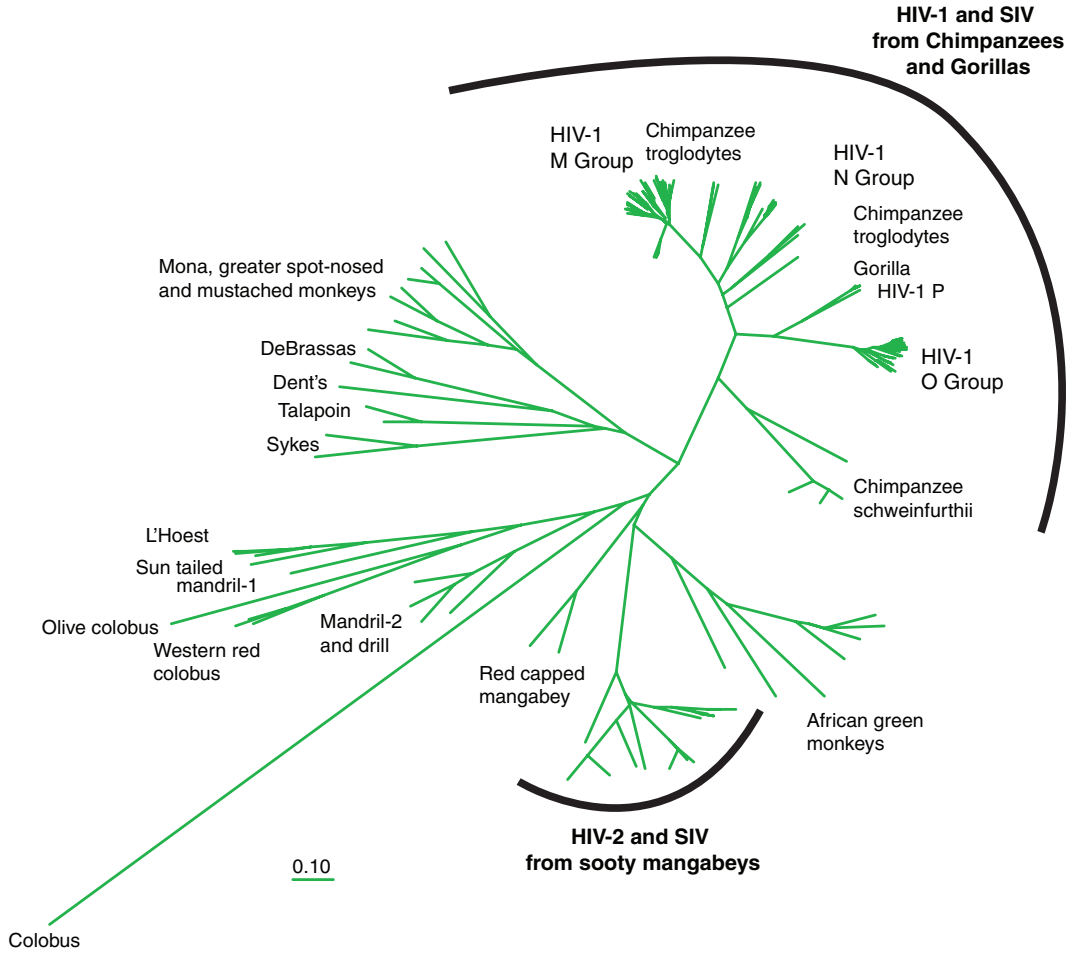
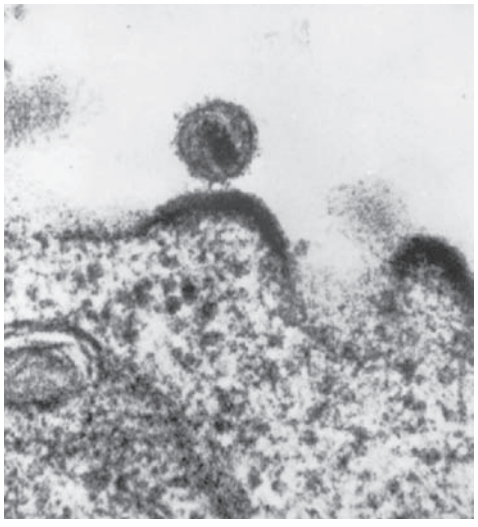
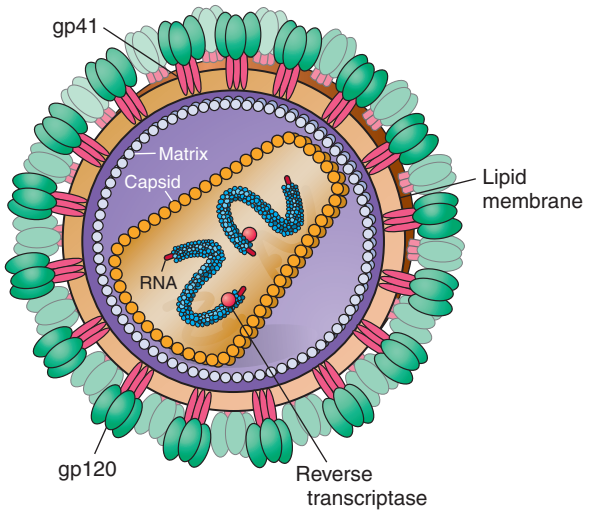


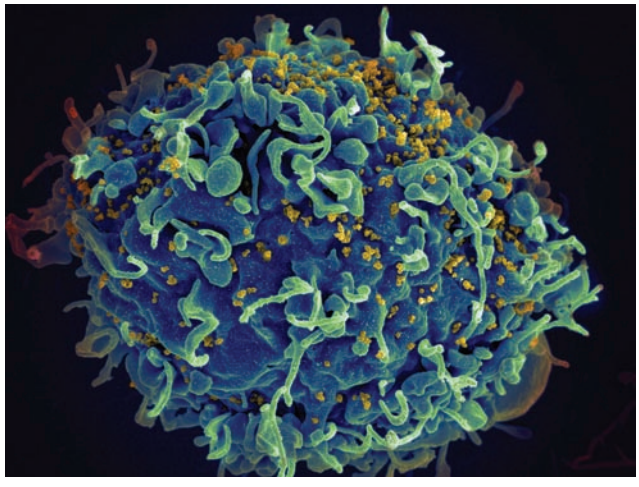
FIGURE 93-1
A phylogenetic tree based on the complete genomes of primate immunodeficiency viruses. The scale (0.10) indicates a 10% difference at the nucleotide level. (*Prepared by Brian Foley, PhD, of the HIV Sequence Database, Theoretical Biology and Biophysics Group, Los Alamos National Laboratory; additional information at www.hiv.lanl.gov/content/sequence/HelpDocs/subtypes.html.*)



A



B



C

FIGURE 93-2

A. **Electron micrograph of HIV.** Figure illustrates a typical virion following budding from the surface of a CD4+ T lymphocyte, together with two additional incomplete virions in the process of budding from the cell membrane. ***B.*** Structure of HIV-1, including the gp120 envelope, gp41 transmembrane components of the envelope, genomic RNA, enzyme reverse transcriptase, p18(17) inner membrane (matrix), and p24 core protein (capsid). (*Copyright by George V. Kelvin*). (*Adapted from RC Gallo: Sci Am 256:46, 1987.*) ***C.*** Scanning electron micrograph of HIV-1 virions infecting a human CD4+ T lymphocyte. The original photograph was imaged at 8000× magnification. (*Courtesy of Elizabeth R. Fischer, Rocky Mountain Laboratories, National Institute of Allergy and Infectious Diseases; with permission.*)

to its receptor on the host cell surface, the CD4 molecule **(Fig. 93-3)**. The CD4 molecule is a 55-kDa protein found predominantly on a subset of T lymphocytes that are responsible for helper function in the immune system. It is also expressed on the surface of monocytes/macrophages and dendritic/Langerhans cells. Once gp120 binds to CD4, the gp120 undergoes a conformational change that facilitates binding to one of two major co-receptors. The two major co-receptors for HIV-1 are CCR5 and CXCR4. Both receptors belong to the family of seven-transmembrane-domain G protein–coupled cellular receptors, and the use of one or the other or both receptors by the virus for entry into the cell is an important determinant of the cellular tropism of the virus. Certain dendritic cells express a diversity of C-type lectin receptors on their surface, one of which is called *DC-SIGN*, that also bind with high affinity to the HIV gp120 envelope protein, allowing the dendritic cell to facilitate the binding of virus to the CD4+ T cell upon engagement of dendritic cells with CD4+ T cells. Following binding of the envelope protein to the CD4 molecule associated with the earlier-mentioned conformational change in the viral envelope gp120, fusion with the host cell membrane occurs via the newly exposed gp41 molecule penetrating the plasma membrane of the target cell and then coiling upon itself to bring the virion and target cell together. Following fusion, the preintegration complex, composed of viral RNA and viral enzymes and surrounded by a capsid protein coat, is released into the cytoplasm of the target

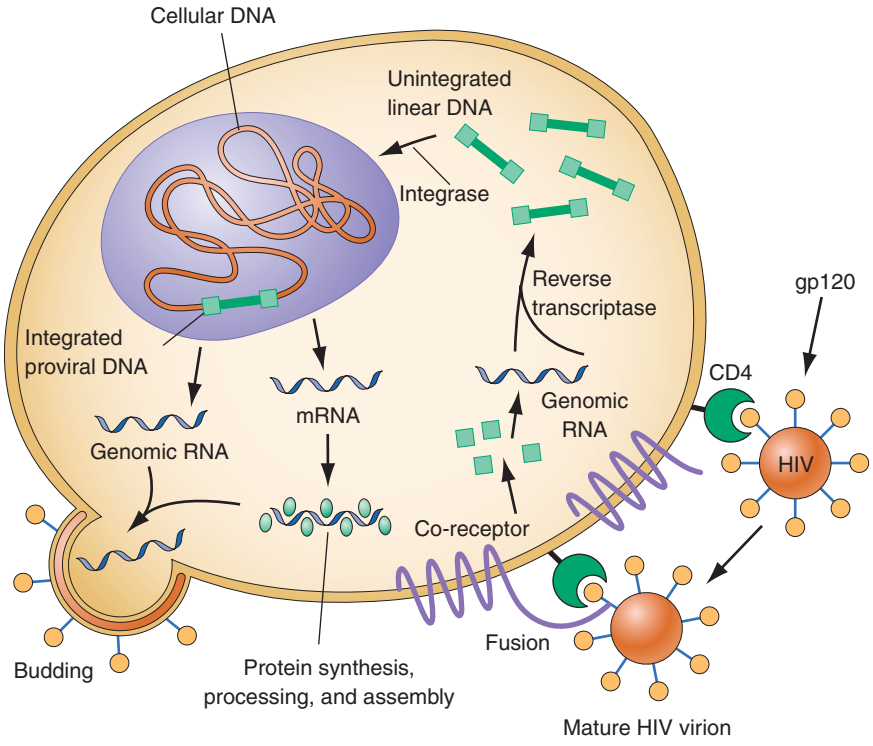


FIGURE 93-3
The replication cycle of HIV. See text for description. (*Adapted from AS Fauci: Nature 384:529, 1996.*)

cell (Fig. 93-4). As the preintegration complex traverses the cytoplasm to reach the nucleus (Fig. 93-3), the viral reverse transcriptase enzyme catalyzes the reverse transcription of the genomic RNA into DNA, and the protein coat opens to release the resulting double-strand proviral HIV-DNA. At this point in the replication cycle, the viral genome is vulnerable to cellular factors that can block the progression of infection. In particular, the cytoplasmic TRIM5-α protein in rhesus macaque cells blocks simian immunodeficiency virus (SIV) replication at a point shortly after the virus fuses with the host cell. Although the exact mechanisms of action of TRIM5-α remain unclear, the human form is inhibited by cyclophilin A and is not effective in restricting HIV replication in human cells. The recently described APOBEC family of cellular proteins also inhibits progression of virus infection after virus has entered the cell. APOBEC proteins bind to nascent reverse transcripts and deaminate viral cytidine, causing hypermutation of HIV genomes. It is still not clear whether viral replication is inhibited by: (1) the binding of APOBEC to the virus genome with subsequent

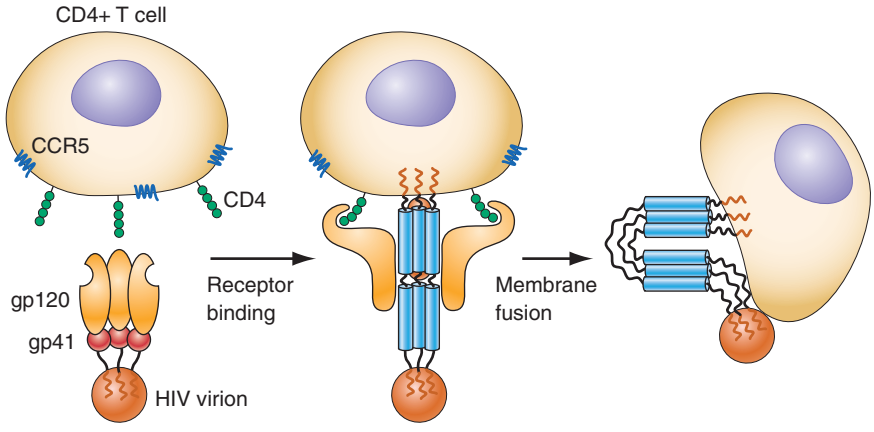


FIGURE 93-4
Binding and fusion of HIV-1 with its target cell. HIV-1 binds to its target cell via the CD4 molecule, leading to a conformational change in the gp120 molecule that allows it to bind to the co-receptor CCR5 (for R5-using viruses). The virus then firmly attaches to the host cell membrane in a coiled-spring fashion via the newly exposed gp41 molecule. Virus-cell fusion occurs as the transitional intermediate of gp41 undergoes further changes to form a hairpin structure that draws the two membranes into close proximity (see text for details). (*Adapted from D Montefiori, JP Moore: Science 283:336, 1999; with permission.*)

accumulation of reverse transcripts, or (2) the hypermutations caused by the enzymatic deaminase activity of APOBEC proteins. HIV has evolved a powerful strategy to protect itself from APOBEC. The viral protein Vif targets APOBEC for proteasomal degradation.

With activation of the cell, the viral DNA accesses the nuclear pore and is exported from the cytoplasm to the nucleus, where it is integrated into the host cell chromosomes through the action of another virally encoded enzyme, *integrase*. HIV provirus (DNA) integrates into the nuclear DNA preferentially within introns of active genes and regional hotspots. This provirus may remain transcriptionally inactive (latent) or it may manifest varying levels of gene expression, up to active production of virus.

Cellular activation plays an important role in the replication cycle of HIV and is critical to the pathogenesis of HIV disease (see "Pathogenesis and Pathophysiology," later in the chapter). Following initial binding and internalization of virions into the target cell, incompletely reverse-transcribed DNA intermediates are labile in quiescent cells and do not integrate efficiently into the host cell genome unless cellular activation occurs shortly after infection. Furthermore, some degree of activation of the host cell is required for the initiation of transcription of the integrated proviral DNA into either genomic RNA or mRNA. This latter process may not necessarily be associated with the detectable expression of the classic cell-surface markers of activation. In this regard, activation of HIV expression from the latent state depends on the interaction of a number of cellular and viral factors. Following transcription, HIV mRNA is translated into proteins that undergo modification through glycosylation, myristoylation, phosphorylation, and cleavage. The viral particle is formed by the assembly of HIV proteins, enzymes, and genomic RNA at the plasma membrane of the cells. Budding of the progeny virion occurs through specialized regions in the lipid bilayer of the host cell membrane known as *lipid rafts*, where the core acquires its external envelope. The virally encoded protease then catalyzes the cleavage of the gag-pol precursor to yield the mature virion. Progression through the virus replication cycle is profoundly influenced by a variety of viral regulatory gene products. Likewise, each point in the replication cycle of HIV is a real or potential target for therapeutic intervention. Thus far, the reverse transcriptase, protease, and integrase enzymes as well as the process of virus–target cell binding and fusion have proved clinically to be susceptible to pharmacologic disruption.

HIV GENOME

Figure 93-5 illustrates schematically the arrangement of the HIV genome. Like other retroviruses, HIV-1 has genes that encode the structural proteins of the virus: *gag* encodes the proteins that form the core of the virion (including p24 antigen); *pol* encodes the enzymes responsible for protease processing of viral proteins, reverse transcription, and integration; and *env* encodes the envelope

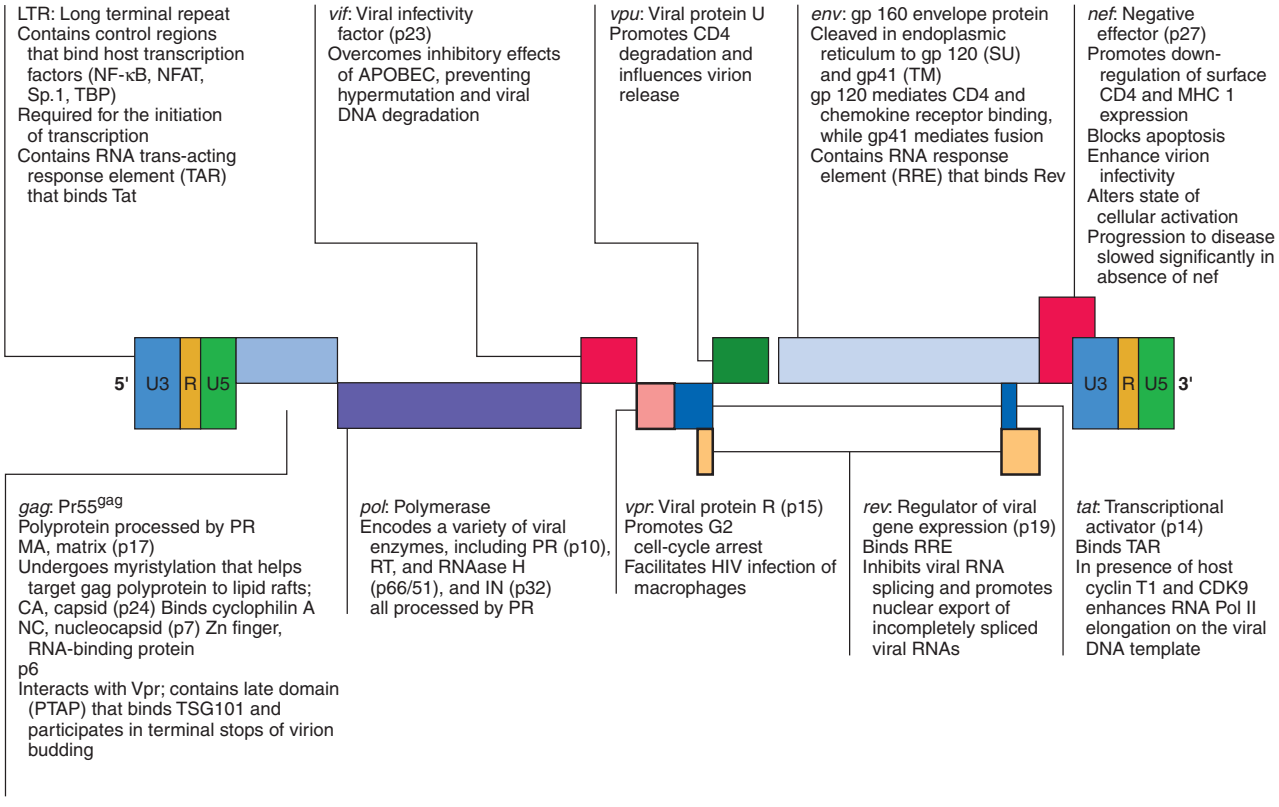


FIGURE 93-5

Organization of the genome of the HIV provirus together with a summary description of its 9 genes encoding 15 proteins. (*Adapted from WC Greene, BM Peterlin: Nat Med 8:673, 2002.*)

glycoproteins. However, HIV-1 is more complex than other retroviruses, particularly those of the nonprimate group, in that it also contains at least six other genes (*tat*, *rev*, *nef*, *vif*, *vpr*, and *vpu*), which code for proteins involved in the modification of the host cell to enhance virus growth and the regulation of viral gene expression. Several of these proteins are thought to play a role in the pathogenesis of HIV disease; their various functions are listed in Fig. 93-5. Flanking these genes are the long terminal repeats (LTRs), which contain regulatory elements involved in gene expression (Fig. 93-5). The major difference between the genomes of HIV-1 and HIV-2 is the fact that HIV-2 lacks the *vpu* gene and has a *vpx* gene not contained in HIV-1.

MOLECULAR HETEROGENEITY OF HIV-1

Molecular analyses of HIV isolates reveal varying levels of sequence diversity over all regions of the viral genome. For example, the degree of difference in the coding sequences of the viral envelope protein ranges from a few percent (very close, among isolates from the same infected individual) to 50% (extreme diversity, among isolates from the different groups of HIV-1, M, N, O, and P). The changes tend to cluster in hypervariable regions. HIV can evolve by several means, including simple base substitution, insertions and deletions, recombination, and gain and loss of glycosylation sites. HIV sequence diversity arises directly from the limited fidelity of the reverse transcriptase. The balance of immune pressure and functional constraints on proteins influences the regional level of variation within proteins. For example, Envelope, which is exposed on the surface of the virion and is under immune selective pressure from both antibodies and cytolytic T lymphocytes, is extremely variable, with clusters of mutations in hypervariable domains. In contrast, reverse transcriptase, with important enzymatic functions, is relatively conserved, particularly around the active site. The extraordinary variability of HIV-1 is in marked contrast to the relative stability of HTLV-I and -II.

Four groups of HIV-1 have been defined. Group M (major) is responsible for most of the infections in the world. Group O (outlier) is a relatively rare viral form found originally in Cameroon, Gabon, and France. Group N was first identified in a Cameroonian woman with AIDS; very few group N isolates have been identified and sequenced. An additional human immunodeficiency virus, related to gorilla SIV and distinct from other HIV-1 groups, was identified in a Cameroonian woman in 2009 and proposed as group P.

Among primate lentiviruses, HIV-1 is most closely related to viruses isolated from chimpanzees and gorillas. The chimpanzee subspecies *Pan troglodytes troglodytes* has been established to be the natural reservoir of the HIV-1 M and N groups. The HIV-1 O group is most closely related to viruses found in Cameroonian gorillas. The M group comprises nine subtypes, or *clades*, designated A, B, C, D, F, G, H, J, and K, as well as a growing number of major and minor circulating recombinant forms (CRFs). CRFs are generated by infection of an individual with two subtypes that then recombine and create a virus with a selective advantage. These CRFs range from highly prevalent forms such as the AE virus, CRF01_AE, which is predominant in southeast Asia and often referred to simply as E, despite the fact that the parental E virus has never been found, and CRF02_AG from west and central Africa, to a large number of CRFs that are relatively rare. The subtypes and CRFs create the major lineages of the M group of HIV-1.

The picture was complicated somewhat when it was found that some subtypes are not equidistant from one another, while others contained sequences so diverse that they could not properly be considered to be the same subtype. Thus, the term *sub-subtype* was introduced, and subtypes A and F are now subdivided into A1 and A2, and F1 and F2, respectively. It has also been argued that subtypes B and D are too close to be separate subtypes and should be considered sub-subtypes; it was decided, however, not to increase the confusion by renaming the clades **(Fig. 93-6)**.

Figure 93-7 schematically diagrams the worldwide distribution of HIV-1 subtypes by region. Seven strains have a global prevalence of >2.5% and account for the majority of HIV infections globally: HIV-1 subtypes A, B, C, D, G and two of the CRFs, CRF01_AE and CRF02_AG. Subtype C viruses (of the M group) are by far the most common form worldwide, accounting for ~50% of prevalent infections worldwide. In sub-Saharan Africa, home to approximately two-thirds of all individuals living with HIV/AIDS, the majority of infections are caused by subtype C, with smaller proportions of infections caused by subtype A, subtype G, CRF02_AG, and other subtypes and recombinants. In Asia, HIV-1 isolates of the CRF01_AE lineage and subtypes C and B predominate. CRF01_AE accounts for most infections in south and southeast Asia, while subtype C is prevalent in India (see "HIV Infection and AIDS Worldwide," later in the chapter). Subtype B viruses are the overwhelmingly predominant viruses seen in the United States, Canada, certain countries in South America, western Europe, and Australia and account for 12–13% of global infections. It is thought that, purely by chance, subtype B was seeded into the United States in the late 1970s, thereby establishing an overwhelming founder effect. Many countries have co-circulating viral subtypes that are giving rise to new CRFs. Sequence analyses of HIV-1 isolates from infected individuals indicate that recombination among viruses of different clades likely occurs as a result of infection of an individual with viruses of more than one subtype, particularly in geographic areas where subtypes overlap.

The extraordinary diversity of HIV, reflected by the presence of multiple subtypes, circulating recombinant forms, and continuous viral evolution, has implications for possible differential rates of disease progression, responses to therapy, and the development of resistance to antiretroviral drugs. This diversity is also a formidable obstacle to HIV vaccine development, as a broadly useful vaccine would need to induce protective responses against a wide range of viral strains.

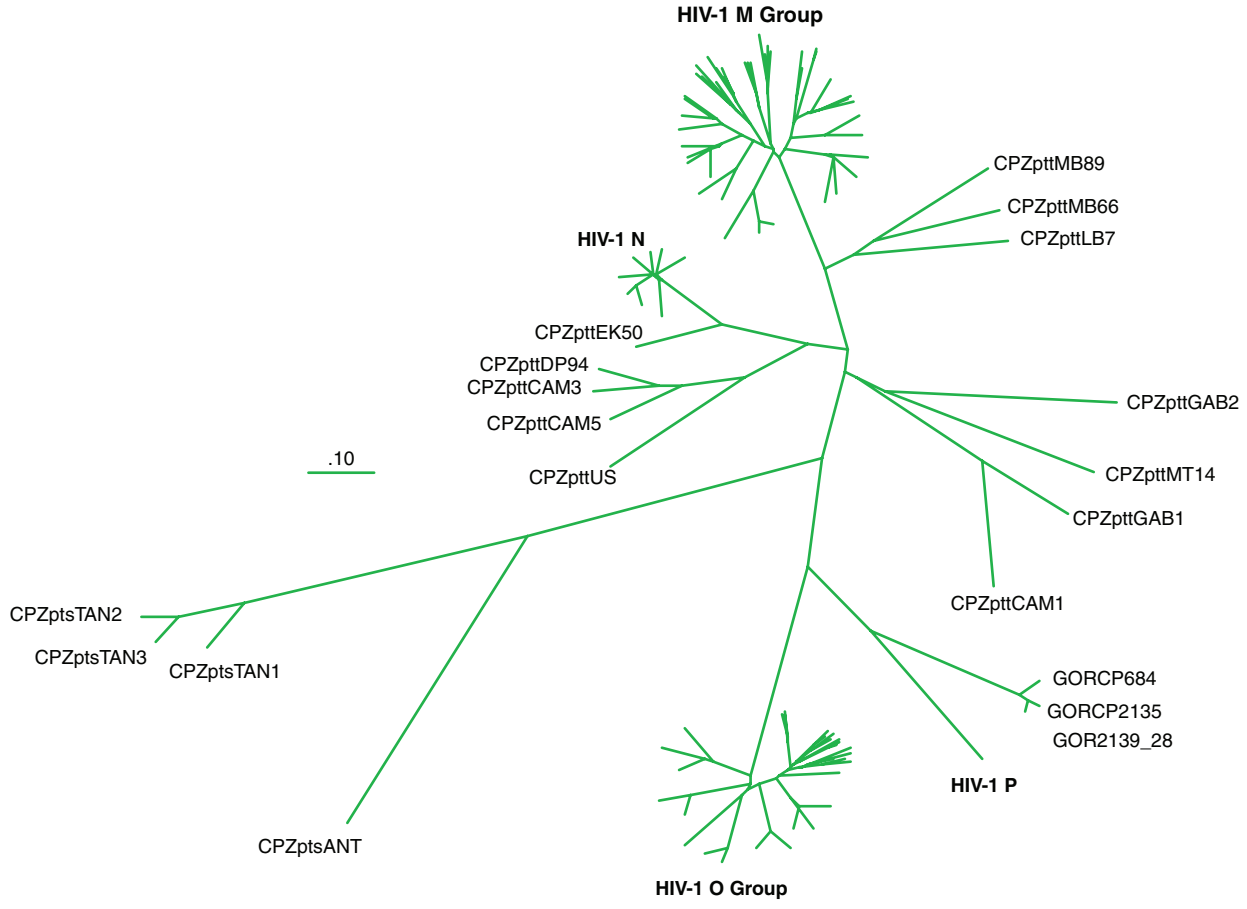


FIGURE 93-6
Phylogenetic tree constructed from representative viral envelope sequences of the subtypes and CRF01 in HIV-1 group M; some isolates from groups N, O, and P (also human HIV-1); CPZ (chimpanzee); and gorilla (GOR). The scale bar indicates the genetic distances between the sequences. (*Prepared by Brian Foley, PhD, of the HIV Sequence Database, Theoretical Biology and Biophysics Group, Los Alamos National Laboratory*.)

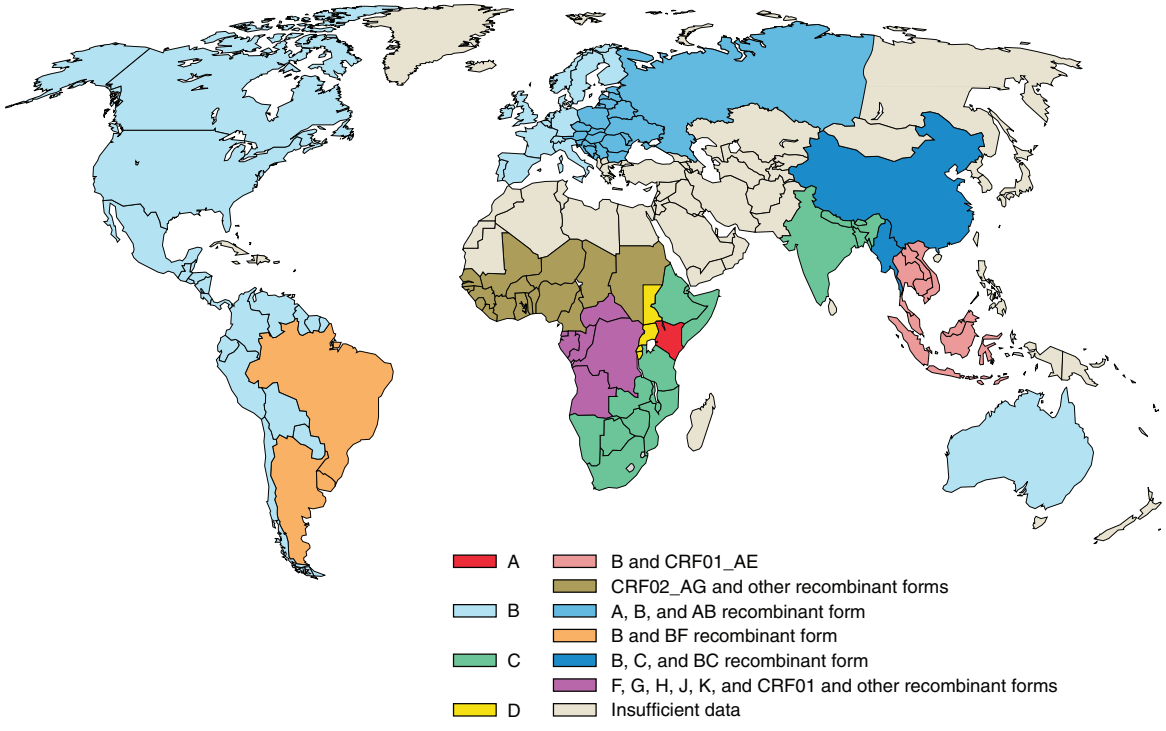


FIGURE 93-7
Geographic distribution of HIV-1 subtypes and recombinant forms. (*Adapted from BS Taylor et al: N Engl J Med 358:1590, 2008; with permission*.)

TRANSMISSION

HIV is transmitted primarily by sexual contact (both heterosexual and male to male); by blood and blood products; and by infected mothers to infants intrapartum, perinatally, or via breast milk. After ~30 years of scrutiny, there is no evidence that HIV is transmitted by casual contact or that the virus can be spread by insects, such as by a mosquito bite.

SEXUAL TRANSMISSION

HIV infection is predominantly a sexually transmitted disease (STD) worldwide. By far the most common mode of infection, particularly in developing countries, is heterosexual transmission, although in many Western countries a resurgence of male-to-male sexual transmission has occurred. Although a wide variety of factors including viral load and the presence of ulcerative genital diseases influence the efficiency of heterosexual transmission of HIV, such transmission is generally inefficient. In a pivotal study of heterosexual couples in the Rakai district of Uganda discordant for HIV infection (one partner was infected and the other was initially uninfected), the overall risk of HIV transmission rate was 0.12% per coital act in the absence of antiretroviral therapy. A meta-analysis of observational studies also found a low risk of heterosexual transmission in the absence of antiretrovirals: in high-income countries the estimated per-act rate was 0.04% for female-to-male transmission and 0.08% for male-to-female transmission. Rates for low-income-country female-to-male and male-to-female transmission were higher in this analysis (0.38% per act and 0.30% per act, respectively) in the absence of reported commercial sex exposure.

HIV has been demonstrated in seminal fluid both within infected mononuclear cells and in cell-free material. The virus appears to concentrate in the seminal fluid, particularly in situations where there are increased numbers of lymphocytes and monocytes in the fluid, as in genital inflammatory states such as urethritis and epididymitis, conditions closely associated with other STDs. The virus has also been demonstrated in cervical smears and vaginal fluid. There is an elevated risk of HIV transmission associated with unprotected receptive anal intercourse (URAI) among both men and women compared to the risk associated with receptive vaginal intercourse. Although data are limited, the per-act risk for HIV transmission via URAI was estimated to be ~1.4% for both men and women in a recent systemic review/meta-analysis. The risk of HIV acquisition associated with URAI is probably higher than that seen in penile-vaginal intercourse because only a thin, fragile rectal mucosal membrane separates the deposited semen from potentially susceptible cells in and beneath the mucosa, and trauma may be associated with anal intercourse. Anal douching and sexual practices that traumatize the rectal mucosa also increase the likelihood of infection. It is likely that anal intercourse provides at least two modalities of infection: (1) direct inoculation into blood in cases of traumatic tears in the mucosa; and (2) infection of susceptible target cells, such as Langerhans cells, in the mucosal layer in the absence of trauma. Insertive anal intercourse also confers an increased risk of HIV acquisition compared to insertive vaginal intercourse. Although the vaginal mucosa is several layers thicker than the rectal mucosa and less likely to be traumatized during intercourse, the virus can be transmitted to either partner through vaginal intercourse. Studies in the United States and Europe have found that male-to-female HIV transmission is usually more efficient than female-to-male transmission. The differences in reported transmission rates between men and women may be due in part to the prolonged exposure to infected seminal fluid of the vaginal and cervical mucosa, as well as the endometrium (when semen enters through the cervical os). By comparison, the penis and urethral orifice are exposed relatively briefly to infected vaginal fluid. Among various cofactors examined in studies of heterosexual HIV transmission, the presence of other STDs has been strongly associated with HIV transmission. In this regard, there is a close association between genital ulcerations and transmission, owing to both susceptibility to infection and infectivity. Infections with microorganisms such as *Treponema pallidum* (Chap. 74), *Haemophilus ducreyi* (Chap. 50), and herpes simplex virus (HSV; Chap. 84) are important causes of genital ulcerations linked to transmission of HIV. In addition, pathogens responsible for nonulcerative inflammatory STDs such as those caused by *Chlamydia trachomatis* (Chap. 81), *Neisseria gonorrhoeae* (Chap. 49), and *Trichomonas vaginalis* (Chap. 125) are also associated with an increased risk of transmission of HIV infection. Bacterial vaginosis, an infection related to sexual behavior, but not strictly an STD, may also be linked to an increased risk of transmission of HIV infection. Several studies suggest that treating other STDs and genital tract syndromes may help prevent transmission of HIV. This effect is most prominent in populations in which the prevalence of HIV infection is relatively low.

The quantity of HIV-1 in plasma is a primary determinant of the risk of HIV-1 transmission. In a cohort of heterosexual couples in Uganda discordant for HIV infection and not receiving antiretroviral therapy, the mean serum HIV RNA level was significantly higher among HIV-infected subjects whose partners seroconverted than among those whose partners did not seroconvert. In fact, transmission was rare when the infected partner had a plasma level of <1700 copies of HIV RNA per milliliter, even when genital ulcer disease was present **(Fig 93-8)**. The rate of HIV transmission per coital act was highest during the early stage of HIV infection when plasma HIV RNA levels were high and in advanced disease as the viral set point increased.

Antiretroviral therapy dramatically reduces plasma viremia in most HIV-infected individuals (see "Treatment," later) and is associated with a reduction in risk of transmission. For example, in an analysis of ~3400 HIV-serodiscordant heterosexual couples from 7 African countries, use of antiretroviral therapy by the infected person was accompanied by a 92% reduction in risk of HIV-1-transmission to the uninfected partner. Several studies

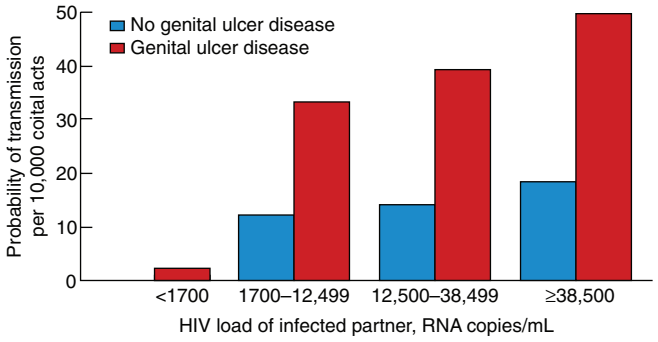


FIGURE 93-8
Probability of HIV transmission per coital act among monogamous, heterosexual, HIV-serodiscordant couples in Uganda. (*From RH Gray et al: Lancet 357:1149, 2001.*)

also have suggested a beneficial effect of antiretroviral treatment at the community level.

A number of studies including large, randomized, controlled trials clearly have indicated that male *circumcision* is associated with a lower risk of HIV infection for heterosexual men. Studies are conflicting as to whether circumcision protects against HIV acquisition among men who have sex with men. The benefit of circumcision may be due to increased susceptibility of uncircumcised men to ulcerative STDs, as well as to other factors such as microtrauma to the foreskin and glans penis. In addition, the highly vascularized inner foreskin tissue contains a high density of Langerhans cells as well as increased numbers of CD4+ T cells, macrophages, and other cellular targets for HIV. Finally, the moist environment under the foreskin may promote the presence or persistence of microbial flora that, via inflammatory changes, may lead to even higher concentrations of target cells for HIV in the foreskin. In some studies the use of oral contraceptives was associated with an increase in incidence of HIV infection over and above that which might be expected by not using a condom for birth control. This phenomenon may be due to drug-induced changes in the cervical mucosa, rendering it more vulnerable to penetration by the virus. Adolescent girls might also be more susceptible to infection upon exposure due to the properties of an immature genital tract with increased cervical ectopy or exposed columnar epithelium.

Oral sex is a much less efficient mode of transmission of HIV than is anal intercourse or vaginal intercourse. A number of studies have reported that the incidence of transmission of infection by oral sex among couples discordant for HIV was extremely low. However, there have been reports of documented HIV transmission resulting solely from receptive fellatio and insertive cunnilingus. Therefore, the assumption that oral sex is completely safe is not warranted.

The association of alcohol consumption and illicit drug use with unsafe sexual behavior, both homosexual and heterosexual, leads to an increased risk of sexual transmission of HIV. Methamphetamine and other so-called club drugs (e.g., ecstasy, ketamine, and gamma hydroxybutyrate), sometimes taken in conjunction with PDE-5 inhibitors such as sildenafil (Viagra), tadalafil (Cialis), or vardenafil (Levitra), have been associated with risky sexual practices and increased risk of HIV infection, particularly among men who have sex with men.

TRANSMISSION BY BLOOD AND BLOOD PRODUCTS

HIV can be transmitted to individuals who receive HIV-tainted blood transfusions, blood products, or transplanted tissue as well as to IDUs who are exposed to HIV while sharing injection paraphernalia such as needles, syringes, the water in which drugs are mixed, or the cotton through which drugs are filtered. Parenteral transmission of HIV during injection drug use does not require IV puncture; SC ("skin popping") or IM ("muscling") injections can transmit HIV as well, even though these behaviors are sometimes erroneously perceived as low-risk. Among IDUs, the risk of HIV infection increases with the duration of injection drug use; the frequency of needle sharing; the number of partners with whom paraphernalia are shared, particularly in the setting of "shooting galleries" where drugs are sold and large numbers of IDUs may share a limited number of "works"; comorbid psychiatric conditions such as antisocial personality disorder; the use of cocaine in injectable form or smoked as "crack"; and the use of injection drugs in a geographic location with a high prevalence of HIV infection, such as certain inner-city areas in the United States.

The first cases of AIDS among transfusion recipients and individuals with hemophilia or other clotting disorders were reported in 1982. The vast majority of HIV infections acquired via contaminated blood transfusions, blood components, or transplanted tissue in resource-rich countries occurred prior to the spring of 1985, when mandatory testing of donated blood for HIV-1 was initiated. It is estimated that >90% of individuals exposed to HIV-contaminated blood products become infected; unfortunately, in resource-poor countries, HIV continues to be transmitted by blood, blood products, and tissues due to the large number of blood donations that are inadequately screened for HIV. Transfusions of whole blood, packed red blood cells, platelets, leukocytes, and plasma are all capable of transmitting HIV infection. In contrast, hyperimmune gamma globulin, hepatitis B immune globulin, plasma-derived hepatitis B vaccine, and Rh_o immune globulin have not been associated with transmission of HIV infection. The procedures involved in processing these products either inactivate or remove the virus.

Currently, in the United States and in most developed countries, the following measures have made the risk of transmission of HIV infection by transfused blood or blood products extremely small: the screening of blood donations for HIV antibodies, HIV p24 antigen, and HIV nucleic acid; the careful selection of potential blood donors with health history questionnaires to exclude individuals with risk behavior; and opportunities for self-deferral and the screening out of HIV-negative individuals with serologic testing for

infections that have shared risk factors with HIV, such as hepatitis B and C. The chance of infection of a hemophiliac via clotting factor concentrates has essentially been eliminated because of the added layer of safety resulting from heat treatment of the concentrates.

It is currently estimated that the risk of infection with HIV in the United States via transfused screened blood is approximately 1 in 1.5 million units. Therefore, among the ~16 million donations collected in the United States each year, there are about 11 infectious donations leading to approximately 20 HIV-positive blood components being released each year that could potentially infect recipients. Thus, despite the best efforts of science, one cannot completely eliminate the risk of transfusion-related transmission of HIV since current technology cannot detect HIV RNA for the first 10–15 days following infection due to the low levels of viremia. In this regard, 4 cases of transfusion-associated HIV infection attributable to infected blood that tested negative for HIV were reported in the United States in the period 2000–2008.

In other countries, there have been reports of sporadic breakdowns in routinely available screening procedures in which contaminated blood was allowed to be transfused, resulting in small clusters of patients becoming infected. For example, in China in the 1990s, a disturbingly large number of persons became infected by selling blood in situations where the collectors reused needles that were contaminated and, in some instances, mixed blood products from a number of individuals, separated the plasma, and reinfused mixed red blood cells back into the individual donors.

There have been no reported cases of transmission of HIV-2 in the United States via donated blood or tissues, and, currently, donated blood is screened for both HIV-1 and HIV-2. Transmission of HIV (both HIV-1 and HIV-2) by blood or blood products is still an ongoing threat in certain developing countries, particularly in sub-Saharan Africa, where routine screening of blood is not universally practiced.

Prior to the screening of donors, a small number of cases of transmission of HIV via semen used in artificial insemination and tissues used in organ transplantation were documented. At present, donors of such tissues are prescreened for HIV infection. With regard to HIV-serodiscordant couples (male, HIV-infected; female, HIV-uninfected) who wish to conceive a child, assisted reproductive techniques using sperm-washing to reduce the risk of HIV transmission have been successfully employed, with only one well-documented seroconversion in the uninfected female partner, reported in 1990.

OCCUPATIONAL TRANSMISSION OF HIV: HEALTH CARE WORKERS, LABORATORY WORKERS, AND THE HEALTH CARE SETTING

There is a small but definite occupational risk of HIV transmission to health care workers and laboratory personnel and potentially others who work with HIV-containing materials, particularly when sharp objects are used. An estimated 600,000 to 800,000 health care workers are stuck with needles or other sharp medical instruments in the United States each year.

Exposures that place a health care worker at potential risk of HIV infection are percutaneous injuries (e.g., a needle stick or cut with a sharp object) or contact of mucous membrane or nonintact skin (e.g., exposed skin that is chapped, abraded, or afflicted with dermatitis) with blood, tissue, or other potentially infectious body fluids. Large, multi-institutional studies have indicated that the risk of HIV transmission following skin puncture from a needle or a sharp object that was contaminated with blood from a person with documented HIV infection is ~0.3% and after a mucous membrane exposure it is 0.09% (see "HIV and the Health Care Worker," later in the chapter) if the injured and/or exposed person is not treated within 24 h with antiretroviral drugs. HIV transmission after nonintact skin exposure has been documented, but the average risk for transmission by this route has not been precisely determined; however, it is estimated to be less than the risk for mucous membrane exposure. Transmission of HIV through intact skin has not been documented. Currently, virtually all puncture wounds and mucous membrane exposures in health care workers involving blood from a patient with documented HIV infection are treated prophylactically with combination antiretroviral therapy (cART). This practice has dramatically reduced the occurrence of puncture-related transmissions of HIV to health care workers.

In addition to blood and visibly bloody body fluids, semen and vaginal secretions also are considered potentially infectious; however, they have not been implicated in occupational transmission from patients to health care workers. The following fluids also are considered potentially infectious: cerebrospinal fluid, synovial fluid, pleural fluid, peritoneal fluid, pericardial fluid, and amniotic fluid. The risk for transmission after exposure to fluids or tissues other than HIV-infected blood also has not been quantified, but it is probably considerably lower than the risk after blood exposures. Feces, nasal secretions, saliva, sputum, sweat, tears, urine, and vomitus are not considered potentially infectious for HIV unless they are visibly bloody. Rare cases of HIV transmission via human bites have been reported, but not in the setting of occupational exposure.

An increased risk for HIV infection following percutaneous exposures to HIV-infected blood is associated with exposures involving a relatively large quantity of blood, as in the case of a device visibly contaminated with the patient's blood, a procedure that involves a hollow-bore needle placed directly in a vein or artery, or a deep injury. Factors that might be associated with mucocutaneous transmission of HIV include exposure to an unusually large volume of blood, prolonged contact, and a potential portal of entry. In addition, the risk increases for exposures to blood from patients with advanced-stage disease or those patients in the acute stage of HIV infection, owing to the higher levels of HIV in the blood under those circumstances. The use of antiretroviral drugs as postexposure prophylaxis decreases the risk of infection compared with historic controls in occupationally exposed health care workers (see "HIV and the

Health Care Worker," later). The risk of hepatitis B virus (HBV) infection following a similar type of exposure is ~6–30% in nonimmune individuals; if a susceptible worker is exposed to HBV, postexposure prophylaxis with hepatitis B immune globulin and initiation of HBV vaccine is >90% effective in preventing HBV infection. The risk of hepatitis C virus (HCV) infection following percutaneous injury is ~1.8% (Chap. 95).

Since the beginning of the HIV epidemic, there have been rare instances where transmission of infection from a health care worker to patients seemed highly probable. One notable cluster of infections involved an HIV-infected dentist in Florida who apparently infected as many as six of his patients, most likely through contaminated instruments. Despite this small number of documented cases, the risk of HIV transmission involving health care workers (infected or not) to patients is extremely low in developed countries—in fact, too low to be measured accurately. In this regard, several epidemiologic studies have been performed tracing thousands of patients of HIV-infected dentists, physicians, surgeons, obstetricians, and gynecologists, and no other cases of HIV transmission that could be linked to the health care providers were identified.

Breaches in infection control and the reuse of contaminated syringes have also resulted in the transmission of HIV from patient to patient in hospitals, nursing homes, and outpatient settings. For example, in the only report of HIV transmission from patient to patient during a surgical procedure, several patients in Australia apparently were infected by an HIV-negative general surgeon during routine outpatient surgery. Although the mechanism of transmission was not definitively identified, a failure on the part of the surgeon to sterilize instruments properly following prior surgery on an HIV-infected patient was considered a likely explanation for this outbreak. Three patients (two in hospitals in the United States and one in the Netherlands) undergoing nuclear medicine procedures were reported to have inadvertently received IV injections of blood or other material from patients infected with HIV. Hemodialysis centers have also been implicated in several reported HIV transmission incidents.

The most dramatic reports of HIV infection in the health care setting involved transmission of HIV to 8000–10,000 children in Romanian orphanages in the 1980s. Other large incidents occurred in hospitals in Russia and Libya in the late 1980s and late 1990s, respectively. Each of these incidents received considerable attention and likely was related to reuse of contaminated needles and/or administration of contaminated blood products. Finally, these very rare occurrences of transmission of HIV as well as HBV and HCV to and from health care workers in the workplace underscore the importance of the use of universal precautions when caring for all patients (see later in this chapter and Chap. 14).

MATERNAL–FETAL/INFANT TRANSMISSION

HIV infection can be transmitted from an infected mother to her fetus during pregnancy, during delivery, or by breast-feeding. This remains an important form of transmission of HIV infection in certain developing countries, where the proportion of infected women to infected men is ~1:1. Virologic analyses of aborted fetuses indicate that HIV can be transmitted to the fetus during the first or second trimesters of pregnancy. However, maternal transmission to the fetus occurs most commonly in the perinatal period. Two studies performed in Rwanda and the former Zaire indicated that the relative proportions of mother-to-child transmissions were 23–30% before birth, 50–65% during birth, and 12–20% via breast-feeding.

In the absence of prophylactic antiretroviral therapy to the mother during pregnancy, labor, and delivery and to the fetus following birth, the probability of transmission of HIV from mother to infant/fetus ranges from 15 to 25% in industrialized countries and from 25 to 35% in developing countries. These differences may relate to the adequacy of prenatal care as well as to the stage of HIV disease and the general health of the mother during pregnancy. Higher rates of transmission have been reported to be associated with many factors, the best documented of which is the presence of high maternal levels of plasma viremia. In one study of 552 singleton pregnancies in the United States, the rate of mother-to-baby transmission was 0% among women with <1000 copies of HIV RNA per milliliter of blood, 16.6% among women with 1000–10,000 copies/mL, 21.3% among women with 10,001–50,000 copies/mL, 30.9% among women with 50,001–100,000 copies/mL, and 40.6% among women with >100,000 copies/mL. However, there may not be a lower "threshold" below which transmission never occurs, since other studies have reported transmission by women with viral RNA levels <50 copies/mL. Low maternal CD4+ T cell counts also have been associated with higher rates of transmission; however, since low CD4+ T cell counts are often associated with high levels of plasma viremia, in one study using multivariate analysis including plasma viral load and CD4+ T cell count, only the level of plasma HIV RNA was significant. Increased mother-to-child transmission is also correlated with closer human leukocyte antigen (HLA) match between mother and child. A prolonged interval between membrane rupture and delivery is another well-documented risk factor for transmission. Other conditions that are potential risk factors, but that have not been consistently demonstrated, are the presence of chorioamnionitis at delivery; STDs during pregnancy; hard drug use during pregnancy; cigarette smoking; preterm delivery; and obstetric procedures such as amniocentesis, amnioscopy, fetal scalp electrodes, and episiotomy. In a seminal study conducted in the United States and France in the 1990s, zidovudine treatment of HIV-infected pregnant women from the beginning of the second trimester through delivery and of the infant for 6 weeks following birth dramatically decreased the rate of intrapartum and perinatal transmission of HIV infection from 22.6% in the untreated group to <5%. Today, the rate of mother-to-child transmission has fallen to 1% or less in pregnant women who are receiving

combination antiretroviral therapy for their HIV infection. Such treatment, combined with cesarean section delivery, has rendered mother-to-child transmission of HIV an unusual event in the United States and other developed nations. In developed countries, current recommendations to reduce perinatal transmission of HIV include universal voluntary HIV testing and counseling of pregnant women, antiretroviral prophylaxis with one or more drugs in cases in which the mother does not require therapy for her HIV infection, combination therapy for women who do require therapy, obstetric management that attempts to minimize exposure of the infant to maternal blood and genital secretions, and avoidance of breast-feeding. It is recommended that the choice of antiretroviral therapy for pregnant women be based on the same considerations used for women who are not pregnant, with discussion of the recognized and unknown risks and benefits of such therapy during pregnancy (see later under "Treatment").

Certain studies have demonstrated that truncated regimens of zidovudine alone or in combination with lamivudine given to the mother during the last few weeks of pregnancy or even only during labor and delivery, and to the infant for a week or less, significantly reduce transmission to the infant compared with placebo. Short-course prophylactic antiretroviral regimens, such as a single dose of nevirapine given to the mother at the onset of labor and a single dose to the infant within 72 h of birth, are of particular relevance to low- to mid-income nations because of the low cost and the fact that in these regions perinatal care is often not available and pregnant women are often seen by a health care provider for the first time at or near the time of delivery. Given that cART is now increasingly available to individuals in developing countries due to the lower cost of drugs and programs that are making drugs available to these regions of the world, combinations of drugs are being used more frequently, where available, to treat HIV-infected pregnant women. This has had the effect of benefitting the women, blocking HIV transmission to the fetus, and protecting against subsequent transmission by breast-feeding.

Breast-feeding is an important modality of transmission of HIV infection in developing countries, particularly where mothers continue to breast-feed for prolonged periods. The risk factors for mother-to-child transmission of HIV via breast-feeding are not fully understood; factors that increase the likelihood of transmission include detectable levels of HIV in breast milk, the presence of mastitis, low maternal CD4+ T cell counts, and maternal vitamin A deficiency. The risk of HIV infection via breast-feeding is highest in the early months of breast-feeding. In addition, exclusive breast-feeding has been reported to carry a lower risk of HIV transmission than mixed feeding. Certainly in developed countries, breast-feeding by an infected mother should be avoided. However, there is disagreement regarding recommendations for breast-feeding in certain developing countries, where breast milk is the only source of adequate nutrition as well as immunity against potentially serious non-HIV infections for the infant. The optimal approach to prevent transmission by infected mothers who choose to breast-feed would be to provide continual treatment to the infected mother. This approach has become more feasible as cART becomes more widely available in developing countries. Despite progress in this regard, such therapy is currently available to only ~30–40% of persons in developing nations who require it.

TRANSMISSION BY OTHER BODY FLUIDS

Although HIV can be isolated typically in low titers from saliva of a small proportion of infected individuals, there is no convincing evidence that saliva can transmit HIV infection, either through kissing or through other exposures, such as occupationally to health care workers. Saliva contains endogenous antiviral factors; among these factors, HIV-specific immunoglobulins of IgA, IgG, and IgM isotypes are detected readily in salivary secretions of infected individuals. It has been suggested that large glycoproteins such as mucins and thrombospondin 1 sequester HIV into aggregates for clearance by the host. In addition, a number of soluble salivary factors inhibit HIV to various degrees in vitro, probably by targeting host cell receptors rather than the virus itself. Perhaps the best studied of these, secretory leukocyte protease inhibitor (SLPI), blocks HIV infection in several cell culture systems, and it is found in saliva at levels that approximate those required for inhibition of HIV in vitro. In this regard, higher salivary levels of SLPI in breast-fed infants were associated with a decreased risk of HIV transmission through breast milk. It has also been suggested that submandibular saliva reduces HIV infectivity by stripping gp120 from the surface of virions, and that saliva-mediated disruption and lysis of HIV-infected cells occurs because of the hypotonicity of oral secretions. There have been outlier cases of suspected transmission by saliva, but these have probably been blood-to-blood transmissions. Transmission of HIV by a human bite can occur but is a rare event. In addition, a most unusual form of HIV transmission from infected children to mothers in the former Soviet Union has been identified. In those cases, the children (infected through transfusion) were said to have bleeding sores in the mouth, and the mothers were said to have lacerations and abrasions on and around the nipples of the breast resulting from trauma from the children's teeth. Breast-feeding had been continued until the children were older than is usual in other developed countries.

Although virus can be identified, if not isolated, from virtually any body fluid, there is no evidence that HIV transmission can occur as a result of exposure to tears, sweat, or urine. However, there have been isolated cases of transmission of HIV infection by body fluids that may or may not have been contaminated with blood. Most of these situations occurred in the setting of a close relative providing intensive nursing care for an HIV-infected person without observing universal precautions, underscoring the importance of adhering to such precautions in the handling of body fluids and wastes from HIV-infected individuals.

EPIDEMIOLOGY

HIV INFECTION AND AIDS WORLDWIDE

HIV infection/AIDS is a global pandemic, with cases reported from virtually every country. At the end of 2009, an estimated 33.3 million individuals were living with HIV infection according to the Joint United Nations Programme on HIV/AIDS (UNAIDS). More than 95% of people living with HIV/AIDS reside in low- and middle-income countries; ~50% are female, and 2.5 million are children <15 years. The global distribution of these cases is illustrated in **Fig. 93-9**. As illustrated in **Fig. 93-10*A***, the estimated number of people living with HIV—i.e., the global prevalence—has increased approximately fourfold since 1990, reflecting the combined effects of continued high rates of new HIV infections and the beneficial (life-prolonging) impact of antiretroviral therapy.

In 2009, there were an estimated 2.6 million new cases of HIV infection worldwide, including 370,000 in children <15 years old. UNAIDS estimates that the global spread of HIV peaked in 1997, when ~3.2 million new HIV infections occurred. In 2009, the estimated number of new HIV infections globally was approximately 21% lower than at the peak of the pandemic (Fig. 93-10*B*). Recent reductions in global HIV incidence likely reflect natural trends in the pandemic as well as the results of prevention programs resulting in behavior change. In 2009, global AIDS deaths totaled 1.8 million (including 260,000 children <15 years). A rapid expansion of access to antiretroviral therapy likely has helped lower AIDS-related death rates in recent years (Fig. 93-10*C*). Since the beginning of the pandemic the cumulative total of AIDS deaths globally exceeds 25 million.

The HIV epidemic has occurred in "waves" in different regions of the world, each wave having somewhat different characteristics depending on the demographics of the country and region in question and the timing of the introduction of HIV into the population. Although the AIDS epidemic was first recognized in the United States and shortly thereafter in Western Europe, it very likely began in sub-Saharan Africa (see earlier), which has been particularly devastated by the epidemic. More than two-thirds of all people with HIV infection (~22.5 million) live in that region, even though sub-Saharan Africa is home to just 10–11% of the world's population (Fig. 93-9). Within the region, southern Africa is worst-affected. In each of the nine southern African countries, available seroprevalence data indicate that >10% of the adult population age 15–49 is HIV-infected. In addition, among high-risk individuals (e.g., commercial sex workers, patients attending STD clinics) who live in urban areas of sub-Saharan Africa, seroprevalence is now >50% in some countries. Sub-Saharan Africa's HIV regional epidemics vary significantly, with most appearing to have stabilized, although frequently at very high levels. Heterosexual exposure is the primary mode of HIV transmission in sub-Saharan Africa, with women and girls disproportionately affected, accounting for ~60 percent of all HIV infections in that region. In 2009, an estimated 460,000 people were living with

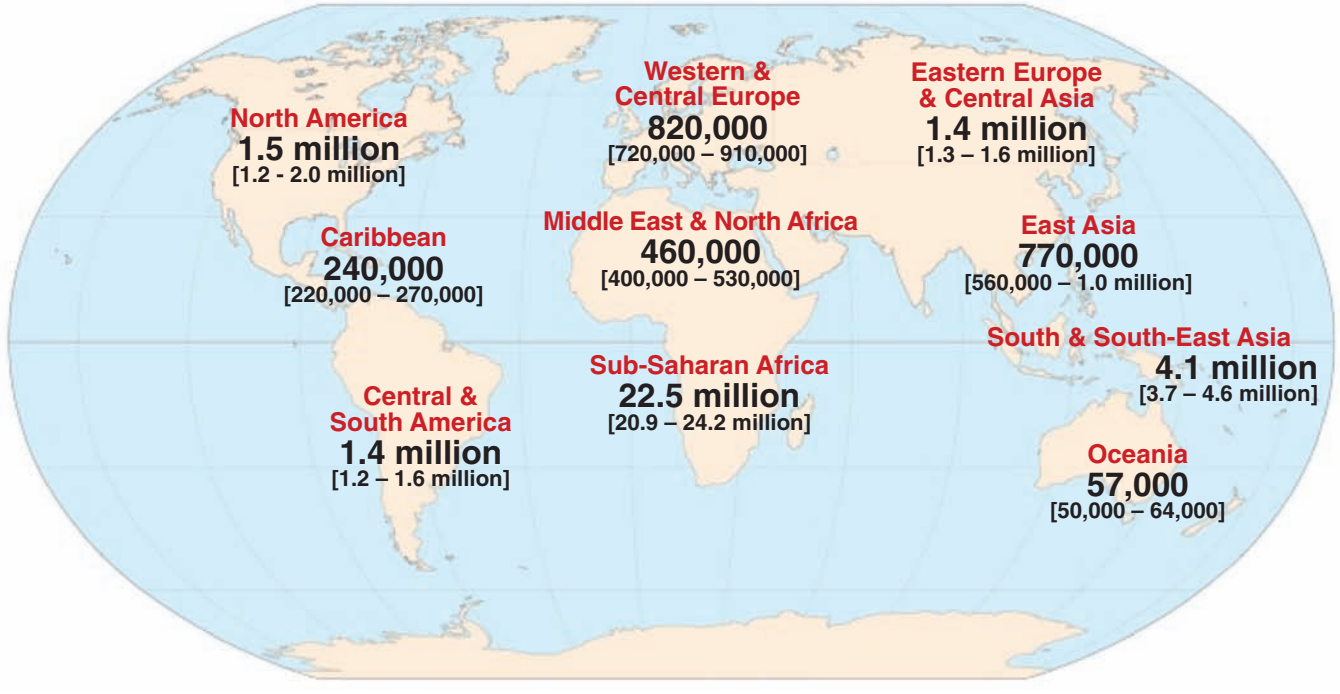


FIGURE 93-9
Estimated number of adults and children living with HIV infection as of December 2009. Total: 33.3 (31.4–35.3) (31.1–35.8) million. (*From Joint United Nations Programme on HIV/AIDS* [*UNAIDS: AIDS epidemic update, 2009*].)

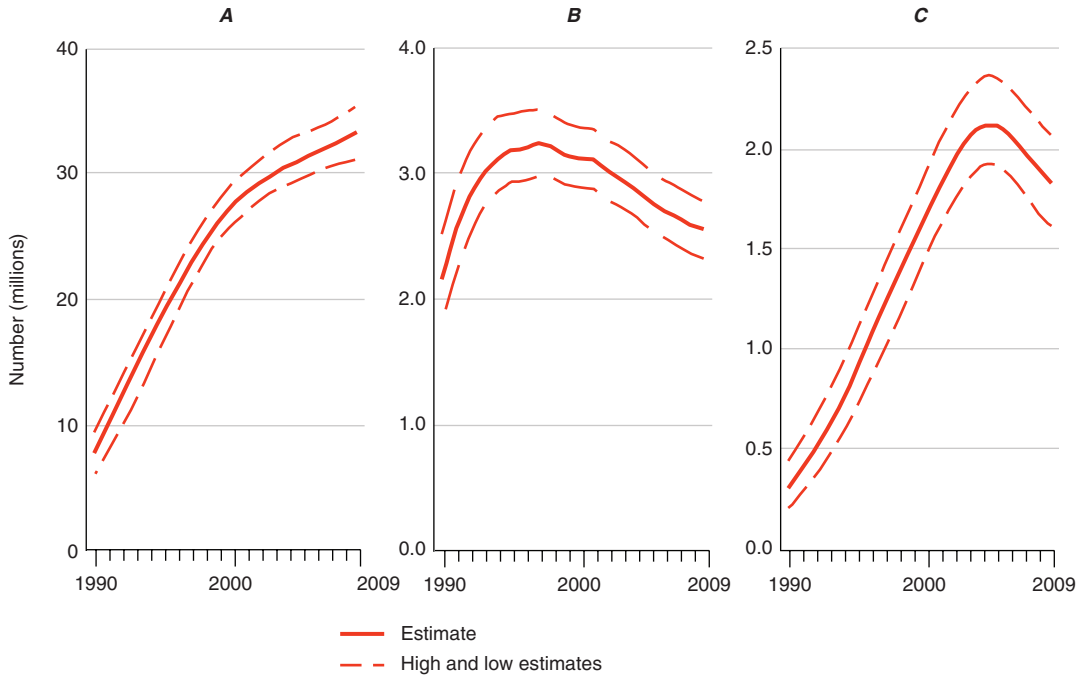


FIGURE 93-10
Global HIV/AIDS epidemiologic estimates, 1990–2009. ***A.*** Number of people living with HIV. ***B.*** Number of people newly infected with HIV globally. ***C.*** Number of adult and child deaths due to AIDS. (*From UNAIDS.*)

HIV in the Middle East/North Africa region. Cases are largely concentrated among IDUs, men who have sex with men, and sex workers and their clients.

In eastern, southern, and Southeast Asia, an estimated 4.9 million people were living with HIV at the end of 2009. In this region of the world, national HIV prevalence is highest in Southeast Asian countries, with wide variation in trends between different countries. Among countries in Asia, only Thailand has an adult seroprevalence rate of >1%. However, the populations of many Asian nations are so large (especially India and China) that even low infection and seroprevalence rates result in large numbers of people living with HIV. Although Asia's epidemic has been concentrated for some time among specific populations—sex workers and their clients, men who have sex with men, and IDUs—it is expanding to the heterosexual partners of those most at risk. While the regional epidemic appears to be stable overall, HIV prevalence has increased in certain countries such as Bangladesh and Pakistan.

The epidemic is expanding in Eastern Europe and Central Asia, where ~1.4 million people were living with HIV at the end of 2009. The Russian Federation and Ukraine account for the majority of HIV cases in the region; the Ukraine has an adult seroprevalence rate of 1.1%, the highest in all of Europe. Driven initially by injection drug use and increasingly by heterosexual transmission, the number of new infections in this region has increased dramatically over the past decade.

Approximately 1.6 million people are living with HIV/AIDS in Central and South America and the Caribbean. Brazil is home to the largest number of HIV-infected people in the region. However, the epidemic has been slowed in that country due to successful treatment and prevention efforts. Men who have sex with men account for the largest proportion of HIV infections in Central and South America. The Caribbean region has the highest regional adult seroprevalence rate after Africa, due in large part to the huge case load in Haiti. Heterosexual transmission, often tied to sex work, is the main driver of transmission in the region.

Approximately 2.4 million people are living with HIV/AIDS in North America, Western and Central Europe, and Oceania. The number of new infections among men who have sex with men has increased over the past decade in these mostly high-income areas, while rates of new infections among heterosexuals have stabilized and infections among IDUs have fallen.

AIDS IN THE UNITED STATES

HIV/AIDS continues to have an extraordinary public health impact in the United States. As of January 1, 2010, an estimated 1,108,611 cases of AIDS had been diagnosed in the United States. Approximately 1.1 million individuals in the United States were living with HIV infection, ~21 percent of whom are unaware of their infection, according to recent analysis. Approximately two-thirds of those living with HIV/AIDS were nonwhite and nearly half (48%) were men who have sex with men. The estimated HIV seroprevalence rate among individuals age 13 years or older in the United States is ~0.5%.

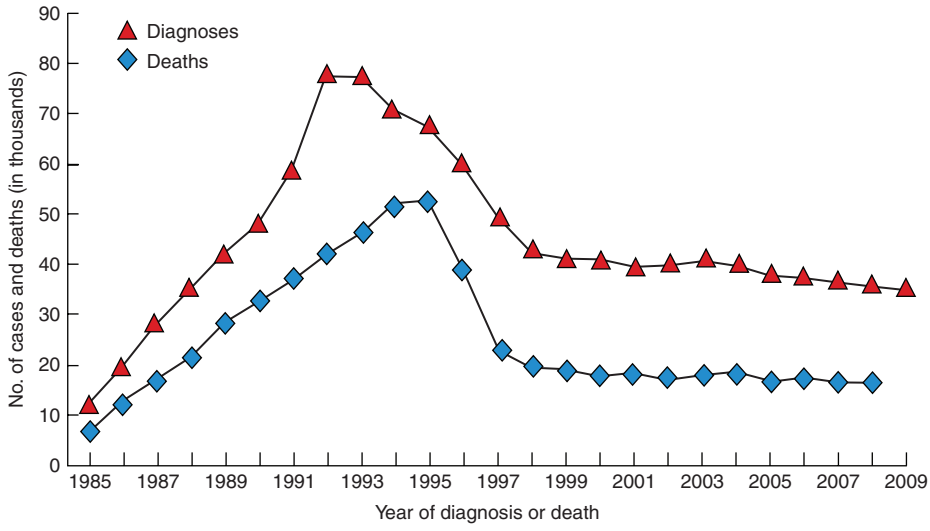


FIGURE 93-11
Estimated number of AIDS cases and AIDS deaths, United States, 1985–2009. (*From CDC: HIV/AIDS Surveillance Report, 2009, 2011. Available at www.cdc.gov/hiv/topics/surveillance/resources/reports/.*)

The number of AIDS cases and deaths in the United States rose steadily through the 1980s; AIDS cases peaked in 1993 and deaths in 1995 **(Fig. 93-11)**. Since then, the annual numbers of AIDS-related deaths in the United States have fallen ~70%. This trend is due to several factors, including the improved prophylaxis and treatment of opportunistic infections, the growing experience among the health professions in caring for HIV-infected individuals, improved access to health care, and a decrease in new infections due to saturational effects and prevention efforts. However, the most influential factor clearly has been the increased use of potent antiretroviral drugs, generally administered in a combination of three or four agents.

An estimated 56,000 individuals are newly infected each year in the United States. This *HIV incidence* figure has remained stable for at least 15 years **(Fig. 93-12)**. Among adults and adolescents newly diagnosed with HIV infection (regardless of AIDS status) in 2009, ~76% were men and ~24% were women **(Fig. 93-13)**. Of new HIV/AIDS *diagnoses* among men, ~75% were due to male-to-male sexual contact, ~14% to heterosexual

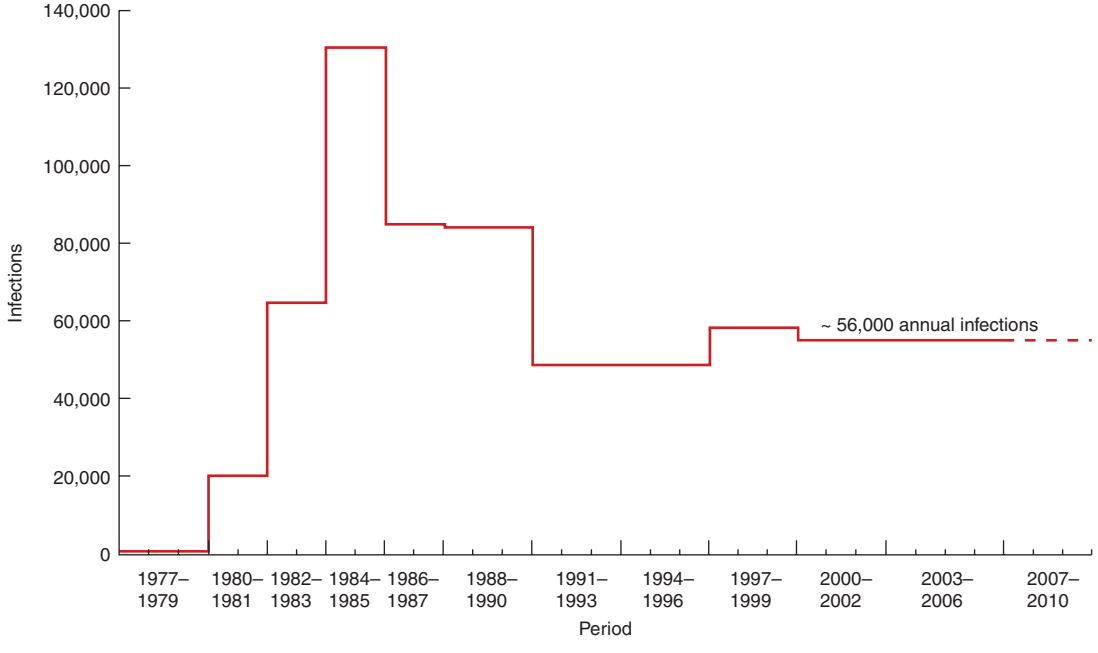


FIGURE 93-12
Estimated number of new HIV infections, United States. (*From HI Hall et al: JAMA 300:520, 2008.*)

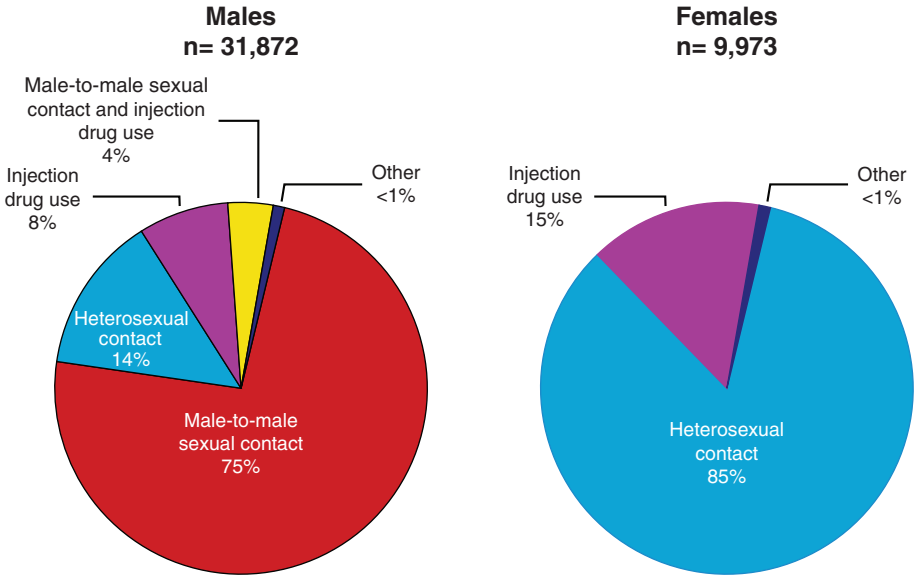


FIGURE 93-13
Transmission categories of adults and adolescents with HIV/AIDS diagnosed during 2009 in the United States. Estimates from 40 states with confidential, name-based HIV infection reporting. Data include persons with a diagnosis of HIV infection regardless of AIDS status at diagnosis. (*From CDC: HIV/AIDS Surveillance Report, 2009, 2011. Available at www.cdc.gov/hiv/topics/surveillance/resources/reports/.*)

contact, ~8% to injection drug use, and ~4% to a combination of male-to-male sexual contact and injection drug use. Of new HIV/AIDS diagnoses among women, ~85% were due to heterosexual contact and ~15% to injection drug use. It is important to note that the number of new diagnoses of HIV infection is not the same as the number of new infections with HIV (incidence): a person may be infected with HIV for years before being diagnosed.

HIV transmission patterns in the United States have shifted over time **(Fig. 93-14)**. When one looks at the totality of data collected from the beginning of the epidemic, ~48% of all AIDS cases are among men who have had sex with men. In 1985, male-to-male sexual contact accounted for an estimated 65% of all AIDS diagnoses; this proportion reached its lowest point in 1999 at ~40% of diagnoses. Since then, the percentage of AIDS diagnoses attributed to male-to-male sexual contact has increased; in 2009 this transmission category accounted for 48% of all AIDS diagnoses. The estimated percentage of AIDS diagnoses attributed to injection drug use increased from 20% to 31% during 1985–1994 and decreased since that time, accounting for 15% of diagnoses in 2009.

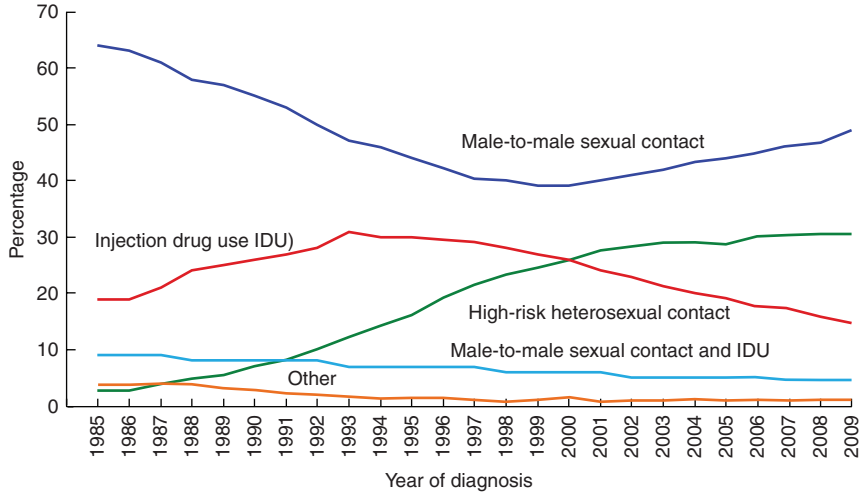


FIGURE 93-14
Estimated AIDS diagnoses among adults and adolescents, by transmission category and year of diagnosis, United States, 1985–2009. (*From CDC: HIV/AIDS Surveillance Report, 2009, 2011. Available at www.cdc.gov/hiv/topics/surveillance/resources/reports/.*)

The estimated percentage of AIDS diagnoses attributed to heterosexual contact increased from 3% in 1985 to 31% in 2009.

HIV infection and AIDS have disproportionately affected minority populations in the United States. Among those diagnosed with HIV (regardless of AIDS status) in 2009, 52% percent were blacks/African Americans, a group that constitutes only 12% of the U.S. population **(Fig. 93-15*A*)**. The estimated rate of new HIV diagnoses in 2009 by race/ethnicity per 100,000 population is shown in **Fig. 93-15*B***.

As of January 1, 2010, an estimated 9448 cases of AIDS in children <13 years old had been diagnosed in the Unites States, and ~59% of these individuals have died. Approximately 91% of these children were born to mothers who were HIV-infected or who were at risk for HIV infection; in the majority of those cases, the mother was either an IDU or the heterosexual partner of an IDU. The estimated number of AIDS cases diagnosed among children perinatally exposed to HIV peaked in 1992 and has decreased in recent years **(Fig. 93-16)**. The decline of these cases is likely associated with the implementation of guidelines for the universal counseling and voluntary HIV testing of pregnant women and the use of cART for pregnant women and newborn infants in order to prevent infection. Another contributing factor is the effective treatment of HIV infection in children who have become infected.

Although the HIV/AIDS epidemic on the whole is plateauing in the United States, it is spreading rapidly among certain populations, stabilizing in others, and decreasing in others. Similar to other STDs, HIV infection will not spread homogeneously throughout the population of the United States. However, it

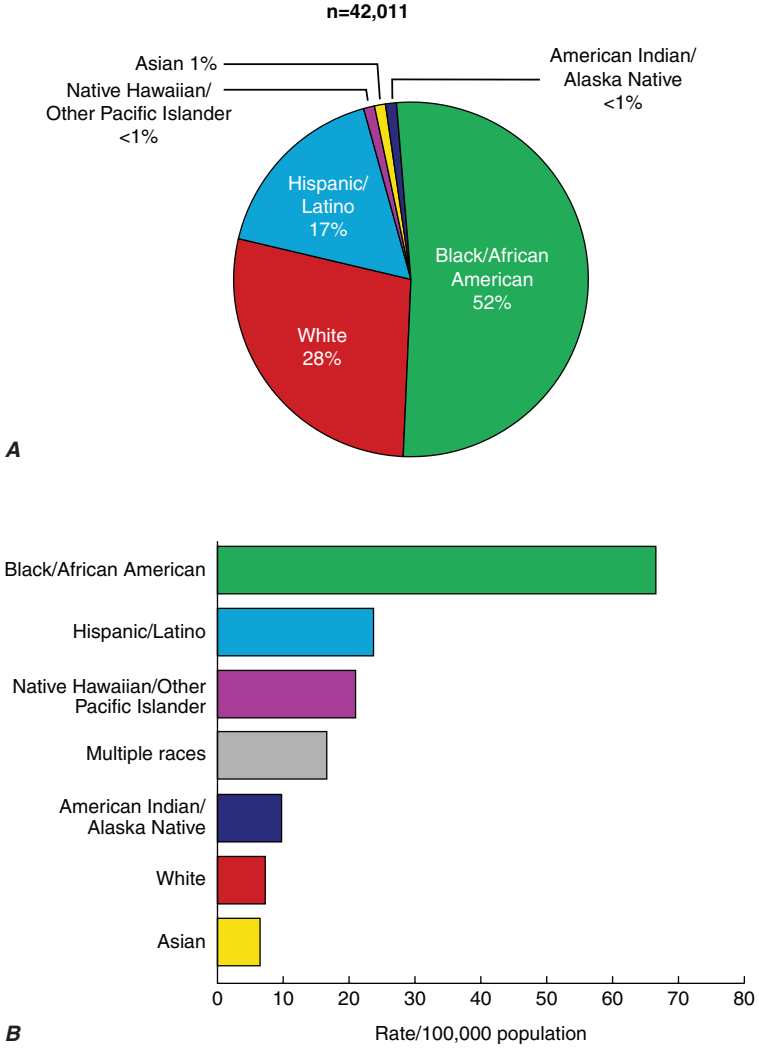


FIGURE 93-15

Race/ethnicity of persons (including children) with HIV/AIDS diagnosed during 2009 in the United States. *A.* Proportion of new infections by race/ethnicity. ***B.*** Rate of new infections by race/ethnicity (per 100,000 population). Estimates from 40 states with confidential, name-based HIV infection reporting. Data include persons with a diagnosis of HIV infection regardless of AIDS status at diagnosis. (*From CDC: HIV/AIDS Surveillance Report, 2009, 2011. Available at www.cdc.gov/hiv/topics/surveillance/resources/reports/.*)

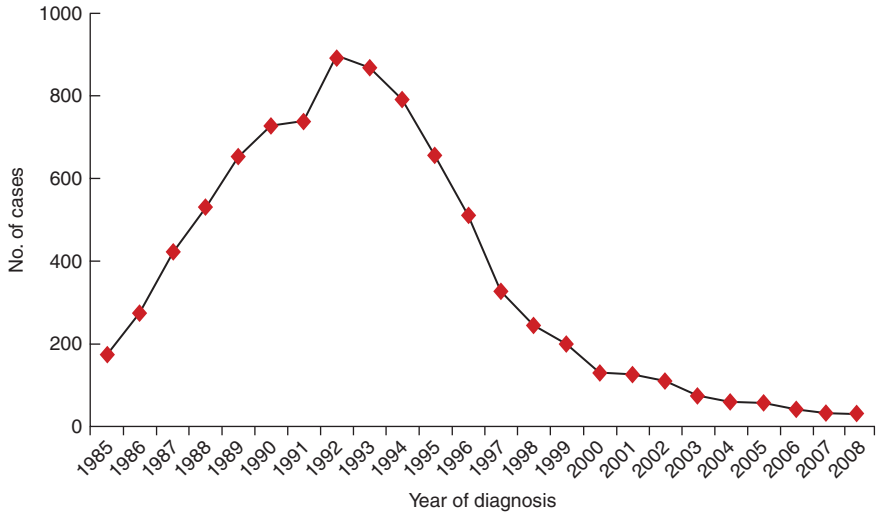


FIGURE 93-16
Estimated numbers of perinatally acquired AIDS cases in children by year of diagnosis, 1985–2009, United States (*From CDC: HIV/AIDS Surveillance Report, 2009, 2011. Available at www.cdc.gov/hiv/topics/surveillance/resources/reports/.*)

is clear that anyone who practices high-risk behavior is at risk for HIV infection. In addition, recent increases in infections and AIDS cases among young men who have sex with men as well as the spread in pockets of poverty in both urban and rural regions (particularly among underserved minority populations in the southern United States with inadequate access to health care) testify that the epidemic of HIV infection in the United States remains a public health problem of major proportions.

PATHOPHYSIOLOGY AND PATHOGENESIS

The hallmark of HIV disease is a profound immunodeficiency resulting primarily from a progressive quantitative and qualitative deficiency of the subset of T lymphocytes referred to as *helper T cells* occurring in a setting of polyclonal immune activation. The *helper* subset of T cells is defined phenotypically by the presence on its surface of the CD4 molecule, which serves as the primary cellular receptor for HIV. A co-receptor must also be present together with CD4 for efficient binding, fusion, and entry of HIV-1 into its target cells (Figs. 93-3 and 93-4). HIV uses two major co-receptors, CCR5 and CXCR4, for fusion and entry; these co-receptors are also the primary receptors for certain chemoattractive cytokines termed *chemokines* and belong to the seven-transmembrane-domain G protein–coupled family of receptors. A number of mechanisms responsible for cellular depletion and/or immune dysfunction of CD4+ T cells have been demonstrated in vitro; these include direct infection and destruction of these cells by HIV, as well as indirect effects such as immune clearance of infected cells, immune exhaustion due to aberrant cellular activation, and activation-induced cell death. Patients with CD4+ T cell levels below certain thresholds are at high risk of developing a variety of opportunistic diseases, particularly the infections and neoplasms that are AIDS-defining illnesses. Some features of AIDS, such as Kaposi's sarcoma and certain neurologic abnormalities, cannot be explained completely by the immunodeficiency caused by HIV infection, since these complications may occur prior to the development of severe immunologic impairment.

The combination of viral pathogenic and immunopathogenic events that occurs during the course of HIV disease from the moment of initial (primary) infection through the development of advanced-stage disease is complex and varied. It is important to appreciate that the pathogenic mechanisms of HIV disease are multifactorial and multiphasic and are different at different stages of the disease. Therefore, it is essential to consider the typical clinical course of an untreated HIV-infected individual in order to more fully appreciate these pathogenic events **(Fig. 93-17)**.

EARLY EVENTS IN HIV INFECTION: PRIMARY INFECTION AND INITIAL DISSEMINATION OF VIRUS

Using mucosal transmission as a model, the earliest events (within hours) that occur following exposure of HIV to the mucosal surface determine whether an infection will be established as well as the subsequent course of events following infection. Although the mucosal barrier is relatively effective in limiting access of HIV to susceptible targets in the lamina propria, the virus can cross the barrier by transport on dendritic cells just beneath the surface or through microscopic rents in the mucosa. Significant disruptions in the mucosal barrier as seen in ulcerative genital disease facilitate viral entry and increase the efficiency of infection. Virus then seeks susceptible targets, which are primarily CD4+ T

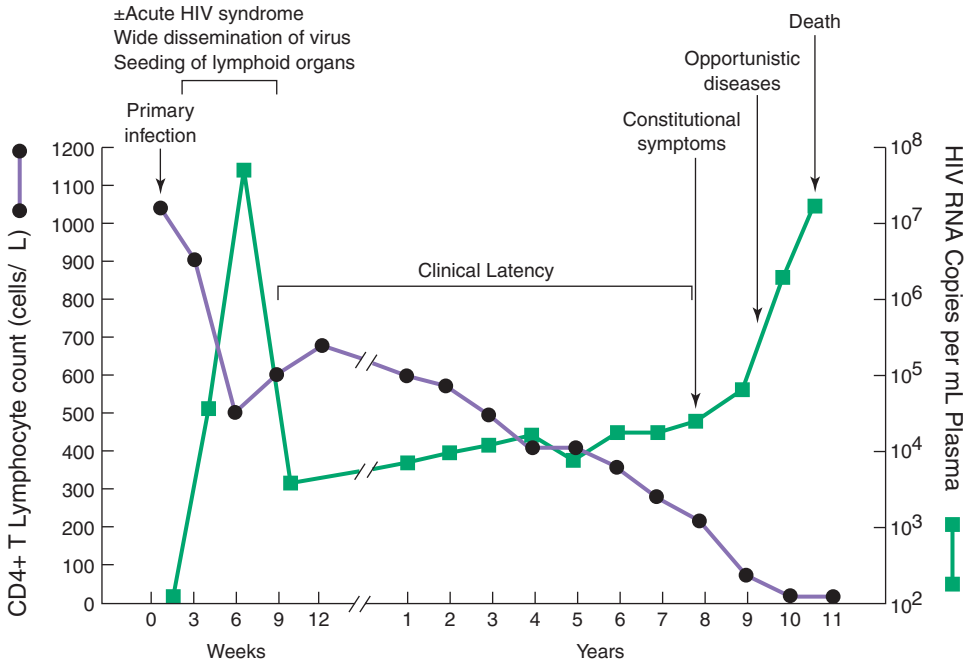


FIGURE 93-17
Typical course of an untreated HIV-infected individual. See text for detailed description. (*From G Pantaleo et al: N Engl J Med 328:327, 1993. Copyright 1993 Massachusetts Medical Society. All rights reserved.*)

cells that are spatially dispersed in the mucosa. This spatial dispersion of targets provides a significant obstacle to the establishment of infection. Such obstacles account for the low efficiency of sexual transmission of HIV (see "Sexual Transmission," earlier in the chapter). Both "partially" resting CD4+ T cells and activated CD4+ T cells serve as early amplifiers of infection. Resting CD4+ T cells are more abundant; however, activated CD4+ T cells produce larger amounts of virus. In order for infection to become established, the basic reproductive rate (R_0) must become greater or equal to 1, i.e., each infected cell would infect at least one other cell. As virus is produced within days to weeks, it is disseminated, first to the draining lymph nodes and then to other lymphoid compartments where it has easy access to dense concentrations of CD4+ T cell targets, allowing for a burst of high-level viremia **(Fig. 93-18)**. An important lymphoid organ, the gut-associated lymphoid tissue (GALT), is a major target of HIV infection and the location where large numbers of CD4+ T cells (usually memory cells) are infected and depleted, both by direct viral effects and by activation-associated apoptosis. Once virus replication reaches this threshold and virus is widely disseminated, infection is firmly established and the process is irreversible. It is important to point out that the initial infection of susceptible cells may vary somewhat with the route of infection. Virus that enters directly into the bloodstream via infected blood or blood products (i.e., transfusions, use of contaminated needles for injection drugs, sharp-object injuries, maternal-to-fetal transmission either intrapartum or perinatally, or sexual intercourse where there is enough trauma to cause bleeding) is likely cleared from the circulation to the spleen and other lymphoid organs, where primary focal infections begin, followed by wider dissemination throughout other lymphoid tissues as described earlier.

It has been demonstrated that sexual transmission of HIV is the result of a single infectious event and that a viral genetic bottleneck exists for transmission. In this regard, certain characteristics of the HIV envelope glycoprotein have a major influence on transmission, at least in subtype A and C viruses. Transmitting viruses, often referred to as "founder viruses," are usually underrepresented in the circulating viremia of the transmitting partner and are less-diverged viruses with signature sequences including shorter V1–V2 loop sequences and fewer predicted N-linked glycosylation sites relative to the major circulating variants. These viruses are usually sensitive to neutralization by antibody from the transmitting partner. Once replication proceeds in the newly infected partner, the founder virus diverges and accumulates glycosylation sites, becoming progressively more resistant to neutralization **(Fig. 93-19)**.

The acute burst of viremia and wide dissemination of virus in primary HIV infection may be associated with an *acute HIV syndrome,* which occurs to varying degrees in ~50% of individuals with primary infection. This syndrome is usually associated with high levels of viremia, measured in millions of copies of HIV RNA per milliliter of plasma, that last for several weeks. Acute mononucleosis-like symptoms are well correlated with the presence of viremia. Virtually all patients develop some degree of viremia during primary infection, which contributes to virus dissemination throughout the lymphoid tissue, even though they may remain

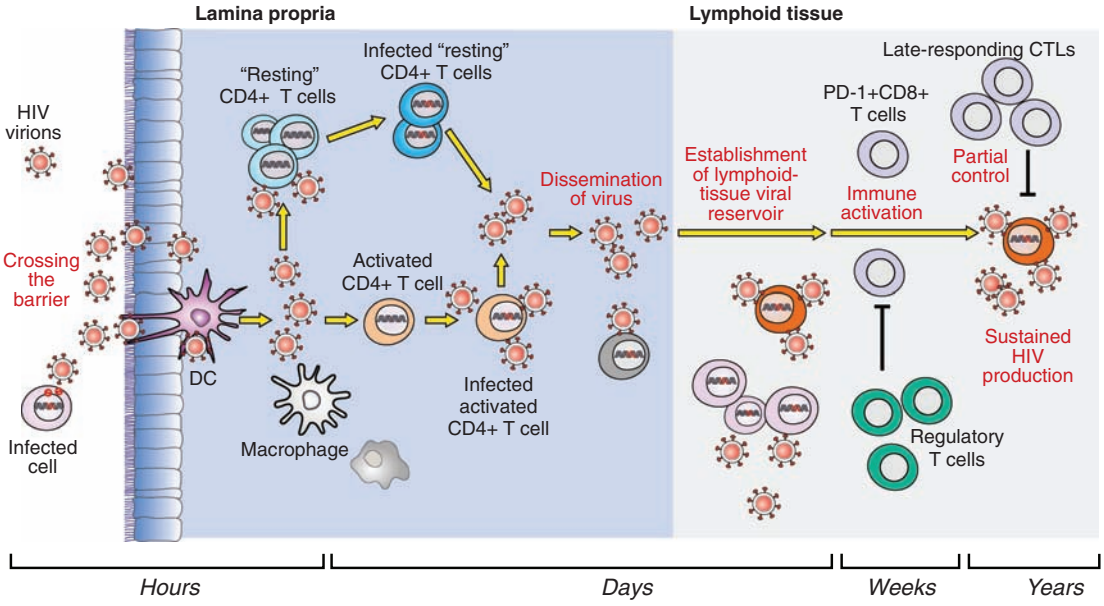


FIGURE 93-18
Summary of early events in HIV infection. See text for detailed description. CTLs, cytolytic T lymphocytes; HIV, human immunodeficiency virus. (*Adapted from AT Haase: Nat Rev Immunol 5:783, 2005.*)

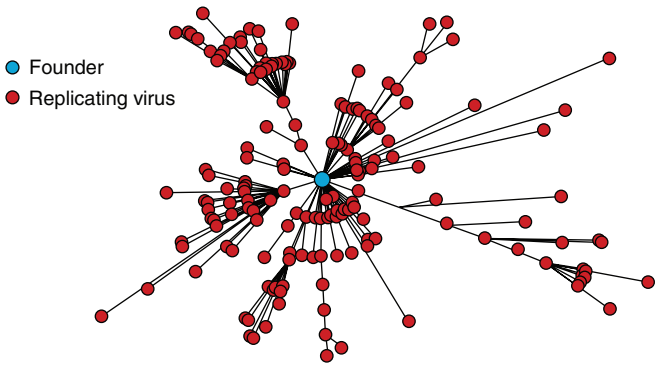


FIGURE 93-19
As HIV diverges from founder to chronically replicating virus, it accumulates N-linked glycosylation sites. See text for detailed description. (*Adapted from CA Derdeyn et al:* Science *303:2019, 2004; B Chohan et al: J Virol 79:6528, 2005; and BF Keele et al: Proc Natl Acad Sci USA 105:7552, 2008.*)

asymptomatic or not recall experiencing symptoms. It appears that the initial level of plasma viremia in primary HIV infection does not necessarily determine the rate of disease progression; however, the set point of the level of steady-state plasma viremia after ~1 year does seem to correlate with the slope of disease progression in the untreated patient.

ESTABLISHMENT OF CHRONIC AND PERSISTENT INFECTION

Persistent virus replication

HIV infection is unique among human viral infections. Despite the robust cellular and humoral immune responses that are mounted following primary infection (see "Immune Response to HIV," later), once infection has been established the virus succeeds in escaping immune-mediated clearance, paradoxically seems to thrive on immune activation, and is never eliminated completely from the body. Rather, a chronic infection develops and persists with varying degrees of continual virus replication in the untreated patient for a median of ~10 years before the patient becomes clinically ill (see "Advanced HIV Disease" later). It is this establishment of a chronic, persistent infection that is the hallmark of HIV disease. Throughout the often protracted course of chronic infection, virus replication can invariably be detected in untreated patients, both by highly sensitive assays for plasma viremia as well as by demonstration of cell-associated HIV RNA in immunocompetent cells (predominantly CD4+ T cells and macrophages) in the circulation and in lymphoid tissue. Recent studies using highly sensitive molecular techniques have demonstrated that even in certain patients in whom plasma viremia is suppressed to below 50 copies of HIV RNA/mL by cART, there is a continual low level of virus replication. In other human viral infections, with very few exceptions, if the host survives, the virus is completely cleared from the body and a state of immunity against subsequent infection develops. HIV infection very rarely kills the host during primary infection. Certain viruses, such as HSV (Chap. 84), are not completely cleared from the body after infection but instead enter a latent state; in these cases, clinical latency is accompanied by microbiologic latency. This is not the case with HIV infection, as described earlier. Chronicity associated with persistent virus replication can also be seen in certain cases of HBV and HCV infections (Chap. 96); however, in these infections the immune system is not a target of the virus.

Evasion of immune system control

Inherent to the establishment of chronicity of HIV infection is the ability of the virus to evade elimination and control by the immune system. There are a number of mechanisms whereby the virus accomplishes this evasion. Paramount among these is the establishment of a sustained level of replication associated with the generation of viral diversity via mutation and recombination, thus providing a means to evade control and elimination by the immune system. The selection of mutants that escape control by CD8+ cytolytic T lymphocytes (CTLs) is critical to the propagation and progression of HIV infection. The high rate of virus replication associated with inevitable mutations also contributes to the inability of neutralizing antibody to contain the virus quasispecies present in an individual at any given time. Extensive analyses of sequential HIV isolates and host responses have demonstrated that viral escape from B cell and CD8+ T cell epitopes occurs early after infection and allows the virus to stay one step ahead of effective immune responses. In addition, clones of CD8+ CTLs that expand greatly during primary HIV infection, and likely represent the high-affinity clones that would be expected to be most efficient in eliminating virus-infected cells, are no longer detectable after their initial burst of expansion. It is thought that the initially expanded clones may have been deleted or rendered dysfunctional owing to the overwhelming immune activation resulting from persistent viral replication, similar to the exhaustion of CD8+ CTLs that has been reported in the murine model of lymphocytic choriomeningitis virus (LCMV) infection. Recent studies have indicated that exhaustion of effector cells during prolonged immune activation is associated with expression of the programmed death (PD) 1 molecule (of the B7-CD28 family of molecules) on activated cells and its interaction with its ligands (L) PD-L1 and PD-L2 on antigen-presenting cells. This interaction results in a partially reversible signal for cell death and/or dysfunction. Another mechanism contributing to the evasion by HIV of immune system control is the downregulation of HLA class I molecules on the surface of HIV-infected cells by the Nef protein of HIV, resulting in the lack of ability of the CD8+ CTL to recognize and kill the infected target cell. Although this downregulation of HLA class I molecules would favor elimination of HIV-infected cells by natural killer (NK) cells, this latter mechanism does not seem to remove HIV-infected cells effectively (see next). The principal targets of neutralizing antibodies to HIV are the envelope proteins gp120 and gp41. HIV employs at least three mechanisms to evade neutralizing responses: hypervariability in the primary sequence of the envelope, extensive glycosylation of the envelope, and conformational masking of neutralizing epitopes.

CD4+ T cell help is essential for the integrity of antigen-specific immune responses, both humoral and cell-mediated. HIV preferentially infects activated CD4+ T cells including HIV-specific CD4+ T cells, and so this loss of viral-specific helper T cell responses has profound negative consequences for the immunologic control of HIV replication. Furthermore, this loss occurs early in the course of infection, and animal studies indicate that 40–70% of all memory CD4+ T cells in the GALT are eliminated during acute infection. Another potential means of escape of HIV-infected cells from elimination by CD8+ CTLs is the sequestration of infected cells in immunologically privileged sites such as the central nervous system (CNS).

Finally, the escape of HIV from elimination during primary infection allows the formation of a pool of latently infected cells that cannot be eliminated by virus-specific CTLs (see later in the chapter). Thus, despite a potent immune response and the marked downregulation of virus replication following primary HIV infection, HIV succeeds in establishing a state of chronic infection with a variable degree of persistent virus replication. During this period most patients make the clinical transition from acute primary infection to variable periods of clinical latency or smoldering disease activity (see later).

Reservoirs of HIV-infected cells: obstacles to the eradication of virus

There exists in virtually all HIV-infected individuals a pool of latently infected, resting CD4+ T cells that serves as at least one component of the persistent reservoir of virus. Such cells manifest postintegration latency in that the HIV provirus integrates into the genome of the cell and can remain in this state until an activation signal drives the expression of HIV transcripts and ultimately replication-competent virus. This form of latency is to be distinguished from preintegration latency, in which HIV enters a resting CD4+ T cell and, in the absence of an activation signal, reverse transcription of the HIV genome occurs to a certain extent but the resulting proviral DNA fails to integrate into the host genome. This period of preintegration latency may last hours to days, and if no activation signal is delivered to the cell, the proviral DNA loses its capacity to initiate a productive infection. If these cells do become activated, reverse transcription proceeds to completion and the virus continues along its replication cycle (see earlier and **Fig. 93-20**). The pool of cells that are in the postintegration state of latency is established early during the course of primary HIV infection. Despite the suppression of plasma viremia to <50 copies of HIV RNA per milliliter by potent combinations of several antiretroviral drugs administered over several years, this pool of latently infected cells persists and can give rise to replication-competent virus. Modeling studies built on projections of decay curves have estimated that in such a setting of prolonged suppression, it would require 7–70 years for the pool of latently infected cells to be completely eliminated. Furthermore, the reservoir of latently infected cells is replenished during minor detectable rebounds or "blips" of virus replication that may occur intermittently, superimposed on the low levels of persistent virus replication that may remain below the limits of detection of current assays (see later in

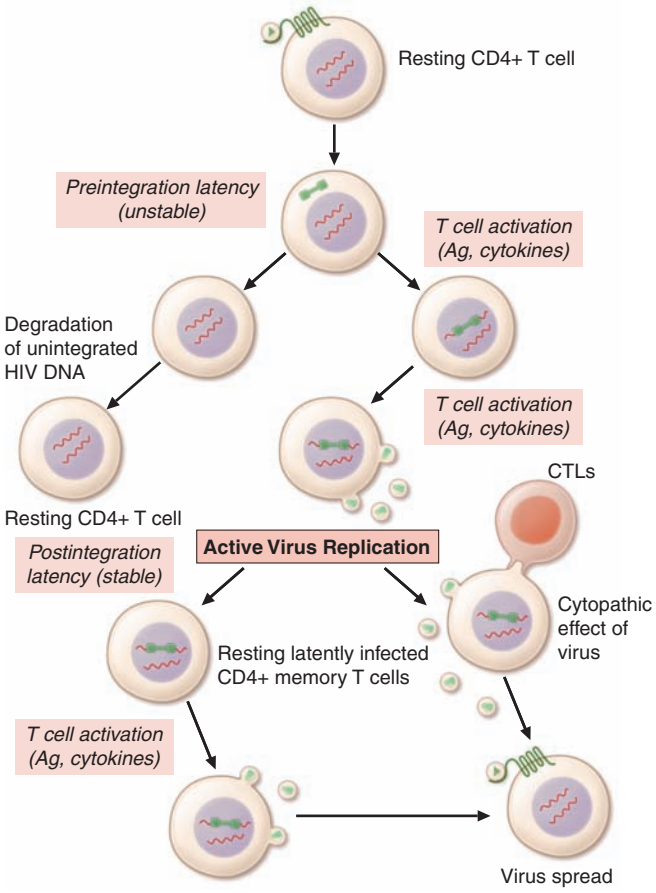


FIGURE 93-20
Generation of latently infected, resting CD4+ T cells in HIV-infected individuals. See text for details. Ag, antigen; CTLs, cytolytic T lymphocytes. (*Courtesy of TW Chun; with permission.*)

the chapter) (Fig. 93-20), even in patients who for the most part are treated successfully. Reservoirs of HIV-infected cells, latent or otherwise, can exist in a number of compartments including the lymphoid tissue, peripheral blood, and the CNS (likely in cells of the monocyte/macrophage lineage) as well as in other unidentified locations. Over the past several years, attempts have been made to eliminate HIV in the latent viral reservoir using agents that stimulate resting CD4+ T cells during the course of antiretroviral therapy; however, such attempts have been unsuccessful. Thus, this persistent reservoir of infected cells at various stages of latency and/or low-level, persistent virus replication are major obstacles to any goal of eradication of virus from infected individuals, despite the favorable clinical outcomes that have resulted from cART.

Viral dynamics

The dynamics of viral production and turnover have been quantified using mathematical modeling in the setting of the administration of reverse transcriptase and protease inhibitors to HIV-infected individuals in clinical studies. Treatment with these drugs resulted in a precipitous decline in the level of plasma viremia, which typically fell by well over 90% within 2 weeks. The number of CD4+ T cells in the blood increased concurrently, which suggested that the killing of CD4+ T cells was linked directly to the levels of replicating virus. However, a significant component of the early rise in CD4+ T cell numbers following the initiation of therapy may be due to the redistribution of cells into the peripheral blood from other body compartments as a consequence of therapy-related diminution in viremia-associated immune system activation. It was determined on the basis of modeling the kinetics of viral decline and the emergence of resistant mutants during therapy that 93–99% of the circulating virus originated from recently infected, rapidly turning over CD4+ T cells and that ~1–7% of circulating virus originated from longer-lived cells, likely monocytes/macrophages. A negligible amount of circulating virus originated from the pool of latently infected cells **(Fig. 93-21)**. It was also determined that the half-life of a circulating virion was ~30–60 min and that of productively infected cells was 1 day. Given the relatively steady level of plasma viremia and of infected cells, it appears that extremely large amounts of virus (~10^{10}–10^{11} virions) are produced and cleared from the circulation each day. In addition,

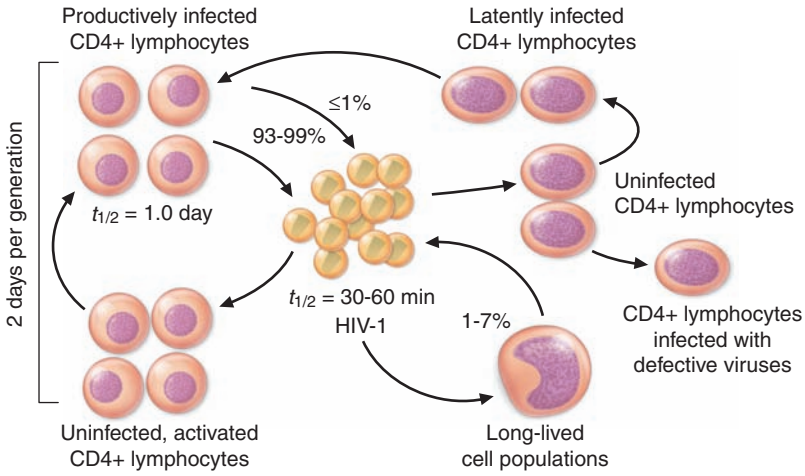


FIGURE 93-21
Dynamics of HIV infection in vivo. See text for detailed description. (*From AS Perelson et al: Science 271:1582, 1996.*)

data suggest that the minimal duration of the HIV-1 replication cycle in vivo is ~2 days. Other studies have demonstrated that the decrease in plasma viremia that results from cART correlates closely with a decrease in virus replication in lymph nodes, further confirming that lymphoid tissue is the main site of HIV replication and the main source of plasma viremia.

The level of steady-state viremia, called the viral *set point*, at ~1 year has important prognostic implications for the progression of HIV disease in the untreated patient. It has been demonstrated that as a group untreated HIV-infected individuals who have a low set point at 6 months to 1 year following infection progress to AIDS much more slowly than individuals whose set point is very high at that time **(Fig. 93-22)**.

Clinical latency versus microbiologic latency

Except in long-term nonprogressors (see "Long-Term Survivors and Long-Term Nonprogressors," later), the level of CD4+ T cells in the blood decreases progressively in HIV-infected individuals. The decline in CD4+ T cells may be gradual or abrupt, the latter usually reflecting a significant spike in the level of plasma viremia. Most patients are relatively asymptomatic while this progressive decline is taking place (see later) and are often described as being in a state of *clinical latency*. However, this term is misleading; it does not mean disease latency, since progression, although slow in many cases, is generally relentless during this period. Furthermore, clinical latency should not be confused with microbiologic latency, since varying levels of virus replication inevitably occur during this period of clinical latency. Even in those rare patients who have <50 copies of HIV RNA per milliliter in the absence of therapy, there is virtually always some degree of ongoing virus replication.

ADVANCED HIV DISEASE

In untreated patients or in patients in whom therapy has not adequately controlled virus replication, after a variable period (usually measured in years), the CD4+ T cell count falls below a critical level (<200/μL) and the patient becomes highly susceptible to opportunistic disease (Fig. 93-17). For this reason, the CDC case definition of AIDS includes all HIV-infected individuals with CD4+ T cell counts below this level (Table 93-1). Patients may experience constitutional signs and symptoms or may develop an opportunistic disease abruptly without any prior symptoms, although the latter scenario is unusual. The depletion of CD4+ T cells continues to be progressive and unrelenting in this phase. It is not uncommon for CD4+ T cell counts in the untreated patient to drop as low as 10/μL or even to zero. In countries where cART and prophylaxis and treatment for opportunistic infections are readily accessible to such patients, survival is increased dramatically even in those patients with advanced HIV disease. In contrast, untreated patients who progress to this severest form of immunodeficiency usually succumb to opportunistic infections or neoplasms (see later).

LONG-TERM SURVIVORS AND LONG-TERM NONPROGRESSORS

It is important to distinguish between the terms *long-term survivor* and *long-term nonprogressor*. Long-term nonprogressors are by definition long-term survivors; however, the reverse is not always true. Predictions from one study that antedated the availability of effective cART estimated that ~13% of homosexual/bisexual men who were infected at an early age may remain free of clinical AIDS for >20 years. Many of

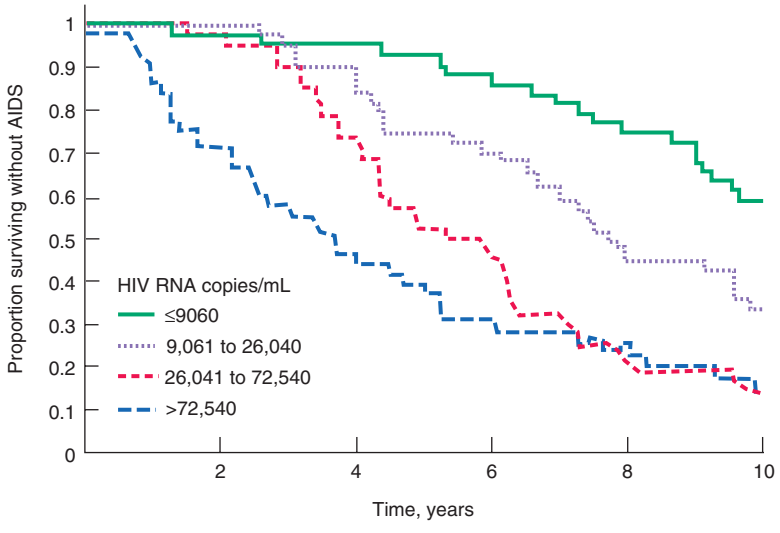


FIGURE 93-22
Relationship between levels of virus and rates of disease progression. Kaplan-Meier curves for AIDS-free survival stratified by baseline HIV-1 RNA categories (copies per milliliter). (*From JW Mellors et al: Science 272:1167, 1996.*)

these individuals may have progressed in their degree of immune deficiency; however, they certainly survived for a considerable period of time. With the advent of effective antiretroviral therapy, the survival of HIV-infected individuals has dramatically increased. Early in the AIDS epidemic, prior to the availability of therapy, if a patient presented with a life-threatening opportunistic infection, the median survival was 26 weeks from the time of presentation. Currently, an HIV-infected 20-year-old individual in a high-income country who is appropriately treated with cART can expect to live at least 50 years according to mathematical model projections. In the face of cART, long-term survival is becoming commonplace. Definitions of long-term nonprogressors have varied considerably over the years, and so such individuals constitute a heterogeneous group. Long-term nonprogressors were first described in the 1990s. Originally, individuals were considered to be long-term nonprogressors if they had been infected with HIV for a long period (≥10 years), their CD4+ T cell counts were in the normal range, and they remained stable over years without receiving cART. Approximately 5–15% of HIV-infected individuals fell into this broader nonprogressor category. However, this group was rather heterogenous and over time a significant proportion of these individuals progressed and ultimately required therapy. From this broader group, a much smaller subgroup of "elite" controllers or nonprogressors was identified, and they constituted less than 1% of HIV-infected individuals. These elite controllers, by definition, have extremely low levels of plasma viremia and normal CD4+ T cell counts. It is noteworthy that certain of their HIV-specific immune responses are robust and clearly superior to those of HIV-infected progressors. In this group of elite controllers certain HLA class I haplotypes are overrepresented, particularly HLA-B57-01 and HLA-B27-05. Outside of the subgroup of elite controllers, a number of other genetic factors have been shown to be involved to a greater or lesser degree in the control of virus replication and thus in the rate of HIV disease progression (see "Genetic Factors in HIV Pathogenesis," later).

LYMPHOID ORGANS AND HIV PATHOGENESIS

Regardless of the portal of entry of HIV, lymphoid tissues are the major anatomic sites for the establishment and propagation of HIV infection. Despite the use of measurements of plasma viremia to determine the level of disease activity, virus replication occurs mainly in lymphoid tissue and not in blood; indeed, the level of plasma viremia directly reflects virus production in lymphoid tissue.

Some patients experience progressive generalized lymphadenopathy early in the course of the infection; others experience varying degrees of transient lymphadenopathy. Lymphadenopathy reflects the cellular activation and immune response to the virus in the lymphoid tissue, which is generally characterized by follicular or germinal center hyperplasia. Lymphoid tissue involvement is a common denominator of virtually all patients with HIV infection, even those without easily detectable lymphadenopathy.

Simultaneous examinations of lymph tissue and peripheral blood in patients and monkeys during various stages of HIV and SIV infection, respectively, have led to substantial insight into the pathogenesis of HIV disease. In most of the original human studies, peripheral lymph nodes have been used predominantly as the source of lymphoid tissue. More recent studies in monkeys and humans have focused on the GALT, where the earliest burst of virus replication occurs in association with marked depletion of CD4+ T cells. In detailed studies of peripheral lymph node tissue, using a combination of polymerase chain reaction (PCR) techniques for HIV DNA and HIV RNA in tissue and HIV RNA in plasma, in situ hybridization for HIV RNA, and light and electron microscopy, the following picture has emerged. During acute HIV infection resulting from mucosal transmission, virus replication progressively amplifies from scattered lymphoid cells in the lamina propria to draining lymphoid tissue, leading to high levels of plasma viremia. The GALT plays a major role in the amplification of virus replication, and virus is disseminated from replication in the GALT to peripheral lymphoid tissue. A profound degree of cellular activation occurs (see later) and is reflected in follicular or germinal center hyperplasia. At this time copious amounts of extracellular virions (both infectious and defective) are trapped on the processes of the follicular dendritic cells (FDCs) in the germinal centers of the lymph nodes. Virions that have bound complement components on their surfaces attach to the surface of FDCs via interactions with complement receptors and likely via Fc receptors that bind to antibodies that are attached to the virions. In situ hybridization reveals expression of virus in individual cells of the paracortical area and, to a lesser extent, the germinal center **(Fig. 93-23)**.

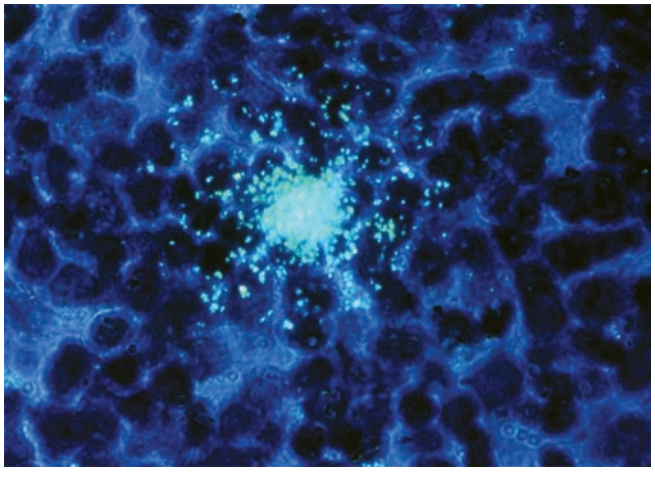


FIGURE 93-23
HIV in the lymph node of an HIV-infected individual. An individual cell infected with HIV shown expressing HIV RNA by in situ hybridization using a radiolabeled molecular probe. Original ×500. (*Adapted from G Pantaleo, AS Fauci: Nature 362:355, 1993.*)

The persistence of trapped virus after the transition from acute to chronic infection likely reflects a steady state whereby trapped virus turns over and is replaced by fresh virions that are continually produced. The trapped virus, either as whole virion or shed envelope, serves as a continual activator of CD4+ T cells, thus driving further virus replication.

During early-stage HIV disease, the architecture of the germinal centers is generally preserved and may even be hyperplastic owing to in situ proliferation of cells (mostly B lymphocytes) and recruitment to the lymph nodes of a number of cell types (B cells, CD4+ and CD8+ T cells). Electron-microscopic studies have demonstrated a fine network of FDCs with many long, fingerlike processes that envelop virtually every lymphocyte in the germinal center. Extracellular virions can be seen attached to the processes, yet the FDCs appear to be relatively healthy. The trapping of antigen is a physiologically normal function for the FDCs, which present antigen to B cells and contribute to the generation of B cell memory. However, in the case of HIV, the trapped virions serve as a persistent source of cellular activation, resulting in the secretion of proinflammatory cytokines such as interleukin (IL) 1β, tumor necrosis factor (TNF) α, and IL-6, which can upregulate virus replication in infected cells (see later). Furthermore, although trapped virus is coated by neutralizing antibodies, it has been demonstrated that certain of these virions remain infectious for CD4+ T cells while attached to the processes of the FDCs. CD4+ T cells that migrate into the germinal center to provide help to B cells in the generation of an HIV-specific immune response are susceptible to infection by these trapped virions. Thus, in HIV infection, a normal physiologic function of the immune system that contributes to the clearance of virus as well as to the generation of a specific immune response, can also have deleterious consequences.

As the disease progresses, the architecture of the germinal centers begins to show disruption. Electron microscopy reveals swollen organelles, and the FDCs begin to undergo cell death. The mechanisms of FDC death remain unclear; there is no indication by electron microscopy of copious virus replication or budding of virions off the cell in great quantities. This process of FDC death is accompanied by the deposition of collagen, leading to irreparable damage to the germinal centers. As the disease progresses to an advanced stage, there is complete disruption of the architecture of the germinal centers, accompanied by dissolution of the FDC network and massive dropout of FDCs. At this point, the lymph nodes are "burnt out." This destruction of lymphoid tissue compounds the immunodeficiency of HIV disease and contributes both to the inability to control HIV replication (leading usually to high levels of plasma viremia in the untreated or inadequately treated patient) and to the inability to mount adequate immune responses against opportunistic pathogens. The events from primary infection to the ultimate destruction of the immune system are illustrated in **Fig. 93-24**. Recently, nonhuman primate studies and some human studies have examined GALT at various stages of HIV disease. Within the GALT, the basal level of activation combined with virus-mediated cellular activation results in the infection and elimination of an estimated 50–90% of CD4+ T cells in the gut. The extent of this early damage to GALT, which constitutes a major component of

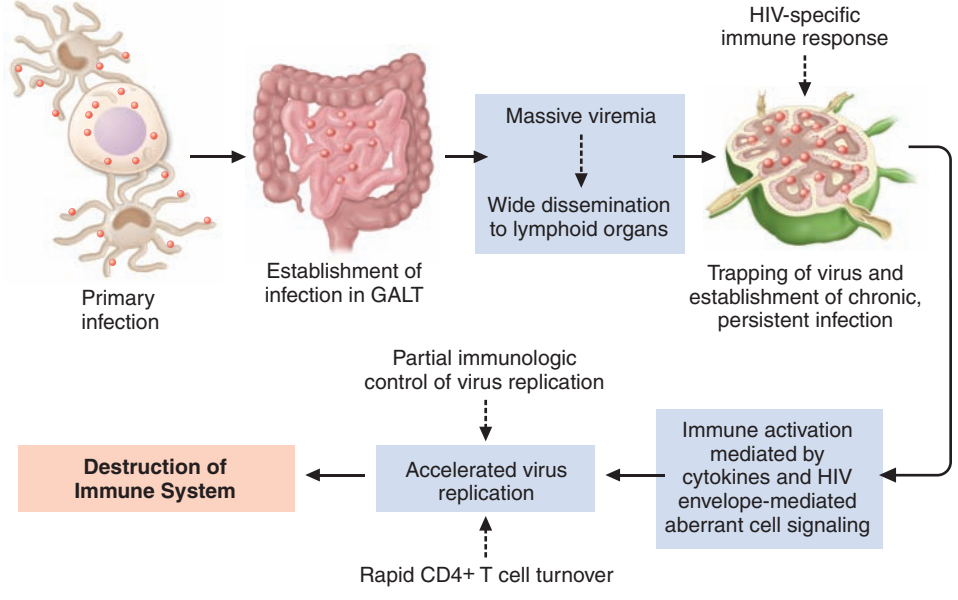


FIGURE 93-24

Events that transpire from primary HIV infection through the establishment of chronic persistent infection to the ultimate destruction of the immune system. See text for details. CTLs, cytolytic T lymphocytes; GALT, gut-associated lymphoid tissue.

lymphoid tissue in the body, may play a role in determining the potential for immunologic recovery of the memory cell subset.

IMMUNE ACTIVATION, INFLAMMATION, AND HIV PATHOGENESIS

Activation of the immune system and variable degrees of inflammation are essential components of any appropriate immune response to a foreign antigen. However, immune activation and inflammation, which can be considered aberrant in HIV-infected individuals, play a critical role in the pathogenesis of HIV disease and other chronic conditions associated with HIV disease. Immune activation and inflammation in the HIV-infected individual contribute substantially to (1) the replication of HIV, (2) the induction of immune dysfunction, and (3) the increased incidence of chronic conditions associated with persistent immune activation and inflammation **(Table 93-3)**.

Induction of HIV replication by aberrant immune activation

The immune system is normally in a state of homeostasis, awaiting perturbation by foreign antigenic stimuli. Once the immune response deals with and clears the antigen, the system returns to relative quiescence. This is generally not the case in HIV infection where, in the untreated patient, virus replication is almost invariably persistent and immune activation is persistent. HIV replicates most efficiently in activated CD4+ T cells; in HIV infection, chronic activation provides the cell substrates necessary for persistent virus replication throughout the course of HIV disease, particularly in the untreated patient and to variable degrees even in certain patients receiving cART whose levels of plasma viremia are suppressed to below the level of detection by standard assays. From a virologic standpoint, although quiescent CD4+ T cells can be infected with HIV, reverse transcription, integration, and virus spread are much more efficient in activated cells. Furthermore, cellular activation induces expression of virus in cells latently infected with HIV. In essence, immune activation and inflammation provide the engine that drives HIV replication. In addition to endogenous factors such as cytokines, a number of exogenous factors such as other microbes that are associated with heightened cellular activation can enhance HIV replication and thus may have important effects on HIV pathogenesis. Co-infection in vivo or in vitro with a range of viruses, such as HSV types 1 and 2, cytomegalovirus (CMV), human herpesvirus (HHV) 6, Epstein-Barr virus (EBV), HBV, adenovirus, and HTLV-I have been shown to upregulate HIV expression. In addition, infestation with nematodes has been shown to be associated with a heightened state of immune activation that facilitates HIV replication; in certain studies deworming of the infected host has resulted in a decrease in plasma viremia. Two diseases of extraordinary global health significance, malaria and tuberculosis (TB), have been shown to increase HIV viral load in dually infected individuals. Globally, *Mycobacterium tuberculosis* is the most common opportunistic infection globally in HIV-infected individuals (Chap. 70). In addition to the fact that HIV-infected individuals are more likely to develop active TB after exposure, it has been demonstrated that active TB can accelerate the course of HIV infection. It has also been shown that levels of plasma viremia are greatly elevated in HIV-infected individuals with active TB who are not on cART, compared with pre-TB levels and levels of viremia after successful treatment of the active TB. The situation is similar in the interaction between HIV and malaria parasites (Chap. 119). Acute infection of HIV-infected individuals with *Plasmodium falciparum* increases HIV viral load, and the increased viral load is reversed by effective malaria treatment.

TABLE 93-3

CONDITIONS ASSOCIATED WITH PERSISTENT IMMUNE ACTIVATION AND INFLAMMATION IN PATIENTS WITH HIV INFECTION

- Accelerated aging syndrome
- Bone fragility
- Cancers
- Cardiovascular disease
- Diabetes
- Kidney disease
- Liver disease
- Neurocognitive dysfunction

Microbial translocation and persistent immune activation

One proposed mechanism of persistent immune activation involves the disruption of the mucosal barrier in the gut due to HIV replication in and disruption of submucosal lymphoid tissue. As a result of this disruption, there is an increase in the products, particularly lipopolysaccharide (LPS), of bacteria that translocate from the bowel lumen through the damaged mucosa to the circulation, leading to persistent systemic immune activation and inflammation. This effect can persist even after the HIV viral load is brought to <50 copies/mL by cART. Depletion in the GALT of IL-17–producing T cells, which are responsible for defense against extracellular bacteria and fungi, is also thought to contribute to HIV pathogenesis.

Persistent immune activation and inflammation induce immune dysfunction

The activated state in HIV infection is reflected by hyperactivation of B cells leading to hypergammaglobulinemia; increased lymphocyte turnover; activation of monocytes; expression of activation markers on CD4+ and CD8+ T cells; increased activation-associated cellular apoptosis; lymph node hyperplasia, particularly early in the course of disease; increased secretion of proinflammatory cytokines, particularly IL-6; elevated levels of high-sensitivity C-reactive protein, fibrinogen, D-dimer, neopterin, β_2-microglobulin, acid-labile interferon, soluble (s) IL-2

receptors (R), sTNFR, sCD27, and sCD40L; and autoimmune phenomena (see "Autoimmune Phenomena," later). Even in the absence of direct infection of a target cell, HIV envelope proteins can interact with cellular receptors (CD4 molecules and chemokine receptors) to deliver potent activation signals resulting in calcium flux, the phosphorylation of certain proteins involved in signal transduction, co-localization of cytoplasmic proteins including those involved in cell trafficking, immune dysfunction, and, under certain circumstances, apoptosis. From an immunologic standpoint, chronic exposure of the immune system to a particular antigen over an extended period may ultimately lead to an inability to sustain an adequate immune response to the antigen in question. In many chronic viral infections, including HIV infection, persistent viremia is associated with "functional exhaustion" and apoptosis of virus-specific T cells. It has been demonstrated that this phenomenon may be mediated, at least in part, by the engagement of PD-1, which is highly expressed on the majority of HIV-specific T cells, with its ligands (PD-L1 and PD-L2) on antigen-presenting cells and epithelial cells, resulting in either T cell death or anergy. Furthermore, the ability of the immune system to respond to a broad spectrum of antigens may be compromised if immunocompetent cells are maintained in a state of chronic activation.

The deleterious effects of chronic immune activation on the progression of HIV disease are well established. As in most conditions of persistent antigen exposure, the host must maintain sufficient activation of antigen (HIV)-specific responses, but must also prevent excessive activation and potential immune-mediated damage to tissues. Certain studies suggest that normal immunosuppressive mechanisms that act to keep hyperimmune activation in check, particularly CD4+, FoxP3+, CD25+ regulatory T cells (T-regs), may be dysfunctional or depleted in the context of advanced HIV disease.

Medical conditions associated with persistent immune activation and inflammation in HIV disease

It has become clear as the survival of HIV-infected individuals has increased that a number of previously unrecognized medical complications are associated with HIV disease and that these complications relate to chronic immune activation and inflammation (Table 93-3). These complications can appear even after patients have experienced years of adequate control of viral replication (plasma viremia below detectable levels) for several years. Of particular note are endothelial cell dysfunction and its relationship to cardiovascular disease. Other chronic conditions that have been reported include bone fragility, certain cancers, persistent immune dysfunction, diabetes, kidney and liver disease, and neurocognitive dysfunction, thus presenting an overall picture of accelerated aging.

Apoptosis

Apoptosis is a form of programmed cell death that is a normal mechanism for the elimination of effete cells in organogenesis as well as in the cellular proliferation that occurs during a normal immune response. Apoptosis is largely dependent on cellular activation, and the aberrant cellular activation associated with HIV disease is correlated with a heightened state of apoptosis. HIV can trigger both Fas-dependent and Fas-independent pathways of apoptosis. Mechanisms involved in this process include upregulation of Fas and Fas ligand, upregulation of caspase-1 and caspase-6, downregulation of the antiapoptotic Bcl-2 protein, and activation of cyclin-dependent kinases. Certain viral gene products have been associated with enhanced susceptibility to apoptosis; these include Env, Tat, and Vpr. In contrast, Nef has been shown to possess antiapoptotic properties. A number of studies, including those examining lymphoid tissue, have demonstrated that the rate of apoptosis is elevated in HIV infection and that apoptosis is seen in "bystander" cells such as CD8+ T cells and B cells as well as in uninfected CD4+ T cells. The intensity of apoptosis correlates with the general state of activation of the immune system and not with the stage of disease or with viral burden. It is likely that nonspecific apoptosis of immunocompetent cells related to immune activation contributes to the immune abnormalities in HIV disease.

Autoimmune phenomena

The autoimmune phenomena that are common in HIV-infected individuals reflect, at least in part, chronic immune system activation as well as molecular mimicry by viral components. Although these phenomena usually occur in the absence of autoimmune disease, a wide spectrum of clinical manifestations that may be associated with autoimmunity have been described (see "Immunologic and Rheumatologic Diseases," later in the chapter). Autoimmune phenomena include antibodies to lymphocytes and, less commonly, to platelets and neutrophils. Antiplatelet antibodies have some clinical relevance, in that they may contribute to the thrombocytopenia of HIV disease (see later). Antibodies to nuclear and cytoplasmic components of cells have been reported, as have antibodies to cardiolipin; CD4 molecules; CD43 molecules; C1q-A; variable regions of the T cell receptor α, β, and γ chains; Fas; denatured collagen; and IL-2. In addition, autoantibodies to a range of serum proteins, including albumin, immunoglobulin, and thyroglobulin, have been reported. There is antigenic cross-reactivity between HIV viral proteins (gp120 and gp41) and MHC class II determinants, and anti-MHC class II antibodies have been reported in HIV infection. These antibodies could potentially lead to the elimination of MHC class II–bearing cells via antibody-dependent cellular cytotoxicity (ADCC), although this has not been clearly demonstrated to occur. In addition, regions of homology exist between HIV envelope glycoproteins and IL-2 as well as MHC class I molecules. The increased occurrence and/or exacerbation of certain autoimmune diseases have been reported in HIV infection; these diseases include psoriasis, idiopathic thrombocytopenic purpura, Graves' disease, antiphospholipid

antibody syndrome, and primary biliary cirrhosis. With the widespread use of effective antiretroviral therapy, an *immune reconstitution inflammatory syndrome* (IRIS) has become increasingly common. IRIS is an autoimmune-like phenomenon characterized by a paradoxical deterioration of clinical condition, which is usually compartmentalized to a particular organ system, in individuals in whom cART has recently been initiated. It is associated with a decrease in viral load and at least partial recovery of immune competence, which is usually associated with increases in CD4+ T cell counts. The immunopathogenesis is felt to be related to an increase in immune response against the presence of residual antigens that are usually microbial and is commonly seen with underlying *Mycobacterium tuberculosis* and cryptococcosis. This syndrome is discussed in more detail next.

THE CYTOKINE NETWORK IN HIV PATHOGENESIS

The immune system is homeostatically regulated by a complex network of immunoregulatory cytokines, which are pleiotropic and redundant and operate in an autocrine and paracrine manner. They are expressed continuously, even during periods of apparent quiescence of the immune system. On perturbation of the immune system by antigenic challenge, the expression of cytokines increases to varying degrees. Cytokines that are important components of this immunoregulatory network have been demonstrated to play a major role in the regulation of HIV expression in vitro. Potent modulation of HIV expression has been demonstrated either by manipulating endogenous cytokines or by adding exogenous cytokines to culture. Cytokines that induce or enhance HIV expression in one or more of these systems include IL-1, IL-2, IL-3, IL-6, IL-12, IL-18, TNF-α, TNF-β, macrophage colony-stimulating factor (M-CSF), and granulocyte-macrophage colony-stimulating factor (GM-CSF). IL-18 has also been shown to play a role in the development of the HIV-associated lipodystrophy syndrome. Among these cytokines, the most consistent and potent inducers of HIV expression are the *proinflammatory cytokines* TNF-α, IL-1β, and IL-6. Interferon (IFN) α and β as well as IL-32 suppress HIV replication, whereas transforming growth factor (TGF) β, IL-4, IL-10, and IFN-γ can either induce or suppress HIV expression, depending on the system involved. IL-27 suppresses HIV replication by inducing IFN-associated genes. The *CC-chemokines* RANTES (CCL5), macrophage inflammatory protein (MIP) 1α (CCL3), and MIP-1β (CCL4) inhibit infection by and spread of R5 HIV-1 strains, while *stromal cell–derived factor* (SDF) 1 inhibits infection by and spread of X4 strains (see later). The alpha defensin family of cytokines has been shown to inhibit both R5 and X4 viruses, and other soluble factors that have not yet been fully characterized have also been shown to suppress HIV replication.

The molecular mechanisms of HIV regulation are best understood for TNF-α, which activates NF-κB proteins that function as transcriptional activators of HIV expression. The HIV-inducing effect of IL-1β is thought to occur at the level of viral transcription in an NF-κB-independent manner. IL-6, GM-CSF, and IFN-γ regulate HIV expression mainly by posttranscriptional mechanisms. Elevated levels of TNF-α and IL-6 have been demonstrated in plasma and cerebrospinal fluid (CSF), and increased expression of TNF-α, IL-1β, IFN-γ, and IL-6 has been demonstrated in the lymph nodes of HIV-infected individuals. The mechanisms whereby the CC-chemokines RANTES (CCL5), MIP-1α (CCL3), and MIP-1β (CCL4) inhibit infection of R5 strains of HIV or SDF-1 blocks X4 strains of HIV involve blocking of the binding of the virus to its co-receptors, the CC-chemokine receptor CCR5 and the CXC-chemokine receptor CXCR4, respectively. However, several CC-chemokines, including but not limited to CCL3, -4, and -5, induce intracellular signals that actually enhance infection by X4 strains of virus at both the entry and postentry levels. The mechanisms whereby other, less-well-characterized factors inhibit HIV replication are not completely understood.

Blocking of endogenous HIV-inducing cytokines or addition of inhibitors of HIV-suppressor cytokines in cultures of peripheral blood and lymph node mononuclear cells from HIV-infected individuals has demonstrated that HIV replication is controlled tightly by endogenous cytokines that act synergistically and in an autocrine and paracrine manner, similar to their physiologic function in the regulation of the immune system. Indeed, the net level of virus replication in an HIV-infected individual reflects at least in part a balance between inductive and suppressive host factors, mediated mainly by cytokines. Finally, the secretion of certain proinflammatory and immunoregulatory cytokines is both a consequence of the aberrant immune activation associated with HIV infection and a mechanism of propagation of the process of aberrant cellular activation (see "Immune Activation, Inflammation, and HIV Pathogenesis," earlier in the chapter).

LYMPHOCYTE TURNOVER IN HIV INFECTION

The immune systems of patients with HIV infection are characterized by a profound increase in lymphocyte turnover that is immediately reduced with effective cART. Studies utilizing in vivo or in vitro labeling of lymphocytes in the S-phase of the cell cycle have demonstrated a tight correlation between the degree of lymphocyte turnover and plasma levels of HIV RNA. This increase in turnover is seen in CD4+ and CD8+ T lymphocytes as well as B lymphocytes and can be observed in peripheral blood and lymphoid tissue. Mathematical models derived from these data suggest that one can view the lymphoid pool as consisting of dynamically distinct subpopulations of cells that are differentially affected by HIV infection. A major consequence of HIV infection appears to be a shift in cells from a more quiescent pool to a pool with a higher turnover rate. It is likely that a consequence of a higher rate of turnover is a higher rate of cell death. The role of the thymus in adult human T cell homeostasis and HIV pathogenesis is an area of controversy. While some

data point to an important role for the thymus in maintaining T cell numbers and suggest that impairment of thymic function may be responsible for the declines in CD4+ T cells seen in the setting of HIV infection, other studies have concluded that the thymus plays a minor role in HIV pathogenesis. Among the data supporting an important role for the thymus are those that demonstrate an increase in the levels of T cell receptor excision circles (TRECs) following initiation of cART. TRECs are a byproduct of T cell development and represent episomal fragments of DNA that are excised during T cell receptor gene rearrangement. Levels of TRECs will be the net result of changes in thymic output together with changes in T cell turnover. An increase in thymic output and/or a decrease in T cell turnover will lead to an increase in levels of TRECs. While it is clear that levels of TRECs increase following initiation of cART, it is not clear whether this is a consequence of increased thymic output or decreased T cell turnover.

THE ROLE OF VIRAL RECEPTORS AND CO-RECEPTORS IN HIV PATHOGENESIS

As mentioned earlier, HIV-1 utilizes two major co-receptors along with CD4 to bind to, fuse with, and enter target cells; these co-receptors are CCR5 and CXCR4, which are also receptors for certain endogenous chemokines. Strains of HIV that utilize CCR5 as a co-receptor are referred to as *R5 viruses*. Strains of HIV that utilize CXCR4 are referred to as *X4 viruses*. Many virus strains are *dual tropic* in that they utilize both CCR5 and CXCR4; these are referred to as *R5X4 viruses*.

The natural chemokine ligands for the major HIV co-receptors can readily block entry of HIV. For example, the CC-chemokines RANTES (CCL5), MIP-1α (CCL3), and MIP-1β (CCL4), which are the natural ligands for CCR5, block entry of R5 viruses, whereas SDF-1, the natural ligand for CXCR4, blocks entry of X4 viruses. The mechanism of inhibition of viral entry is a steric inhibition of binding that is not dependent on signal transduction **(Fig. 93-25)**.

The transmitting virus is almost invariably an R5 virus that predominates during the early stages of HIV disease. In ~40% of HIV-infected individuals, there is a transition to a predominantly X4 virus that is associated with a relatively rapid progression of disease. However, at least 60% of infected individuals progress in their disease while maintaining predominance of an R5 virus. It should be pointed out that clade C viruses, unlike other subgroups, almost never switch from CCR5 tropism to CXCR4 tropism; the reason for this difference is unclear.

The basis for the tropism of different envelope glycoproteins for either CCR5 or CXCR4 relates to the ability of the HIV envelope, including the third variable region (V3 loop) of gp120, to interact with these co-receptors. In this regard, binding of gp120 to CD4 induces a conformational change in gp120 that increases its affinity for CCR5 (see earlier). Finally, R5 viruses are more efficient in infecting monocytes/macrophages and microglial cells of the brain (see "Neuropathogenesis," later).

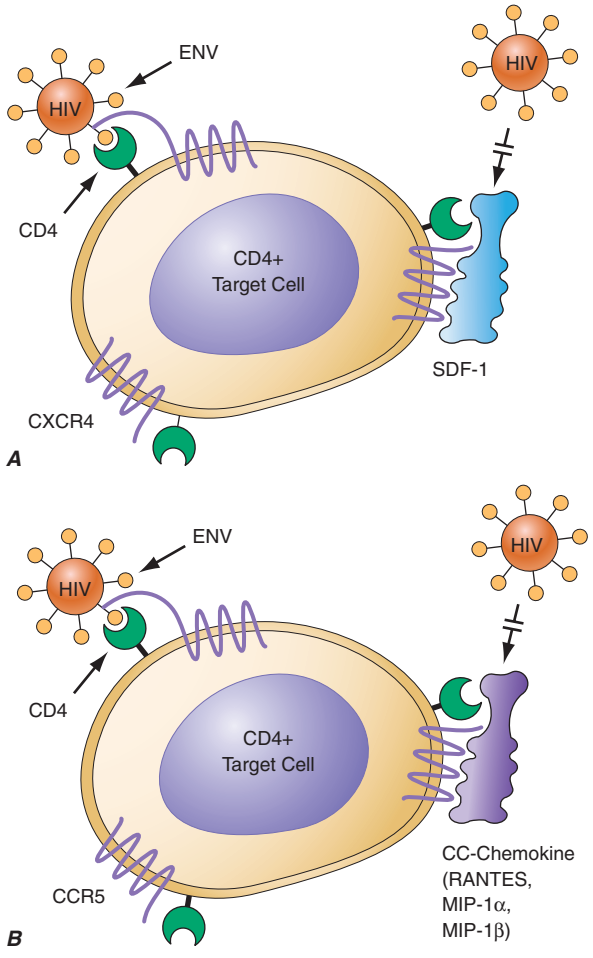


FIGURE 93-25
Model for the role of co-receptors CXCR4 and CCR5 in the efficient binding and entry of X4 (***A***) and R5 (***B***) strains of HIV-1, respectively, into CD4+ target cells. Blocking of this initial event in the virus life cycle can be accomplished by inhibition of binding to the co-receptor by the normal ligand for the receptor in question. The ligand for CXCR4 is stromal cell–derived factor 1 (SDF-1); the ligands for CCR5 are RANTES, MIP-1α, and MIP-1β.

The integrin α4β7 and mucosal transmission of HIV

A recently identified receptor for HIV has been reported; this receptor is not necessary for virus binding and fusion to its target CD4+ T cell or for virus replication, but it likely plays an important role in the transmission of HIV at mucosal surfaces such as the genital tract and gut. The integrin α4β7, which is the gut homing receptor for peripheral T cells, binds in its activated form to a specific tripeptide in the V2 loop of gp120 resulting in rapid activation of leukocyte function-associated antigen 1 (LFA-1), the central integrin in the establishment of virologic synapses, which facilitate efficient cell-to-cell spread of HIV. It has been demonstrated that $\alpha4\beta7^{high}$ CD4+ T cells are more susceptible to productive infection than are $\alpha4\beta7^{low-neg}$ CD4+ T cells because this cellular subset is enriched with metabolically active CD4+ T cells that are $CCR5^{high}$. These cells are present at the

gut and genital tract mucosal surfaces. Importantly, it has been demonstrated that the virus that is transmitted during sexual exposure binds much more efficiently to $\alpha 4\beta 7$ than does the virus that diversifies from the transmitting virus over time by mutation, particularly involving the accumulation of glycosylation sites (see "Early Events in HIV Infection: Primary Infection and Initial Dissemination of Virus," earlier).

CELLULAR TARGETS OF HIV

Although the CD4+ T lymphocytes and to a lesser extent CD4+ cells of monocyte lineage are the principal targets of HIV, virtually any cell that expresses the CD4 molecule together with co-receptor molecules (see earlier and next) can potentially be infected with HIV. Circulating dendritic cells have been reported to express low levels of CD4, and, depending on their stage of maturation, these cells can be infected with HIV. Epidermal Langerhans cells express CD4 and have been infected by HIV in vivo, although as has been shown in vivo for dendritic cells, FDCs, and B cells, these cells are more likely to bind and transfer virus to activated CD4+ T cells than to themselves be productively infected.

In vitro, HIV has been reported also to infect a wide range of cells and cell lines that express low levels of CD4, no detectable CD4, or only CD4 mRNA. However, since the only cells that have been shown unequivocally to be infected with HIV and to support replication of the virus are CD4+ T lymphocytes and cells of monocyte/macrophage lineage, the relevance of the in vitro infection of these other cell types is questionable.

Of potentially important clinical relevance is the demonstration that thymic precursor cells, which were assumed to be negative for CD3, CD4, and CD8 molecules, actually do express low levels of CD4 and can be infected with HIV in vitro. In addition, human thymic epithelial cells transplanted into an immunodeficient mouse can be infected with HIV by direct inoculation of virus into the thymus. Since these cells may play a role in the normal regeneration of CD4+ T cells, it is possible that their infection and depletion contribute, at least in part, to the impaired ability of the CD4+ T cell pool to completely reconstitute itself in certain infected individuals in whom cART has suppressed viral replication to <50 copies of HIV RNA per milliliter (see later). In addition, CD34+ monocyte precursor cells have been shown to be infected in vivo in patients with advanced HIV disease. It is likely that these cells express low levels of CD4, and therefore it is not essential to invoke CD4-independent mechanisms to explain the infection.

ABNORMALITIES OF MONONUCLEAR CELLS

CD4+ T cells

The primary immunopathogenic lesion in HIV infection involves CD4+ T cells, and the range of CD4+ T cell abnormalities in advanced HIV infection is broad. The defects are both quantitative and qualitative and ultimately impact virtually every limb of the immune system, indicating the critical dependence of the integrity of the immune system on the inducer/helper function of CD4+ T cells. In advanced HIV disease, most of the observed immune defects can ultimately be explained by the quantitative depletion of CD4+ T cells. However, T cell dysfunction can be demonstrated in patients early in the course of infection, even when the CD4+ T cell count is in the low-normal range. The degree and spectrum of dysfunctions increase as the disease progresses. One of the first abnormalities to be detected is a defect in response to remote recall antigens, such as tetanus toxoid and influenza, at a time when mononuclear cells can still respond normally to mitogenic stimulation. Indeed, defects of central memory cells are a critical component of HIV immunopathogenesis. The progressive loss of antigen-specific CD4+ T cells has important implications for the control of HIV infection. In this regard, there is a correlation between the maintenance of HIV-specific CD4+ T cell proliferative responses and improved control of infection. Essentially every T cell function has been reported to be abnormal at some stage of HIV infection. Loss of polyfunctional HIV-specific CD4+ T cells, especially those that produce IL-2, occurs early in disease, whereas IFN-producing CD4+ T cells are maintained longer and do not correlate with control of HIV viremia. Loss of IL-2-producing polyfunctional CD4+ T cells is also associated with decreased capacity to upregulate CD40 ligand, which may contribute to the dysregulation of B cell function observed in HIV disease. Other abnormalities include impaired expression of IL-2 receptors, defective IL-2 production, reduced expression of the IL-7 receptor (CD127), and decreased proportion of CD4+ T cells that express CD28, a major co-stimulatory molecule necessary for the normal activation of T cells. Cells lacking expression of CD28 do not respond normally to activation signals and may express markers of terminal activation including HLA-DR, CD38, and CD45RO. As mentioned earlier ("Immune Activation, Inflammation, and HIV Pathogenesis"), a subset of CD4+ T cells referred to as *T regulatory cells*, or T-regs, may be involved in damping aberrant immune activation that propagates HIV replication. The presence of these T-reg cells correlates with lower viral loads and higher CD4+/CD8+ T cell ratios. A loss of this T-reg capability with advanced disease may be detrimental to the control of virus replication.

It is difficult to explain completely the profound immunodeficiency noted in HIV-infected individuals solely on the basis of direct infection and quantitative depletion of CD4+ T cells. This is particularly apparent during the early stages of HIV disease, when CD4+ T cell numbers may be only marginally decreased. In this regard, it is likely that CD4+ T cell dysfunction results from a combination of depletion of cells due to direct infection of the cell and a number of virus-related but indirect effects on the cell **(Table 93-4)**. Certain of these effects have been demonstrated by exposure of cells to

TABLE 93-4

MECHANISMS OF CD4+ T CELL DYSFUNCTION AND DEPLETION

DIRECT MECHANISMS	INDIRECT MECHANISMS
Loss of plasma membrane integrity due to viral budding	Aberrant intracellular signaling events
Accumulation of unintegrated viral DNA	Autoimmunity
Interference with cellular RNA processing	Innocent bystander killing of viral antigen–coated cells
Intracellular gp120-CD4 autofusion events	Apoptosis
Syncytium formation	Inhibition of lymphopoiesis
	Activation-induced cell death
	Elimination of HIV-infected cells by virus-specific immune responses

virus in vitro and so their clinical relevance is not completely clear. However, it has been clearly demonstrated that patients with high levels of plasma viremia have a variety of subtle abnormalities of CD4+ T cell function, particularly involving aberrancies in signal transduction pathways. These abnormalities could be due either to aberrant activation induced by the cascade of cytokines that are expressed in viremic patients or to the direct effect of virus on the cell. In this regard, certain of these abnormalities can be reproduced by exposing CD4+ T cells of normal individuals to oligomeric HIV envelope proteins in vitro.

Humoral and cellular immune responses to HIV may contribute to protective immunity by eliminating virus and virus-infected cells (see "Immune Response to HIV," later). However, since the main targets of HIV infection are immunocompetent cells, these responses may contribute to immune cell depletion and immunologic dysfunction by eliminating both infected cells and "innocent bystander" cells. Soluble viral proteins, particularly gp120, can bind with high affinity to the CD4 molecules on uninfected T cells and monocytes; in addition, virus and/or viral proteins can bind to dendritic cells or FDCs. HIV-specific antibody can recognize these bound molecules and potentially collaborate in the elimination of the cells by ADCC.

HIV envelope glycoproteins gp120 and gp160 manifest high-affinity binding to CD4 as well as to various chemokine receptors. Intracellular signals transduced by gp120 through both CD4 and CCR5/CXCR4 have been associated with a number of immunopathogenic processes including anergy, apoptosis, and abnormalities of cell trafficking. The molecular mechanisms responsible for these abnormalities include dysregulation of the T cell receptor–phosphoinositide pathway, p56lck activation, phosphorylation of focal adhesion kinase, activation of the MAP kinase and ras signaling pathways, and downregulation of the co-stimulatory molecules CD40 ligand and CD80.

The inexorable decline in CD4+ T cell counts that occurs in most HIV-infected individuals may result in part from the inability of the immune system to regenerate over an extended period of time the rapidly turning over CD4+ T cell pool efficiently enough to compensate for both HIV-mediated and naturally occurring attrition of cells. In this regard, the degree and duration of decline of CD4+ T cells at the time of initiation of therapy is an important predictor of the restoration of these cells. A person who maintains a very low CD4+ T cell count for a considerable period of time before the initiation of ART almost invariably has an incomplete reconstitution of such cells. At least two major mechanisms may contribute to the failure of the CD4+ T cell pool to reconstitute itself adequately over the course of HIV infection. The first is the destruction of lymphoid precursor cells, including thymic and bone marrow progenitor cells; the other is the gradual disruption of the lymphoid tissue microenvironment, which is essential for efficient regeneration of immunocompetent cells. Finally, during the advanced stages of CD4+ T lymphopenia, there are increased serum levels of the homeostatic cytokine IL-7. It was initially felt that this elevation was a homeostatic response to the lymphopenia; however, recent findings suggest that the increase in serum IL-7 was a result of reduced utilization of the cytokine related to the loss of cells expressing the IL-7 receptor, CD127, which serves as a normal physiologic regulator of IL-7 production.

CD8+ T cells

A relative CD8+ T lymphocytosis is generally associated with high levels of HIV plasma viremia and likely reflects dysregulated homeostasis associated with generalized immune activation. During the late stages of HIV infection, there may be a significant reduction in the numbers of CD8+ T cells despite the presence of high levels of viremia. HIV-specific CD8+ CTLs have been demonstrated in HIV-infected individuals early in the course of disease. The emergence of HIV escape mutants may ultimately permit evasion of these HIV-specific CD8+ T cells. However, as the disease progresses, the functional capability of these cells gradually decreases and may be lost entirely. The cause of this loss of cytolytic activity is unclear, although functional impairment is thought to be associated with the persistent nature of HIV infection and disease progression. In this regard, as chronic immune activation persists, CD8+ T cells assume an abnormal phenotype characterized by expression of activation markers such as HLA-DR and CD38 with an absence of expression of the IL-2 receptor (CD25), and a reduced expression of the IL-7 receptor (CD127). In addition, CD8+ T cells lacking CD28 expression are increased in HIV disease, reflecting a skewed expansion of a less differentiated CD8+ T cell subset. This skewing of subsets is also associated with diminished polyfunctionality, a qualitative difference that distinguishes nonprogressors from progressors. It has been reported that nonprogressors can also be distinguished from progressors by

the maintenance in the former of a high proliferative capacity of their HIV-specific CD8+ T cells coupled to increases in perforin expression, characteristics that are markedly diminished in advanced HIV disease. It has been reported that the phenotype of CD8+ T cells in HIV-infected individuals may be of prognostic significance. Those individuals whose CD8+ T cells developed a phenotype of HLA-DR+/CD38– following seroconversion had stabilization of their CD4+ T cell counts, whereas those whose CD8+ T cells developed a phenotype of HLA-DR+/CD38+ had a more aggressive course and a poorer prognosis. In addition to the defects in HIV-specific CD8+ CTLs, functional defects in other MHC-restricted CTLs, such as those directed against influenza and CMV, have been demonstrated. CD8+ T cells secrete a variety of soluble factors that inhibit HIV replication including the CC-chemokines RANTES (CCL5), MIP-1α (CCL3), and MIP-1β (CCL4) as well as one or more as yet poorly identified factors. The presence of high levels of HIV viremia in vivo as well as exposure of CD8+ T cells in vitro to HIV envelope, both of which are associated with aberrant immune activation, have been shown to be associated with a variety of cellular functional abnormalities. Furthermore, since the integrity of CD8+ T cell function depends in part on adequate inductive signals from CD4+ T cells, the defect in CD8+ CTLs is likely compounded by the quantitative loss and qualitative dysfunction of CD4+ T cells. Finally, certain cell surface negative regulatory molecules such as CTLA-4 and PD-1 are upregulated on activated T cells, and engagement of these molecules with their ligands may play a role in the exhaustion and death of CD8+, HIV-specific T cells.

B cells

The predominant defect in B cells from HIV-infected individuals is one of aberrant cellular activation, which is reflected by spontaneous proliferation and immunoglobulin secretion and by increased spontaneous secretion of TNF-α and IL-6. In addition, B cells from HIV viremic patients manifest a decreased capacity to mount a proliferative response to ligation of the B cell antigen receptor and other B cell stimuli in vitro, yet at the same time they are capable of robust differentiation in vivo as a result of HIV-induced immune activation. B cells from HIV-infected individuals manifest enhanced spontaneous secretion of immunoglobulins in vitro, a process that reflects their highly differentiated state in vivo. There is also an increased incidence of EBV-related B cell lymphomas in HIV-infected individuals that are likely due to combined effects of defective T cell immune surveillance and increased turnover that increases the risk of oncogenesis. Untransformed B cells cannot be infected with HIV, although HIV or its products can activate B cells directly. B cells from patients with high levels of viremia bind virions to their surface via the CD21 complement receptor. It is likely that in vivo activation of B cells by replication-competent or -defective virus as well as viral products during the viremic state accounts at least in part for the spontaneous activation of these cells noted ex vivo. B cell subpopulations from HIV-infected individuals undergo a number of changes over the course of HIV disease, including the attrition of resting memory B cells and replacement with several aberrant memory and differentiated B cell subpopulations that collectively express reduced levels of CD21 and either increased expression of activation markers or inhibitory receptors associated with functional exhaustion. The more activated and differentiated B cells are also responsible for increased secretion of immunoglobulins and increased susceptibility to Fas-mediated apoptosis. In more advanced disease, there is also the appearance of immature B cells associated with CD4+ T cell lymphopenia. Cognate B cell–CD4+ T cell interactions are abnormal in viremic HIV-infected individuals in that B cells respond poorly to CD4+ T cell help and CD4+ T cells receive inadequate co-stimulatory signals from activated B cells. In vivo, the aberrant activated state of B cells manifests itself by hypergammaglobulinemia and by the presence of circulating immune complexes and autoantibodies. HIV-infected individuals respond poorly to primary and secondary immunizations with protein and polysaccharide antigens. Using immunization with influenza vaccine, it has been demonstrated that there is a memory B cell defect in HIV-infected individuals, particularly those with high levels of HIV viremia. Taken together, these B cell defects are likely responsible in part for the decreased response to vaccinations and the increase in certain bacterial infections seen in advanced HIV disease in adults, as well as for the important role of bacterial infections in the morbidity and mortality rates of HIV-infected children, who cannot mount an adequate humoral response to common bacterial pathogens. The absolute number of circulating B cells may be depressed in HIV infection; this phenomenon likely reflects increased activation-induced apoptosis as well as a redistribution of cells out of the circulation and into the lymphoid tissue—phenomena that are associated with ongoing viral replication.

Monocytes/macrophages

Circulating monocytes are generally normal in number in HIV-infected individuals. Monocytes express the CD4 molecule and several co-receptors for HIV on their surface, including CCR5, CXCR4, and CCR3, and thus are targets of HIV infection. The degree of cytopathicity of HIV for cells of the monocyte lineage is low, and HIV can replicate extensively in cells of the monocyte lineage with relatively little cytopathic effect. Hence, monocyte-lineage cells may play a role in the dissemination of HIV in the body and can serve as reservoirs of HIV infection, thus representing an obstacle to the eradication of HIV by antiretroviral drugs. In vivo infection of circulating monocytes is difficult to demonstrate; however, infection of tissue macrophages and macrophage-lineage cells in the brain (infiltrating macrophages or resident microglial cells) and lung (pulmonary alveolar macrophages) can be demonstrated easily. Tissue macrophages are an important source of

HIV during the inflammatory response associated with opportunistic infections. Infection of monocyte precursors in the bone marrow may directly or indirectly be responsible for certain of the hematologic abnormalities in HIV-infected individuals. A number of abnormalities of circulating monocytes have been reported in HIV-infected individuals, many of which may be related directly or indirectly to aberrant in vivo immune activation. In this regard, increased levels of lipopolysaccharide (LPS) are found in the sera of HIV-infected individuals due, at least in part, to translocation across the gut mucosal barrier (see earlier). LPS is a highly inflammatory bacterial product that preferentially binds to macrophages through CD14 and Toll-like receptors, resulting in cellular activation. Increased levels of soluble CD14 in plasma are associated with poor overall clinical outcomes. Monocyte/macrophage functional abnormalities in HIV disease include decreased secretion of IL-1 and IL-12; increased secretion of IL-10; defects in antigen presentation and induction of T cell responses due to decreased MHC class II expression; and abnormalities of Fc receptor function, C3 receptor–mediated clearance, oxidative burst responses, and certain cytotoxic functions such as ADCC, possibly related to low levels of expression of Fc and complement receptors. Exposure of monocytes in vitro to viral proteins such as gp120 and Tat, as well as to certain cytokines, can cause abnormal activation, and this may play a role in cellular dysfunction.

Dendritic and Langerhans cells

Dendritic cells (DCs) may play an important role in the initiation of HIV infection by virtue of the ability of HIV to bind to cell-surface C-type lectin receptors, particularly DC-SIGN (see earlier). This allows efficient presentation of virus to CD4+ T cell targets that become infected; complexes of infected CD4+ T cells and DCs provide an optimal microenvironment for virus replication. There has been considerable disagreement regarding the HIV infectibility and hence the depletion as well as the dysfunction of DCs themselves. The situation has recently been clarified by the recognition that DCs can be classified into myeloid (mDC) and plasmacytoid (pDC) subsets, leading to an appreciation of specific DC dysfunction in HIV disease. pDCs are an important component of the innate immune system and secrete large amounts of IFN-α in response to viral infections. The numbers of circulating pDCs are decreased in HIV infection through mechanisms that remain unclear. It has recently been demonstrated that HIV gp120 interacts directly with pDCs and interferes with TLR9 activation, resulting in a decreased ability of pDCs to secrete antiviral and inflammatory factors that play a role in immune responses against invading pathogens.

Natural killer cells

The role of NK cells is to provide immunosurveillance against virus-infected cells, certain tumor cells, and allogeneic cells. There are no convincing data that HIV productively infects NK cells in vivo; however, functional abnormalities in NK cells have been observed throughout the course of HIV disease, and the severity of these abnormalities increases as disease progresses. In addition, it has been reported that HIV envelope induces aberrant signaling in NK cells that increases their susceptibility to apoptosis. HIV infection of target cells downregulates HLA-A and -B—but not HLA-C and -D—molecules; this may explain in part the relative inability of NK cells to kill HIV-infected target cells. Most studies report that NK cells are normal in number; however, patients with high levels of virus replication manifest an abnormal representation of a functionally defective CD56–/CD16+ NK cell subset. This abnormal subset of NK cells manifests an increased expression of inhibitory NK cell receptors (iNKRs) and a substantial decrease in expression of natural cytotoxicity receptors (NCRs) and shows a markedly impaired lytic activity. The overrepresentation of this abnormal subset of NK cells may explain in part the observed defects in NK cell function in HIV-infected individuals. NK cells also serve as important sources of HIV-inhibitory CC-chemokines. NK cells isolated from HIV-infected individuals constitutively produce high levels of MIP-1α (CCL3), MIP-1β (CCL4), and RANTES (CCL5). In addition, high levels of these chemokines are seen when NK cells are stimulated with IL-2 or IL-15 or when CD16 is cross-linked or during the process of lytic killing of target cells. HIV-infected patients with high levels of plasma viremia manifest a decreased ability, compared with HIV-infected individuals who are aviremic, of their NK cells to block HIV replication in vitro in assays of both cell contact and supernatant-mediated suppression of virus. Finally, NK cell–dendritic cell interactions are important for normal immune function. NK cells and dendritic cells reciprocally modulate each other's activation and maturation. These interactions are markedly impaired in HIV-infected individuals with high levels of plasma viremia.

GENETIC FACTORS IN HIV PATHOGENESIS

Genetic association studies have served as a powerful means to identify host factors that influence HIV-AIDS pathogenesis in vivo. Polymorphisms in several genes have now been identified that influence several phenotypes relevant to HIV infection: risk of acquiring HIV, rates of disease progression, long-term nonprogression, spontaneous virologic control, and immunologic responses following initiation of ART. These include polymorphisms in genes in the MHC locus, chemokine receptors and chemokines, cytokines, and other host factors **(Table 93-5)**. Recent studies have capitalized on genome-wide association studies to identify novel genetic factors that influence HIV disease progression rates, and rapid progress is anticipated in this area. Moreover, in vitro genome-wide functional scanning using RNA interference techniques suggests that up to hundreds of host factors may be involved in the

TABLE 93-5

HOST GENETIC FACTORS THAT INFLUENCE RISK OF HIV-1 ACQUISITION AND RATES OF HIV-1 DISEASE PROGRESSION

GENE[a]	GENETIC VARIATION	MECHANISMS[b]	GENETIC EFFECT ON HIV-AIDS[c]
Genes in MHC Locus			
HLA-B	B*27 and B*57	Presentation of specific immunogenic HIV antigens	Slow progression to AIDS; low viral load
	B*35Px	Restriction of specific immunogenic HIV peptide presentation	Fast progression to AIDS; high viral load
	HLA-Bw4	Providing ligands for activating KIR	Slow progression to AIDS
HLA class I allele	Homozygosity of HLA-A, B, C alleles	Reduced epitope recognition repertoire	Faster progression to AIDS; increased risk of mother-to-child transmission
	Shared donor-recipient HLA alleles	Preadaptation of HIV strains	Faster disease progression
	Rare HLA alleles	Limited adaptation of HIV strains; less frequent escape mutants	Protection against HIV infection
HLA extended haplotype	A1-B8-DR3-DQ2 (8.1)	Unknown; may influence immunologic hyperresponsiveness	Faster progression to AIDS
HLA-C	rs9264942-C	Increased expression of HLA-C; association may be due to linkage disequilibrium with HLA-B57	Decreased viral load set point
HCP5	rs2395029-G	Linkage disequilibrium with HLA-B*5701	Reduced viremia
ZNRD1	rs9261174-C	Possible interference in processing of HIV transcripts; influences ZNRD1 expression; linkage disequilibrium with *HLA-A10*	AIDS disease retardation
Chemokine Receptors			
CCR5	32-bp deletion in the ORF (Δ32)	Truncated CCR5 protein	Δ32/Δ32: resistance to acquiring HIV infection Δ32/wt: delays AIDS onset; improves immune reconstitution during ART
	Promoter SNPs/ haplotypes (HHA to HHG*2)	Altered CCR5 expression; e.g., HHE allele correlates with high CCR5 expression	HHE/HHE genotype associates with increased HIV/AIDS susceptibility
CCR2	Valine to isoleucine change (64 V→ I)	Possibly due to linkage with polymorphism in *CCR5* promoter	Delayed AIDS onset
CX3CR1	SNPs in ORF (*249 V→ I*, *280 T → M*)	280M reduces receptor expression and binding of fractalkine, the CX3CR1 ligand	249I and 280M are associated with faster AIDS onset in some Caucasian cohorts; inconsistent effects were detected in other cohorts
DARC	African-specific promoter SNP (*46T → C*)	–46C/C associates with low neutrophil counts; influences circulating chemokine levels; alters HIV binding to RBCs and transinfection of HIV-1	–46C/C: increased risk of acquiring HIV but slow HIV disease progression; the disease-retarding effects associated with –46C/C occur mainly in those HIV+ African Americans who are also leukopenic
Chemokines			
CCL3L, CCL4L	Gene copy number of *CCL3L* and *CCL4L*	High gene copies correlate with high CCL3L and CCL4L levels	Gene copy number lower than population median associates with increased HIV/AIDS susceptibility and reduced immune reconstitution during ART
CCL5	Promoter SNPs	Altered gene expression	Altered HIV-AIDS susceptibility
CCL2	Promoter SNP (–2578 T → G)	*–2578G* allele*:* increased CCL2 expression and monocyte recruitment	–2578G/G associates with increased risk of developing HIV-1-associated dementia and a rapid AIDS onset

(*continued*)

TABLE 93-5

HOST GENETIC FACTORS THAT INFLUENCE RISK OF HIV-1 ACQUISITION AND RATES OF HIV-1 DISEASE PROGRESSION (*CONTINUED*)

GENE[a]	GENETIC VARIATION	MECHANISMS[b]	GENETIC EFFECT ON HIV-AIDS[c]
Cytokines			
IL-6	Promoter SNP (–174 G → C)	–174C associates with altered IL-6 and CRP levels	Altered risk of KS development and variable recovery of CD4 cells during ART
IL-10	Promoter SNP	–592A results in decreased IL-10 levels	Increased HIV-AIDS susceptibility
Innate Immunity Genes			
MBL	Coding alleles (O)	Low plasma concentration and structural damage of MBL	Slow progression to AIDS in heterozygous subjects (A/O)
	X allele (promoter SNP –221)	Decreased levels of MBL	Faster progression to AIDS in homozygous X/X subjects
Apobec-3G	ORF SNP (186 H → R)	Reduced anti-HIV-1 activity	186R associates with rapid AIDS onset in African Americans
Others			
ApoE	E4, E3, E2 allele	E4 enhances HIV cell entry in vitro	ApoE4/E4 associates with rapid AIDS onset and dementia
Gene–Gene Interaction			
KIR+HLA	KIR3DS1 with HLA Bw4-80I + or 80I –	Altered NK cell activity required to kill HIV-infected cells	KIR3DS1 with HLA Bw4-80I +: delayed AIDS onset KIR3DS1 with HLA Bw4-80I –: rapid AIDS onset
CCL3L1 + CCR5	Low *CCL3L1* gene copies + detrimental *CCR5* genotypes	Low CCL3L1 and high CCR5 expression	Increased HIV/AIDS susceptibility and reduced immune reconstitution during ART

[a]Representative genes and polymorphisms and
[b]possible mechanisms are listed.
[c]Some of the associations are population specific and may display cohort-specific effects.
Note: Apobec, apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like; ApoE, apolipoprotein E; ART, antiretroviral therapy; CCL, CC ligand; CCL3L, CCL3-like; CCR5, CC chemokine receptor 5; CRP, C-reactive protein; DARC, Duffy antigen receptor for chemokines; HCP5, HLA class I histocompatibility antigen protein P5; HHE, human haplogroup E; HLA, human leukocyte antigen; IL, interleukin; KIR, killer cell immunoglobulin-like receptors; KS, Kaposi's sarcoma; MBL, mannose-binding lectin; MHC, major histocompatibility complex; ORF, open reading frame; SNP, single-nucleotide polymorphism; VL, viral load; wt, wild-type; ZNRD1, zinc ribbon domain containing 1; +, present, –, absent.
Source: Sunil K. Ahuja, MD, Weijing He, MD, and *www.hiv-pharmacogenomics.org*. Reviews for additional information: P An et al: Trends Genet 26:119, 2010; J Fellay: Antivir Ther 14:731, 2009; RA Kaslow et al: J Infect Dis 191:S68, 2005.

HIV replication life cycle. Theoretically, variations in all these genes could impact HIV susceptibility and/or disease progression. Next is a discussion of some representative genes.

Researchers recently employed a genome-wide association strategy and identified polymorphisms within *HLA-B* (e.g., *HCP-5* gene) and *HLA-C* that explained approximately 15% of the variation in viral load among individuals during the asymptomatic period of infection. A number of mechanisms have been proposed whereby MHC-encoded molecules might predispose an individual either to rapid progression or to nonprogression to AIDS. These proposed mechanisms include the ability to present certain immunodominant HIV T helper or CTL epitopes, leading to a relatively protective immune response against HIV and hence to a slower rate of disease progression. In contrast, certain MHC class I or class II alleles might predispose an individual to an immunopathogenic response against viral epitopes in certain tissues, such as the CNS or lungs, or against certain HIV-infected cell types, such as macrophages or dendritic cells/Langerhans cells. In addition, certain rare MHC class I and class II alleles might facilitate rapid recognition of HIV-infected cells from the infecting partner in primary HIV infection and promote rejection of these cells by alloreactive responses. Similarly, common MHC alleles could lead to less effective removal of HIV-infected allogeneic cells. In this regard, it has been demonstrated that allele sharing at *HLA-B* locus is associated with increased risk of transmission

of HIV infection between heterosexual Zambian couples discordant for HIV. It has also been demonstrated that *HLA* heterozygosity for class I loci (A, B, and C) is associated with a delayed onset of AIDS among HIV-infected individuals, whereas homozygosity for these loci is associated with a more rapid progression to AIDS and death. This observation is likely due to the fact that individuals who are heterozygous at *HLA* loci are able to present a greater variety of antigenic peptides to cytotoxic T lymphocytes than are homozygotes, resulting in a more effective immune response against a number of pathogens including HIV. Of particular note is the fact that the *HLA* class I alleles B*35 and Cw*04 were consistently associated with rapid development of AIDS. Other data have indicated that transporter associated with antigen-processing (*TAP*) genes play a role in determining the outcome of HIV infection. HLA profiles that reflect certain combinations of MHC-encoded *TAP* and class I and class II genes are strongly associated with different rates of progression to AIDS. It is noteworthy that the extended *HLA* haplotype 8.1 (A1-B8-DR3) has also been consistently correlated with a rapid decline in CD4+ T cells and development of HIV-related symptoms.

Recent genetic association studies have also highlighted the role for NK cells in HIV disease. A single-nucleotide polymorphism (SNP) in the killer immunoglobulin-like receptor (*KIR*) gene was shown to be strongly associated with rapid progression to AIDS. However, when KIR3DS1 was present with HLA-Bw4-80I, the resultant phenotype was delayed progression to AIDS, even though this *HLA-B* allele alone has no effect on HIV disease progression. Furthermore, KIR3DS1/HLA-Bw4-80I-carrying individuals had a significantly reduced viral load, beginning early in the course of infection, and protection against opportunistic infections during the later stages of the disease. This observation points to the potential role of NK cells in the maintenance of the viral set point and strongly suggests that HLA-Bw4-80I serves as the ligand activating the KIR, resulting in the death of the target cell. These gene-gene interactions between *KIR* and MHC genes are illustrated in Table 93-5.

The most dramatic example of a genetic factor influencing HIV infection and/or pathogenesis relates to the gene that encodes for CC-chemokine receptor 5 (CCR5), the major HIV co-receptor for cell entry. There are reports of rare individuals who have remained uninfected despite repeated sexual exposure to HIV in high-risk situations (e.g., commercial sex workers). The peripheral blood mononuclear cells of two such individuals were found to be highly resistant to infection in vitro with R5 strains of HIV-1, but were readily infected with X4 strains. Genetic analysis revealed that these two individuals inherited a homozygous defect in the gene that encodes for CCR5. The defective *CCR5* allele contained a 32-bp deletion corresponding to the second extracellular loop of the receptor (Δ*32* allele). The encoded protein is severely truncated and is not expressed on the cell surface; it is therefore nonfunctional, explaining the refractoriness to infection with R5 strains of HIV-1. Population studies revealed that ~1% of the Caucasian population of Western European ancestry possessed the homozygous defect for the *CCR5* Δ*32* allele, and subjects with this genotype are highly resistant to HIV infection. A number of studies have found that the frequency of *CCR5* Δ*32* allele was enriched in exposed, uninfected individuals of European descent. It is noteworthy that several individuals have been identified as homozygous for the *CCR5* Δ*32* defect and in fact did become infected with HIV. These individuals were found to have an X4 strain of HIV that was associated in some cases with an accelerated disease course. X4 strain uses CXCR4 as the co-receptor for cell entry instead of CCR5. Up to 20% of individuals of European descent are heterozygous for the *CCR5* Δ*32* allele and display partial resistance to acquiring HIV and a delayed disease course. Cohort studies of hundreds of DNA samples originating from western and central Africa and Far East Asia indicate that the *CCR5* Δ*32* allele is either absent or extremely rare in these populations.

A number of SNPs in the *CCR5* promoter have been associated with varied rates of disease progression and altered risk of acquiring HIV. The promoter SNPs along the *CCR5* Δ*32* and *CCR2-V64I* alleles define nine *CCR5* human haplogroups (HH) designated as HHA through HHE, HHF*1, HHF*2, HHG*1 and HHG*2 (Table 93-5). Studies have shown that homozygosity for the *CCR5* HHE haplotype is associated with an increased risk of acquiring HIV and progressing rapidly to AIDS. Pairing of the HHC and the *CCR5* Δ*32*-containing HHG*2 haplotype is associated with a slower rate of disease progression and reduced risk of acquiring HIV. Heterozygosity for the *CCR2-64I* polymorphism associates with a slow rate of HIV disease course. This *CCR2-64I* allele–associated effect could be due to its linkage with SNPs in the *CCR5* promoter that are known to influence disease progression rates and/or due to dimerization of CXCR4 with the mutated *CCR2-64I*, resulting in a decreased expression of CXCR4 on the cell surface. Variations in the ligands of CCR5 (e.g., copy number of *CCL3L* genes) and CCR2 (e.g., *CCL2*) may also influence HIV-AIDS susceptibility.

NEUROPATHOGENESIS

While there has been a remarkable decrease in the incidence of HIV encephalopathy among those with access to treatment in the era of effective cART, HIV-infected individuals can still experience a variety of neurologic abnormalities due either to opportunistic infections and neoplasms or to direct effects of HIV or its products. With regard to the latter, HIV has been demonstrated in the brain and CSF of infected individuals with and without neuropsychiatric abnormalities. The main cell types that are infected in the brain in vivo are the perivascular macrophages and the microglial cells; monocytes that have already been infected in the blood can migrate into the brain, where they then reside as macrophages, or macrophages can be directly infected

within the brain. The precise mechanisms whereby HIV enters the brain are unclear; however, they are thought to relate, at least in part, to the ability of virus-infected and immune-activated macrophages to induce adhesion molecules such as E-selectin and vascular cell adhesion molecule 1 (VCAM-1) on brain endothelium. Other studies have demonstrated that HIV gp120 enhances the expression of intercellular adhesion molecule 1 (ICAM-1) in glial cells; this effect may facilitate entry of HIV-infected cells into the CNS. Virus isolates from the brain are preferentially R5 strains as opposed to X4 strains; in this regard, HIV-infected individuals who are heterozygous for *CCR5-Δ32* appear to be relatively protected against the development of HIV encephalopathy compared with wild-type individuals. Distinct HIV envelope sequences are associated with the clinical expression of the AIDS dementia complex (see later). There is no convincing evidence that brain cells other than those of monocyte/macrophage lineage can be productively infected in vivo.

HIV-infected individuals may manifest white matter lesions as well as neuronal loss. Given the absence of evidence of HIV infection of neurons either in vivo or in vitro, it is highly unlikely that direct infection of these cells accounts for their loss. Rather, the HIV-mediated effects on neurons and oligodendrocytes are thought to involve indirect pathways whereby viral proteins, particularly gp120 and Tat, trigger the release of endogenous neurotoxins from macrophages and to a lesser extent from astrocytes. In addition, it has been demonstrated that both HIV-1 Nef and Tat can induce chemotaxis of leukocytes, including monocytes, into the CNS. Neurotoxins can be released from monocytes as a consequence of infection and/or immune activation. Monocyte-derived neurotoxic factors have been reported to kill neurons via the *N*-methyl-D-aspartate (NMDA) receptor. In addition, HIV gp120 shed by virus-infected monocytes could cause neurotoxicity by antagonizing the function of vasoactive intestinal peptide (VIP), by elevating intracellular calcium levels, and by decreasing nerve growth factor levels in the cerebral cortex. A variety of monocyte-derived cytokines can contribute directly or indirectly to the neurotoxic effects in HIV infection; these include TNF-α, IL-1, IL-6, TGF-β, IFN-γ, platelet-activating factor, and endothelin. Furthermore, among the CC-chemokines, elevated levels of monocyte chemotactic protein (MCP) 1 in the brain and CSF have been shown to correlate best with the presence and degree of HIV encephalopathy. In addition, infection and/or activation of monocyte-lineage cells can result in increased production of eicosanoids, quinolinic acid, nitric oxide, excitatory amino acids such as L-cysteine and glutamate, arachidonic acid, platelet activating factor, free radicals, TNF-α, and TGF-β, which may contribute to neurotoxicity. Astrocytes may play diverse roles in HIV neuropathogenesis. Reactive gliosis or astrocytosis has been demonstrated in the brains of HIV-infected individuals, and TNF-α and IL-6 have been shown to induce astrocyte proliferation. In addition, astrocyte-derived IL-6 can induce HIV expression in infected cells in vitro. Furthermore, it has been suggested that astrocytes may downregulate macrophage-produced neurotoxins. It has been reported that HIV-infected individuals with the E4 allele for apolipoprotein E (apo E) are at increased risk for AIDS encephalopathy and peripheral neuropathy. The likelihood that HIV or its products are involved in neuropathogenesis is supported by the observation that neuropsychiatric abnormalities may undergo remarkable and rapid improvement upon the initiation of cART.

It has also been suggested that the CNS may serve as a relatively sequestered site for a reservoir of latently infected cells that might be a barrier for the eradication of virus by cART (see "Reservoirs of HIV-Infected Cells: Obstacles to the Eradication of Virus," earlier in the chapter).

PATHOGENESIS OF KAPOSI'S SARCOMA

There are at least four distinct epidemiologic forms of KS: (1) the classic form that occurs in older men of predominantly Mediterranean or Eastern European Jewish backgrounds with no recognized contributing factors; (2) the equatorial African form that occurs in all ages, also without any recognized precipitating factors; (3) the form associated with organ transplantation and its attendant iatrogenic immunosuppressed state; and (4) the form associated with HIV-1 infection. In the latter two forms, KS is an opportunistic disease; in HIV-infected individuals, unlike typical opportunistic infections, its occurrence is not strictly related to the level of depression of CD4+ T cell counts. The pathogenesis of KS is complex; fundamentally, it is an angioproliferative disease that is not a true neoplastic sarcoma, at least not in its early stages. It is a manifestation of excessive proliferation of spindle cells that are believed to be of vascular origin and have features in common with endothelial and smooth-muscle cells. In HIV disease the development of KS is dependent on the interplay of a variety of factors including HIV-1 itself, human herpesvirus 8 (HHV-8), immune activation, and cytokine secretion. A number of epidemiologic and virologic studies have clearly linked HHV-8, which is also referred to as *Kaposi's sarcoma–associated herpesvirus* (KSHV), to KS not only in HIV-infected individuals but also in individuals with the other forms of KS. HHV-8 is a γ-herpesvirus related to EBV and herpesvirus saimiri. It encodes a homologue to human IL-6 and, in addition to KS, has been implicated in the pathogenesis of body cavity lymphoma, multiple myeloma, and monoclonal gammopathy of undetermined significance. Sequences of HHV-8 are found universally in the lesions of KS, and patients with KS are virtually all seropositive for HHV-8. HHV-8 DNA sequences can be found in the B cells of 30–50% of patients with KS and 7% of patients with AIDS without clinically apparent KS.

Between 1 and 2% of eligible blood donors are positive for antibodies to HHV-8, while the prevalence of HHV-8 seropositivity in HIV-infected men is 30–35%.

The prevalence of HHV-8 seropositivity in HIV-infected women is ~4%. This finding is reflective of the lower incidence of KS in women. It has been debated whether HHV-8 is actually the transforming agent in KS; the bulk of the cells in the tumor lesions of KS are not neoplastic cells. However, it has been demonstrated that endothelial cells can be transformed in vitro by HHV-8. In this regard, HHV-8 possesses a number of genes, including homologues of the IL-8 receptor, Bcl-2, and cyclin D, that can potentially transform the host cell. Despite the complexity of the pathogenic events associated with the development of KS in HIV-infected individuals, HHV-8 is the etiologic agent of this disease. The initiation and/or propagation of KS requires an activated state and is mediated, at least in part, by cytokines. A number of factors, including TNF-α, IL-1β, IL-6, GM-CSF, basic fibroblast growth factor, and oncostatin M, function in an autocrine and paracrine manner to sustain the growth and chemotaxis of the KS spindle cells. In this regard, KSHV-derived IL-6 has been demonstrated to induce proliferation of lymphoma cells and to inhibit the cytostatic effects of INF-α on KSHV-infected lymphoma cells.

IMMUNE RESPONSE TO HIV

As detailed earlier and next, following the initial burst of viremia during primary infection, HIV-infected individuals mount robust immune responses that in most cases substantially curtail the levels of plasma viremia and likely contribute to delaying the ultimate development of clinically apparent disease for a median of 10 years in untreated individuals. This immune response contains elements of both humoral and cell-mediated immunity involving both innate and adaptive immune responses **(Table 93-6; Fig. 93-26)**. It is directed against multiple antigenic determinants of the HIV virion as well as against viral proteins expressed on the surface of infected cells. Ironically, those CD4+ T cells with T cell receptors specific for HIV are theoretically those CD4+ T cells most likely to be activated—and thus to serve as early targets for productive HIV infection and the cell death or dysfunction associated with infection. Thus, an early consequence of HIV infection is interference with and decrease of the helper T cell population needed to generate an effective immune response.

Although a great deal of investigation has been directed toward delineating and better understanding the components of this immune response, it remains unclear which immunologic effector mechanisms are most important in delaying progression of infection and which, if any, play a role in the pathogenesis of HIV disease. This lack of knowledge has also hampered the ability to develop an effective vaccine for HIV disease.

TABLE 93-6

ELEMENTS OF THE IMMUNE RESPONSE TO HIV

- Humoral immunity
  - Binding antibodies
  - Neutralizing antibodies
    - Type specific
    - Group specific
  - Antibodies participating in antibody-dependent cellular cytotoxicity (ADCC)
    - Protective
    - Pathogenic (bystander killing)
  - Enhancing antibodies
  - Complement
- Cell-mediated immunity
  - Helper CD4+ T lymphocytes
  - Class I MHC–restricted cytotoxic CD8+ T lymphocytes
  - CD8+ T cell–mediated inhibition (noncytolytic)
  - ADCC
  - Natural killer cells

Abbreviation: MHC, major histocompatibility complex.

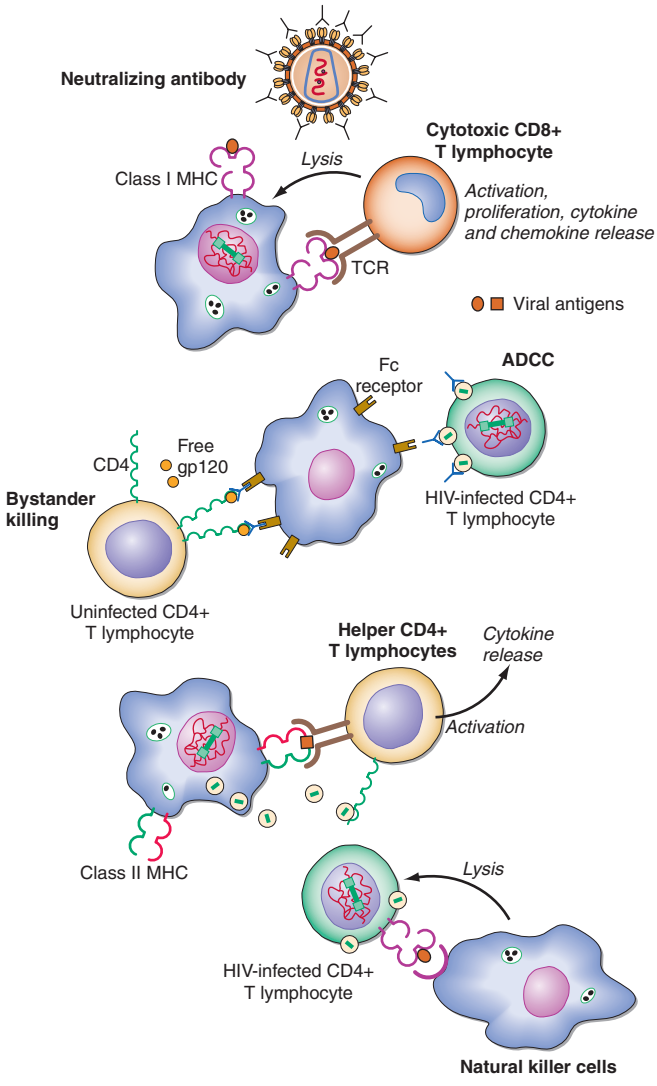


FIGURE 93-26

Schematic representation of the different immunologic effector mechanisms thought to be active in the setting of HIV infection. Detailed descriptions are given in the text. ADCC, antibody-dependent cellular cytotoxicity; MHC, major histocompatibility complex; TCR, T cell receptor.

HUMORAL IMMUNE RESPONSE

Antibodies to HIV usually appear within 3–6 weeks and almost invariably within 12 weeks of primary infection **(Fig. 93-27)**; rare exceptions are individuals who have defects in the ability to produce HIV-specific antibodies. Detection of these antibodies forms the basis of most diagnostic screening tests for HIV infection. The appearance of HIV-binding antibodies detected by ELISA and Western blot assays occurs prior to the appearance of neutralizing antibodies; the latter generally appear following the initial decreases in plasma viremia, which is more closely related to the appearance of HIV-specific CD8+ T lymphocytes. The first antibodies detected are those directed against the immunodominant region of the envelope gp41, followed by the appearance of antibodies to the structural or gag protein p24 and the gag precursor p55. Antibodies to p24 gag are followed by the appearance of antibodies to the outer envelope glycoprotein (gp120), the gag protein p17, and the products of the *pol* gene (p31 and p66). In addition, one may see antibodies to the low-molecular-weight regulatory proteins encoded by the HIV genes *vpr*, *vpu*, *vif*, *rev*, *tat*, and *nef*. On rare occasion, levels of HIV-specific antibodies may decline during treatment of acute HIV infection.

While antibodies to multiple antigens of HIV are produced, the precise functional significance of these different antibodies is unclear. The only viral proteins that elicit neutralizing antibodies are the envelope proteins gp120 and gp41. Antibodies directed toward the envelope proteins of HIV have been characterized both as being protective and as possibly contributing to the pathogenesis of HIV disease. Among the protective antibodies are those that function to neutralize HIV directly and prevent the spread of infection to additional cells, as well as those that participate in ADCC. Within the first 6 months of infection, neutralizing antibodies appear; however, the virus quickly escapes these neutralizing antibodies. One of the principal mechanisms of immune escape is the addition of N-linked glycosylation sites. The added carbohydrate moieties interfere with envelope recognition by these initial antibodies. The hyperglycosylation of the envelope protein has been termed the *glycan shield*. Neutralizing antibodies appear to be of two forms, type-specific and group-specific. *Type-specific neutralizing antibodies* are generally directed to the V3 loop region. These antibodies appear early after infection and are generally directed toward linear epitopes within the V2 and V3 variable regions of gp120. They neutralize only viruses of a given strain and are present in low titer in most infected individuals. *Group-specific neutralizing antibodies* appear later in infection and are capable of neutralizing a wide variety of HIV isolates. At least two forms of group-specific antibodies have been identified: those directed toward the CD4 binding site (CD4bs) of gp120, and those binding to the membrane-proximal region of gp41 **(Fig. 93-28)**. The other major class of protective antibodies are those that participate in ADCC, which is actually a form of cell-mediated immunity in which NK cells that bear Fc receptors are armed with specific anti-HIV antibodies that bind to the NK cells via their Fc portion. These armed NK cells then bind to and destroy cells expressing HIV antigens. Antibodies to both gp120 and gp41 have been shown to participate in ADCC-mediated killing of HIV-infected cells. The levels of antienvelope antibodies capable of mediating ADCC are highest in the earlier stages of HIV infection. In vitro, IL-2 can augment ADCC-mediated killing.

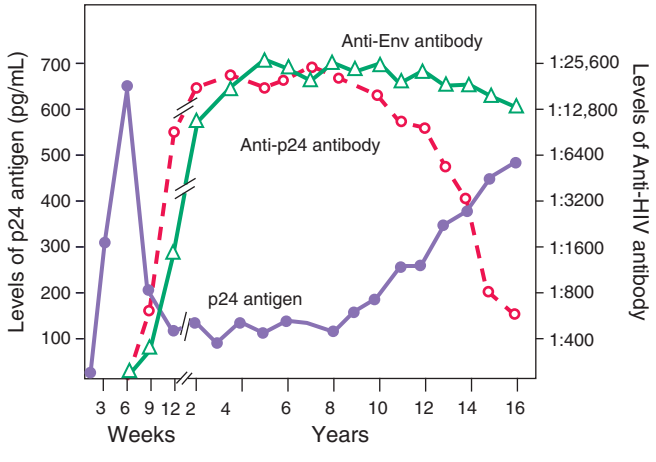


FIGURE 93-27

Relationship between antigenemia and the development of antibodies to HIV. Antibodies to HIV proteins are generally seen 6–12 weeks following infection and 3–6 weeks after the development of plasma viremia. Late in the course of illness, antibody levels to p24 decline, generally in association with a rising titer of p24 antigen.

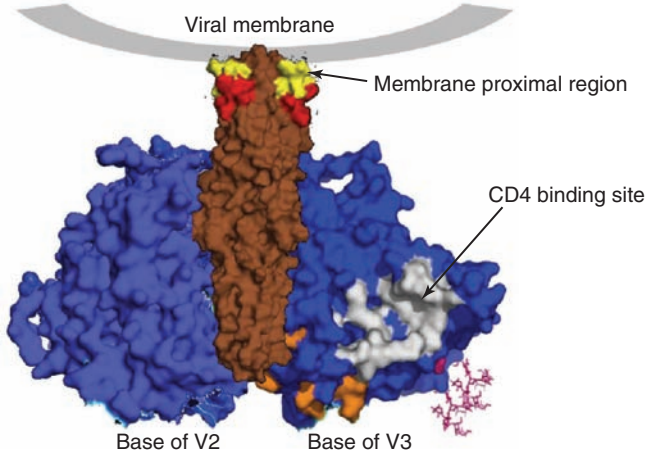


FIGURE 93-28

Known targets of neutralizing antibodies to HIV-1. Group-specific antibody-binding regions include the membrane proximal region and the CD4 binding site. Type-specific antibody-binding regions include V2 and V3 loops. (*Adapted from DR Burton et al: Nat Immunol 5:233, 2004.*)

In addition to playing a role in host defense, HIV-specific antibodies have also been implicated in disease pathogenesis. Antibodies directed to gp41, when present in low titer, have been shown in vitro to be capable of facilitating infection of cells through an Fc receptor–mediated mechanism known as *antibody enhancement*. Thus, the same regions of the envelope protein of HIV that give rise to antibodies capable of mediating ADCC also elicit the production of antibodies that can facilitate infection of cells in vitro. In addition, it has been postulated that anti-gp120 antibodies that participate in the ADCC killing of HIV-infected cells might also kill uninfected CD4+ T cells if the uninfected cells had bound free gp120, a phenomenon referred to as *bystander killing*. One of the most primitive components of the humoral immune system is the complement system. This element of innate immunity consists of ~30 proteins that are found circulating in blood or associated with cell membranes. While HIV alone is capable of directly activating the complement cascade, the resulting lysis is weak due to the presence of host cell regulatory proteins captured in the virion envelope during budding. It is possible that complement-opsonized HIV virions have increased infectivity in a manner analogous to antibody-mediated enhancement.

CELLULAR IMMUNE RESPONSE

Given the fact that T cell–mediated immunity is known to play a major role in host defense against most viral infections, it is generally thought to be an important component of the host immune response to HIV. T cell immunity can be divided into two major categories: that mediated by *helper/inducer CD4+ T cells* and that mediated by *cytotoxic/immunoregulatory CD8+ T cells*.

HIV-specific CD4+ T cells can be detected in the majority of HIV-infected patients through the use of flow cytometry to measure intracellular cytokine production in response to MHC class II tetramers pulsed with HIV peptides or through lymphocyte proliferation assays utilizing HIV antigens such as p24. These cells likely play a critical role in the orchestration of the immune response to HIV by providing help to HIV-specific B cells and CD8+ T cells. They may also be capable of directly killing HIV-infected cells. HIV-specific CD4+ T cells may be preferential targets of HIV infection by HIV-infected antigen-presenting cells during the generation of an immune response to HIV (Fig. 93-26). However, they also are likely to undergo clonal expansions in response to HIV antigens and thus survive as a population of cells. No clear correlations exist between levels of HIV-specific CD4+ T lymphocytes and plasma HIV RNA levels; however, in the setting of high viral loads, CD4+ T cell responses to HIV antigens appear to shift from one of proliferation and IL-2 production to one of IFN-γ production. Thus, while a reverse correlation exists between the level of p24-specific proliferation and levels of plasma HIV viremia, the nature of the causal relationship between these parameters is unclear.

MHC class I–restricted, HIV-specific CD8+ T cells have been identified in the peripheral blood of patients with HIV-1 infection. These cells include CTLs that produce perforins and T cells that can be induced by HIV antigens to express an array of cytokines such as IFN-γ, IL-2, and TNF-α. CTLs have been identified in the peripheral blood of patients within weeks of HIV infection and prior to the appearance of plasma virus. The selective pressure they exert on the evolution of the population of circulating viruses reflects their potential role in control of HIV infection. These CD8+ T lymphocytes, through their HIV-specific antigen receptors, bind to and cause the lytic destruction of target cells bearing autologous MHC class I molecules presenting HIV antigens. Two types of CTL activity can be demonstrated in the peripheral blood or lymph node mononuclear cells of HIV-infected individuals. The first type directly lyses appropriate target cells in culture without prior in vitro stimulation (*spontaneous CTL activity*). The other type of CTL activity reflects the *precursor frequency of CTLs* (CTLp); this type of CTL activity can be demonstrated by stimulation of CD8+ T cells in vitro with a mitogen such as phytohemagglutinin or anti-CD3 antibody.

In addition to CTLs, CD8+ T cells capable of being induced by HIV antigens to express cytokines such as IFN-γ also appear in the setting of HIV-1 infection. It is not clear whether these are the same or different effector pools compared with those cells mediating cytotoxicity; in addition, the relative roles of each in host defense against HIV are not fully understood. It does appear that these CD8+ T cells are driven to in vivo expansion by HIV antigen. There is a direct correlation between levels of CD8+ T cells capable of producing IFN-γ in response to HIV antigens and plasma levels of HIV-1 RNA. Thus, while these cells are clearly induced by HIV-1 infection, their overall ability to control infection remains unclear. Multiple HIV antigens, including Gag, Env, Pol, Tat, Rev, and Nef, can elicit CD8+ T cell responses. Among patients who control viral replication in the absence of antiretroviral drugs are a subset of patients referred to as elite nonprogressors (see "Long-Term Survivors and Long-Term Nonprogressors," earlier) whose peripheral blood contains a population of CD8+ T cells that undergo substantial proliferation and perforin expression in response to HIV antigens. It is possible that these cells play an important role in HIV-specific host defense.

At least three other forms of cell-mediated immunity to HIV have been described: CD8+ T cell–mediated suppression of HIV replication, ADCC, and NK cell activity. *CD8+ T cell–mediated suppression of HIV replication* refers to the ability of CD8+ T cells from an HIV-infected patient to inhibit the replication of HIV in tissue culture in a noncytolytic manner. There is no requirement for HLA compatibility between the CD8+ T cells and the HIV-infected cells. This effector mechanism is thus nonspecific and appears to be mediated by soluble factor(s) including the CC-chemokines RANTES (CCL5), MIP-1α (CCL3), and MIP-1β (CCL4). These CC-chemokines are potent suppressors of

HIV replication and operate at least in part via blockade of the HIV co-receptor (*CCR5*) for R5 (macrophage-tropic) strains of HIV-1 (see earlier). *ADCC*, as described earlier in relation to humoral immunity, involves the killing of HIV-expressing cells by NK cells armed with specific antibodies directed against HIV antigens. Finally, *NK cells* alone have been shown to be capable of killing HIV-infected target cells in tissue culture. This primitive cytotoxic mechanism of host defense is directed toward nonspecific surveillance for neoplastic transformation and viral infection through recognition of altered MHC class I molecules.

DIAGNOSIS AND LABORATORY MONITORING OF HIV INFECTION

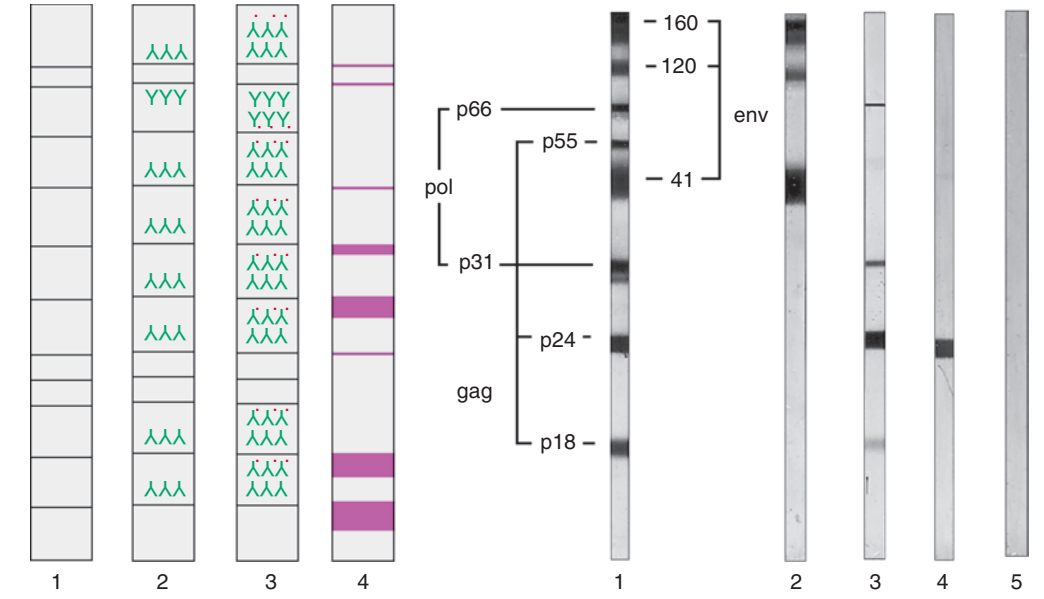
The establishment of HIV as the causative agent of AIDS and related syndromes early in 1984 was followed by the rapid development of sensitive screening tests for HIV infection. By March 1985, blood donors in the United States were routinely screened for antibodies to HIV. In 1996, blood banks in the United States added the p24 antigen capture assay to the screening process to help identify the rare infected individuals who were donating blood in the time (up to 3 months) between infection and the development of antibodies. In 2002, the ability to detect early infection with HIV was further enhanced by the licensure of nucleic acid testing (NAT) as a routine part of blood donor screening. These refinements decreased the interval between infection and detection (window period) from 22 days for antibody testing to 16 days with p24 antigen testing and subsequently to 12 days with nucleic acid testing. The development of sensitive assays for monitoring levels of plasma viremia ushered in a new era of being able to monitor the progression of HIV disease more closely. Utilization of these tests, coupled with the measurement of levels of CD4+ T lymphocytes in peripheral blood, is essential in the management of patients with HIV infection.

DIAGNOSIS OF HIV INFECTION

The CDC has recommended that screening for HIV infection be performed as a matter of routine health care. The diagnosis of HIV infection depends on the demonstration of antibodies to HIV and/or the direct detection of HIV or one of its components. As noted earlier, antibodies to HIV generally appear in the circulation 3–12 weeks following infection.

The standard blood screening test for HIV infection is the ELISA, also referred to as an *enzyme immunoassay* (EIA). This solid-phase assay is an extremely good screening test with a sensitivity of >99.5%. Most diagnostic laboratories use a commercial EIA kit that contains antigens from both HIV-1 and HIV-2 and thus are able to detect either. These kits use both natural and recombinant antigens and are continuously updated to increase their sensitivity to newly discovered species, such as group O viruses (Fig. 93-6). The fourth-generation EIA tests combine detection of antibodies to HIV with detection of the p24 antigen of HIV. EIA tests are generally scored as positive (highly reactive), negative (nonreactive), or indeterminate (partially reactive). While the EIA is an extremely sensitive test, it is not optimal with regard to specificity. This is particularly true in studies of low-risk individuals, such as volunteer blood donors. In this latter population, only 10% of EIA-positive individuals are subsequently confirmed to have HIV infection. Among the factors associated with false-positive EIA tests are antibodies to class II antigens (such as may be seen following pregnancy, blood transfusion, or transplantation), autoantibodies, hepatic disease, recent influenza vaccination, and acute viral infections. For these reasons, anyone suspected of having HIV infection based on a positive or inconclusive EIA result must have the result confirmed with a more specific assay such as the Western blot. One can estimate whether an individual has a recent infection with HIV-1 by comparing the results on a standard EIA test that will score positive for all infected individuals with the results on an assay modified to be less sensitive ("detuned assay") that will score positive only for individuals with established HIV infection. In rare instances, an HIV-infected individual treated early in the course of infection may revert to a negative EIA. This does *not* indicate clearing of infection; rather, it signifies levels of ongoing exposure to virus insufficient to maintain a measurable antibody response. When these individuals have discontinued therapy, viruses and antibodies have reappeared.

The most commonly used confirmatory test is the Western blot **(Fig. 93-29)**. This assay takes advantage of the fact that multiple HIV antigens of different, well-characterized molecular weights elicit the production of specific antibodies. These antigens can be separated on the basis of molecular weight, and antibodies to each component can be detected as discrete bands on the Western blot. A negative Western blot is one in which no bands are present at molecular weights corresponding to HIV gene products. In a patient with a positive or indeterminate EIA and a negative Western blot, one can conclude with certainty that the EIA reactivity was a false positive. On the other hand, a Western blot demonstrating antibodies to products of all three of the major genes of HIV (*gag*, *pol*, and *env*) is conclusive evidence of infection with HIV. Criteria established by the U.S. Food and Drug Administration (FDA) in 1993 for a positive Western blot state that a result is considered positive if antibodies exist to two of the three HIV proteins: p24, gp41, and gp120/160. Using these criteria, ~10% of all blood donors deemed positive for HIV-1 infection lacked an antibody band to the *pol* gene product p31. Some 50% of these blood donors were subsequently found to be false positives. Thus, the absence of the p31 band should increase the suspicion that one may be dealing with a false-positive test result. In this setting it is prudent to obtain additional confirmation with an RNA-based test for HIV-1 and/or a follow-up Western blot. By definition, Western blot patterns of reactivity that do not fall into the positive



A
1. Virus digested: digest separated into components by molecular weight
2. Proteins transferred to filter paper: reaction with test serum
3. Enzyme-conjugated antihuman antibody added
4. Substrate added and color noted

B
1. Positive HIV-1 infection
2. gp 160 immunization
3. Indeterminate (HIV-2 infection)
4. Indeterminate (cross-reacting antibody to p24)
5. Negative

FIGURE 93-29
Western blot assay for detection of antibodies to HIV. ***A.*** Schematic representation of how a Western blot is performed. ***B.*** Examples of patterns of Western blot reactivity. In each instance the Western blot strip contains antigens to HIV-1. The serum from the patient immunized to the HIV-1 envelope gp160 contains only antibodies to the HIV-1 envelope proteins. The serum from the patient with HIV-2 infection cross-reacts with both *reverse transcriptase* and *gag* gene products of HIV-1.

or negative categories are considered "indeterminate." There are two possible explanations for an indeterminate Western blot result. The most likely explanation in a low-risk individual is that the patient being tested has antibodies that cross-react with one of the proteins of HIV. The most common patterns of cross-reactivity are antibodies that react with p24 and/or p55. The least likely explanation in this setting is that the individual is infected with HIV and is in the process of mounting a classic antibody response. In either instance, the Western blot should be repeated in 1 month to determine whether the indeterminate pattern is a pattern in evolution. In addition, one may attempt to confirm a diagnosis of HIV infection with the p24 antigen capture assay or one of the tests for HIV RNA (discussed later). While the Western blot is an excellent confirmatory test for HIV infection in patients with a positive or indeterminate EIA, it is a poor screening test. Among individuals with a negative EIA and PCR for HIV, 20–30% may show one or more bands on Western blot. While these bands are usually faint and represent cross-reactivity, their presence creates a situation in which other diagnostic modalities (such as DNA PCR, RNA PCR, the bDNA assay, or p24 antigen capture) must be employed to ensure that the bands do not indicate early HIV infection.

A guideline for the use of these serologic tests in attempting to make a diagnosis of HIV infection is depicted in **Fig. 93-30**. In patients in whom HIV infection is suspected, the appropriate initial test is the EIA. If the result is negative, unless there is strong reason to suspect early HIV infection (as in a patient exposed within the previous 3 months), the diagnosis is ruled out and retesting should be performed only as clinically indicated. If the EIA is indeterminate or positive, the test should be repeated. If the repeat is negative on two occasions, one can assume that the initial positive reading was due to a technical error in the performance of the assay and that the patient is negative. If the repeat is indeterminate or positive, one should proceed to the HIV-1 Western blot. If the Western blot is positive, the diagnosis is HIV-1 infection. If the Western blot is negative, the EIA can be assumed to have been a false positive for HIV-1 and the diagnosis of HIV-1 infection is ruled out. It would also be prudent at this point to perform specific serologic testing for HIV-2 following the same type of algorithm. If the Western blot for HIV-1 is indeterminate, it should be repeated in 4–6 weeks; in addition, one may proceed to a p24 antigen capture assay, HIV-1 RNA assay, or HIV-1 DNA PCR and specific serologic testing for HIV-2. If the p24 and HIV RNA assays are negative and there is no progression in

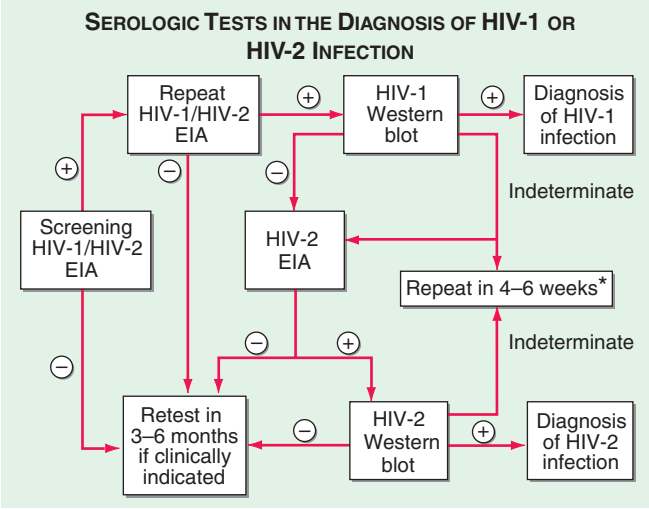


FIGURE 93-30

Algorithm for the use of serologic tests in the diagnosis of HIV-1 or HIV-2 infection. *Stable indeterminate Western blot 4–6 weeks later makes HIV infection unlikely. However, it should be repeated twice at 3-month intervals to rule out HIV infection. Alternatively, one may test for HIV-1 p24 antigen or HIV RNA. EIA, enzyme immunoassay.

the Western blot, a diagnosis of HIV-1 is ruled out. If either the p24 or HIV-1 RNA assay is positive and/or the HIV-1 Western blot shows progression, a tentative diagnosis of HIV-1 infection can be made and later confirmed with a follow-up Western blot demonstrating a positive pattern. In addition to these standard laboratory-based assays for detecting antibodies to HIV, a series of point-of-care tests are also available that can provide results in 1–60 minutes. Among the most popular of these is the OraQuick Rapid HIV-1 antibody test that can be run on blood, plasma, or saliva. The sensitivity and specificity of this test are each ~99%. While negative results from this test are adequate to rule out a diagnosis of HIV infection, a positive finding should be considered preliminary and confirmed with standard serologic testing, as described earlier.

A variety of laboratory tests are available for the direct detection of HIV or its components **(Table 93-7; Fig. 93-31)**. These tests may be of considerable help in making a diagnosis of HIV infection when the Western blot results are indeterminate. In addition, the tests detecting levels of HIV RNA can be used to determine prognosis and to assess the response to antiretroviral therapies. The simplest of the direct detection tests is the *p24 antigen capture assay*. This is an EIA-type assay in which the solid phase consists of antibodies to the p24 antigen of HIV. It detects the viral protein p24 in the blood of HIV-infected individuals where it exists either as free antigen or complexed to anti-p24 antibodies. Overall, ~30% of individuals with untreated HIV infection have detectable levels of free p24 antigen. This increases to ~50% when samples are treated with a weak acid to dissociate antigen-antibody complexes. Throughout the course of HIV infection, an equilibrium exists between p24 antigen and anti-p24 antibodies. During the first few weeks of infection, before an immune response develops, there is a brisk rise in p24 antigen levels (Fig. 93-27). After the

TABLE 93-7

CHARACTERISTICS OF TESTS FOR DIRECT DETECTION OF HIV

TEST	TECHNIQUE	SENSITIVITY[a]	COST/TEST[b]
Immune complex–dissociated p24 antigen capture assay	Measurement of levels of HIV-1 core protein in an EIA-based format following dissociation of antigen-antibody complexes by weak acid treatment	Positive in 50% of patients; detects down to 15 pg/mL of p24 protein	$1–2
HIV RNA by PCR	PCR amplification of cDNA generated from viral RNA (target amplification)	Reliable to 40 copies/mL of HIV RNA	$75–150
HIV RNA by bDNA	Measurement of levels of particle-associated HIV RNA in a nucleic acid capture assay employing signal amplification	Reliable to 50 copies/mL of HIV RNA	$75–150
HIV RNA by NASBA	Isothermic nucleic acid amplification with internal controls	Reliable to 80 copies/mL of HIV RNA	$75–150

[a]Sensitivity figures refer to those approved by the U.S. Food and Drug Administration.
[b]Prices may be lower in large-volume settings.
Abbreviations: bDNA, branched DNA; cDNA; complementary DNA;. EIA, enzyme immunoassay; NASBA, nucleic acid sequence–based amplification; PCR, polymerase chain reaction.

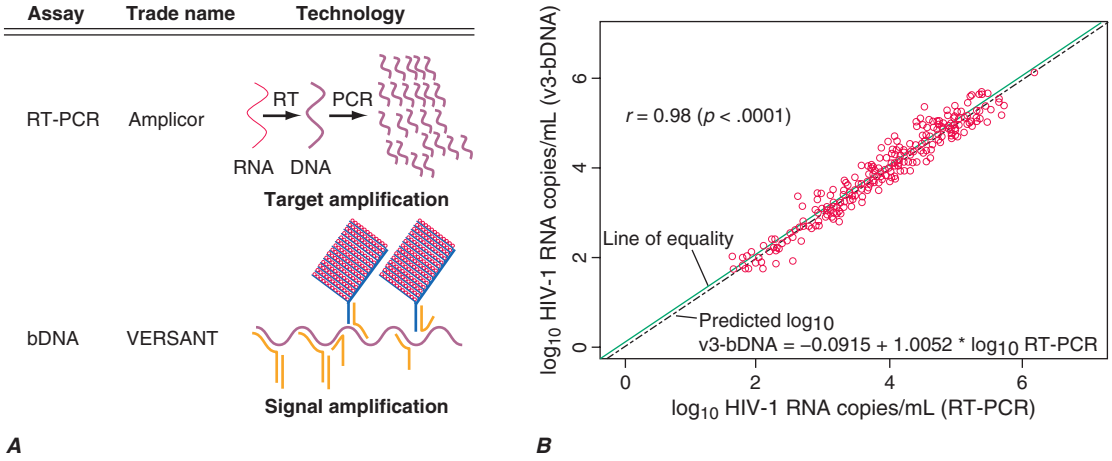


FIGURE 93-31

Comparison of RT-PCR and bDNA assays. ***A***. Schematic representation of reverse transcriptase–polymerase chain reaction (RT-PCR) and bDNA assays. See text for detailed description. ***B.*** Scatter plot of $\log_{10}$ v3-bDNA versus $\log_{10}$ RT-PCR with the line of equality (solid) and the fitted regression line (hatched). The equation for the fitted regression line is given in the lower-right-hand corner. There is good agreement between the two assays. v3, version 3 of the bDNA assay. (*Adapted from HC Highbarger et al: J Clin Microbiol 37:3612, 1999.*)

development of anti-p24 antibodies, these levels decline. Late in the course of infection, when circulating levels of virus are high, p24 antigen levels also increase, particularly when detected by techniques involving dissociation of antigen-antibody complexes. The p24 antigen capture assay has its greatest use as a screening test for HIV infection in patients suspected of having the acute HIV syndrome, as high levels of p24 antigen are present prior to the development of antibodies. Its use for routine blood donor screening for HIV infection has been replaced by use of nucleic acid testing. The ability to measure and monitor levels of HIV RNA in the plasma of patients with HIV infection has been of extraordinary value in furthering our understanding of the pathogenesis of HIV infection and in providing a diagnostic tool in settings where measurements of anti-HIV antibodies may be misleading, such as in acute infection and neonatal infection. Three assays are predominantly used for this purpose. They are reverse transcriptase PCR (*RT-PCR*; Amplicor); branched DNA (*bDNA*; VERSANT); and nucleic acid sequence–based amplification (*NASBA*; NucliSens). These tests are of value in making a diagnosis of HIV infection, in establishing initial prognosis, in determining the need for therapy, and for monitoring the effects of therapy. In addition to these three commercially available tests, the *DNA PCR* is also employed by research laboratories for making a diagnosis of HIV infection by amplifying HIV proviral DNA from peripheral blood mononuclear cells. The commercially available RNA detection tests have a sensitivity of 40–80 copies of HIV RNA per milliliter of plasma. Research laboratory–based RNA assays can detect as few as one HIV RNA copy per milliliter, while the DNA PCR tests can detect proviral DNA at a frequency of one copy per 10,000–100,000 cells. Thus, these tests are extremely sensitive. One frequent consequence of a high degree of sensitivity is some loss of specificity, and false-positive results have been reported with each of these techniques. For this reason, a positive EIA with a confirmatory Western blot remains the "gold standard" for a diagnosis of HIV infection, and the interpretation of other test results must be done with this in mind.

In the RT-PCR technique, following DNAse treatment, a cDNA copy is made of all RNA species present in plasma. Insofar as HIV is an RNA virus, this will result in the production of DNA copies of the HIV genome in amounts proportional to the amount of HIV RNA present in plasma. This cDNA is then amplified and characterized using standard PCR techniques, employing primer pairs that can distinguish genomic cDNA from messenger cDNA. The bDNA assay involves the use of a solid-phase nucleic acid capture system and signal amplification through successive nucleic acid hybridizations to detect small quantities of HIV RNA. Both tests can achieve a tenfold increase in sensitivity to 40–50 copies of HIV RNA per milliliter with a preconcentration step in which plasma undergoes ultracentrifugation to pellet the viral particles. The NASBA technique involves the isothermal amplification of a sequence within the gag region of HIV in the presence of internal standards and employs the production of multiple RNA copies through the action of T7-RNA polymerase. The resulting RNA species are quantitated through hybridization with a molecular beacon DNA probe that is quenched in the absence of hybridization. The lower limit of detection for the NucliSens assay is 80 copies/mL.

In addition to being diagnostic and prognostic tools, RT-PCR and DNA-PCR are also useful for amplifying defined areas of the HIV genome for sequence analysis and have become an important technique for studies of sequence diversity and microbial resistance to

antiretroviral agents. In patients with a positive or indeterminate EIA test and an indeterminate Western blot, and in patients in whom serologic testing may be unreliable (such as patients with hypogammaglobulinemia or advanced HIV disease), these tests for quantitating HIV RNA in plasma or detecting proviral DNA in peripheral blood mononuclear cells are valuable in making a diagnosis of HIV infection; however, they should be used for diagnosis only when standard serologic testing has failed to provide a definitive result.

LABORATORY MONITORING OF PATIENTS WITH HIV INFECTION

The epidemic of HIV infection and AIDS has provided the clinician with new challenges for integrating clinical and laboratory data to effect optimal patient management. The close relationship between clinical manifestations of HIV infection and CD4+ T cell count has made measurement of CD4+ T cell numbers a routine part of the evaluation of HIV-infected individuals. The discovery of HIV as the cause of AIDS led to the development of sensitive tests that allow one to monitor the levels of HIV in the blood. Determinations of peripheral blood CD4+ T cell counts and measurements of the plasma levels of HIV RNA provide a powerful set of tools for determining prognosis and monitoring response to therapy.

CD4+ T cell counts

The CD4+ T cell count is the laboratory test generally accepted as the best indicator of the immediate state of immunologic competence of the patient with HIV infection. This measurement, which can be made directly or calculated as the product of the percent of CD4+ T cells (determined by flow cytometry) and the total lymphocyte count (determined by the white blood cell [WBC] count multiplied by the lymphocyte differential percent), has been shown to correlate very well with the level of immunologic competence. Patients with CD4+ T cell counts <200/μL are at high risk of disease from *P. jiroveci*, while patients with CD4+ T cell counts <50/μL are at high risk of disease from CMV, mycobacteria of the *M. avium* complex (MAC), and/or *T. gondii* **(Fig. 93-32)**. Patients with HIV infection should have CD4+ T cell measurements performed at the time of diagnosis and every 3–6 months thereafter. More frequent measurements should be made if a declining trend is noted. According to U.S. Department of Health and Human Services Guidelines, a CD4+ T cell count <500/μL is an indication for initiating cART, and a decline in CD4+ T cell count of >25% is an indication for considering a change in therapy. Once the CD4+ T cell count is <200/μL, patients should be placed on a regimen for *P. jiroveci* prophylaxis, and once the count is <50/μL, primary prophylaxis for MAC infection is indicated. As with any laboratory measurement, one may wish to obtain two determinations prior to any significant changes in patient management based on CD4+ T cell count alone. There are a handful of clinical situations in which the CD4+ T cell count may be misleading. Patients with HTLV-I/HIV co-infection may have elevated CD4+ T cell counts that do not accurately reflect their degree of immune competence. In patients with hypersplenism or those who have undergone splenectomy, and in patients receiving medications that suppress the bone marrow such as IFN-α,

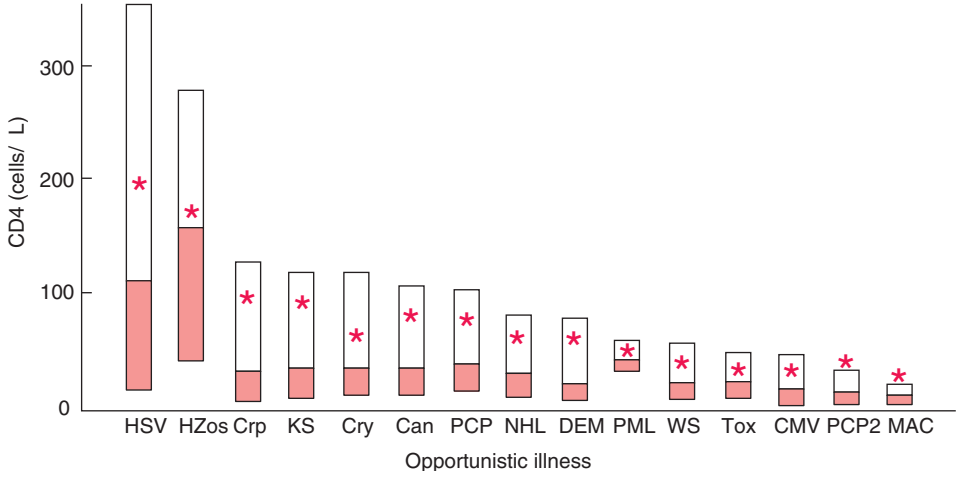


FIGURE 93-32

Relationship between CD4+ T cell counts and the development of opportunistic diseases. Boxplot of the median (line inside the box), first quartile (bottom of the box), third quartile (top of the box), and mean (asterisk) CD4+ lymphocyte count at the time of the development of opportunistic disease. Can, candidal esophagitis; CMV, cytomegalovirus infection; Crp, cryptosporidiosis; Cry, cryptococcal meningitis; DEM, AIDS dementia complex; HSV, herpes simplex virus infection; HZos, herpes zoster; KS, Kaposi's sarcoma; MAC, *Mycobacterium avium* complex bacteremia; NHL, non-Hodgkin's lymphoma; PCP, primary *Pneumocystis jiroveci* pneumonia; PCP2, secondary *P. jiroveci* pneumonia; PML, progressive multifocal leukoencephalopathy; Tox, *Toxoplasma gondii* encephalitis; WS, wasting syndrome. (*From RD Moore, RE Chaisson: Ann Intern Med 124:633, 1996.*)

the CD4+ T cell percentage may be a more reliable indication of immune function than the CD4+ T cell count. A CD4+ T cell percent of 15 is comparable to a CD4+ T cell count of 200/μL.

HIV RNA determinations

Facilitated by highly sensitive techniques for the precise quantitation of small amounts of nucleic acids, the measurement of serum or plasma levels of HIV RNA has become an essential component in the monitoring of patients with HIV infection. As discussed earlier under "Diagnosis of HIV Infection," the two most commonly used techniques are the RT-PCR assay and the bDNA assay. Both assays generate data in the form of number of copies of HIV RNA per milliliter of serum or plasma. Standard assays can detect as few as 40–50 copies of HIV RNA per milliliter of plasma, while research-based assays can detect down to one copy per milliliter. While it is common practice to describe levels of HIV RNA below these cut-offs as "undetectable," this is a term that should be avoided as it is imprecise and leaves the false impression that the level of virus is 0. By utilizing more sensitive, nested PCR techniques and by studying tissue levels of virus as well as plasma levels, HIV RNA can be detected in virtually every patient with HIV infection. One notable exception is the patient who has undergone cytoreduction therapy and then received a bone marrow transplant from a ccr5Δ32 homozygous donor. Measurements of changes in HIV RNA levels over time have been of great value in delineating the relationship between levels of virus and rates of disease progression (Fig. 93-22), the rates of viral turnover, the relationship between immune system activation and viral replication, and the time to development of drug resistance. HIV RNA measurements are greatly influenced by the state of activation of the immune system and may fluctuate greatly in the setting of secondary infections or immunization. For these reasons, decisions based on HIV RNA levels should never be made on a single determination. Measurements of plasma HIV RNA levels should be made at the time of HIV diagnosis and every 3–6 months thereafter in the untreated patient. Following the initiation of therapy or any change in therapy, plasma HIV RNA levels should be monitored approximately every 4 weeks until the effectiveness of the therapeutic regimen is determined by the development of a new steady-state level of HIV RNA. In most instances of effective antiretroviral therapy, the plasma level of HIV RNA will drop to <50 copies per milliliter within 6 months of the initiation of treatment. During therapy, levels of HIV RNA should be monitored every 3–4 months to evaluate the continuing effectiveness of therapy.

HIV resistance testing

The availability of multiple antiretroviral drugs as treatment options has generated a great deal of interest in the potential for measuring the sensitivity of an individual's HIV virus(es) to different antiretroviral agents. HIV resistance testing can be done through either genotypic or phenotypic measurements. In the genotypic assays, sequence analyses of the HIV genomes obtained from patients are compared with sequences of viruses with known antiretroviral resistance profiles. In the phenotypic assays, the in vivo growth of viral isolates obtained from the patient is compared to the growth of reference strains of the virus in the presence or absence of different antiretroviral drugs. A modification of this phenotypic approach utilizes a comparison of the enzymatic activities of the reverse transcriptase or protease genes obtained by molecular cloning of patients' isolates to the enzymatic activities of genes obtained from reference strains of HIV in the presence or absence of different drugs targeted to these genes. These tests are quite good at identifying those antiretroviral agents that have been utilized in the past and suggesting agents that may be of future value in a given patient. Drug resistance testing in the setting of virologic failure should be performed while the patient is still on the failing regimen because of the propensity for the pool of HIV quasispecies to rapidly revert to wild-type in the absence of the selective pressures of cART. In the hands of experts, resistance testing enhances the short-term ability to decrease viral load by ~0.5 log compared with changing drugs merely on the basis of drug history. In addition to the use of resistance testing to help in the selection of new drugs in patients with virologic failure, it may also be of value in selecting an initial regimen for treatment of therapy-naïve individuals. This is particularly true in geographic areas with a high level of background resistance.

Co-receptor tropism assays

Following the licensure of maraviroc as the first CCR5 antagonist for the treatment of HIV infection (see later), it became necessary to be able to determine whether a patient's virus was likely to respond to this treatment. Patients tend to have CCR5-tropic virus early in the course of infection, with a trend toward CXCR4 viruses later in disease. The antiretroviral agent maraviroc is effective only against CCR5-tropic viruses. Because the genotypic determinants of cellular tropism are poorly defined, a phenotypic assay is necessary to determine this property of HIV. Two commercial assays, the Trofile assay (Monogram Biosciences) and the Phenoscript assay (VIRalliance), are available to make this determination. These assays clone the envelope regions of the patient's virus into an indicator virus that is then used to infect target cells expressing either CCR5 or CXCR4 as their co-receptor. These assays take weeks to perform and are expensive. Although commercial genotypic assays of proviral DNA are available, their role as predictors of response to CCR5 inhibitor therapy is unclear.

TABLE 93-8

ASSOCIATION BETWEEN HIGH-SENSITIVITY CRP, IL-6, AND D-DIMER WITH ALL-CAUSE MORTALITY IN PATIENTS WITH HIV INFECTION

	UNADJUSTED		ADJUSTED	
MARKER	ODDS RATIO (FOURTH/ FIRST)	*P*	ODDS RATIO (FOURTH/ FIRST)	*P*
Hs-CRP	2.0	.05	2.8	.03
IL-6	8.3	<.0001	11.8	<.0001
D-dimer	12.4	<.0001	26.5	<.0001

Note: Hs-CRP, high-sensitivity C-reactive protein; IL-6, interleukin 6.
Source: From LH Kuller et al: PLoS Med 5:e203, 2008.

Other tests

A variety of other laboratory tests have been studied as potential markers of HIV disease activity. Among these are quantitative culture of replication-competent HIV from plasma, peripheral blood mononuclear cells, or resting CD4+ T cells; circulating levels of β_2-microglobulin, soluble IL-2 receptor, IgA, acid-labile endogenous IFN, or TNF-α; and the presence or absence of activation markers such as CD38, HLA-DR, or PD-1 on CD8+ T cells. Nonspecific serologic markers of inflammation and/or coagulation such as IL-6, D-dimer, and sCD14 have been shown to have a high correlation with all-cause mortality (Table 93-8). While these measurements have value as markers of disease activity and help to increase our understanding of the pathogenesis of HIV disease, they do not currently play a major role in the monitoring of patients with HIV infection.

CLINICAL MANIFESTATIONS

The clinical consequences of HIV infection encompass a spectrum ranging from an acute syndrome associated with primary infection to a prolonged asymptomatic state to advanced disease. It is best to regard HIV disease as beginning at the time of primary infection and progressing through various stages. As mentioned earlier, active virus replication and progressive immunologic impairment occur throughout the course of HIV infection in most patients. With the exception of the rare, true, "elite" long-term nonprogressors (see "Long-Term Survivors and Long-Term Nonprogressors," earlier in the chapter), HIV disease in untreated patients inexorably progresses even during the clinically latent stage. Since the mid-1990s, cART has had a major impact on preventing and reversing the progression of disease over extended periods of time in a substantial proportion of adequately treated patients.

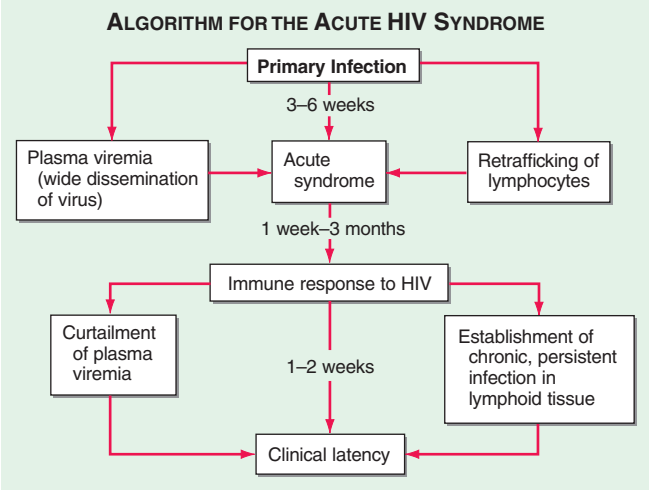


FIGURE 93-33
The acute HIV syndrome. See text for detailed description. (*Adapted from G Pantaleo et al: N Engl J Med 328:327, 1993. Copyright 1993 Massachusetts Medical Society. All rights reserved.*)

THE ACUTE HIV SYNDROME

It is estimated that 50–70% of individuals with HIV infection experience an acute clinical syndrome ~3–6 weeks after primary infection (Fig. 93-33). Varying degrees of clinical severity have been reported, and although it has been suggested that symptomatic seroconversion leading to the seeking of medical attention indicates an increased risk for an accelerated course of disease, there does not appear to be a correlation between the level of the initial burst of viremia in acute HIV infection and the subsequent course of disease. The typical clinical findings in the acute HIV syndrome are listed in Table 93-9; they occur along with a burst of plasma viremia. It has been reported that several symptoms of the acute HIV syndrome (fever, skin rash, pharyngitis, and myalgia) occur less frequently in those infected by injection drug use than in those infected by sexual contact. The syndrome is typical of an acute viral syndrome and has been likened to acute infectious mononucleosis.

TABLE 93-9

CLINICAL FINDINGS IN THE ACUTE HIV SYNDROME

General	Neurologic
Fever	Meningitis
Pharyngitis	Encephalitis
Lymphadenopathy	Peripheral neuropathy
Headache/retroorbital pain	Myelopathy
Arthralgias/myalgias	Dermatologic
Lethargy/malaise	Erythematous maculopapular rash
Anorexia/weight loss	Mucocutaneous ulceration
Nausea/vomiting/diarrhea	

Source: From B Tindall, DA Cooper: AIDS 5:1, 1991.

Symptoms usually persist for one to several weeks and gradually subside as an immune response to HIV develops and the levels of plasma viremia decrease. Opportunistic infections have been reported during this stage of infection, reflecting the immunodeficiency that results from reduced numbers of CD4+ T cells and likely also from the dysfunction of CD4+ T cells owing to viral protein and endogenous cytokine-induced perturbations of cells (Table 93-4) associated with the extremely high levels of plasma viremia. A number of immunologic abnormalities accompany the acute HIV syndrome, including multiphasic perturbations of the numbers of circulating lymphocyte subsets. The numbers of total lymphocytes and T cell subsets (CD4+ and CD8+) are initially reduced. An inversion of the CD4+/CD8+ T cell ratio occurs later because of a rise in the number of CD8+ T cells. In fact, there may be a selective and transient expansion of CD8+ T cell subsets, as determined by T cell receptor analysis (see earlier). The total circulating CD8+ T cell count may remain elevated or return to normal; however, CD4+ T cell levels usually remain somewhat depressed, although there may be a slight rebound toward normal. Lymphadenopathy occurs in ~70% of individuals with primary HIV infection. Most patients recover spontaneously from this syndrome and many are left with only a mildly depressed CD4+ T cell count that remains stable for a variable period before beginning its progressive decline; in some individuals, the CD4+ T cell count returns to the normal range. Approximately 10% of patients manifest a fulminant course of immunologic and clinical deterioration after primary infection, even after the disappearance of initial symptoms. In most patients, primary infection with or without the acute syndrome is followed by a prolonged period of clinical latency or smoldering low disease activity. A small percentage of HIV-infected individuals treated with antiretroviral drugs during acute infection may revert to a negative EIA during the time they remain on therapy. They rapidly re-seroconvert with the discontinuation of treatment.

THE ASYMPTOMATIC STAGE—CLINICAL LATENCY

Although the length of time from initial infection to the development of clinical disease varies greatly, the median time for untreated patients is ~10 years. As emphasized earlier, HIV disease with active virus replication is ongoing and progressive during this asymptomatic period. The rate of disease progression is directly correlated with HIV RNA levels. Patients with high levels of HIV RNA in plasma progress to symptomatic disease faster than do patients with low levels of HIV RNA (Fig. 93-22). Some patients referred to as *long-term nonprogressors* show little if any decline in CD4+ T cell counts over extended periods of time. These patients generally have extremely low levels of HIV RNA; a subset, referred to as *elite nonprogressors*, exhibits HIV RNA levels <50 copies per milliliter. Certain other patients remain entirely asymptomatic despite the fact that their CD4+ T cell counts show a steady progressive decline to extremely low levels. In these patients, the appearance of an opportunistic disease may be the first manifestation of HIV infection. During the asymptomatic period of HIV infection, the average rate of CD4+ T cell decline is ~50/μL per year. When the CD4+ T cell count falls to <200/μL, the resulting state of immunodeficiency is severe enough to place the patient at high risk for opportunistic infection and neoplasms and, hence, for clinically apparent disease.

SYMPTOMATIC DISEASE

Symptoms of HIV disease can appear at any time during the course of HIV infection. Generally speaking, the spectrum of illnesses that one observes changes as the CD4+ T cell count declines. The more severe and life-threatening complications of HIV infection occur in patients with CD4+ T cell counts <200/μL. A diagnosis of AIDS is made in anyone with HIV infection and a CD4+ T cell count <200/μL and in anyone with HIV infection who develops one of the HIV-associated diseases considered to be indicative of a severe defect in cell-mediated immunity (category C, Table 93-2). While the causative agents of the secondary infections are characteristically opportunistic organisms such as *P. jiroveci*, atypical mycobacteria, CMV, and other organisms that do not ordinarily cause disease in the absence of a compromised immune system, they also include common bacterial and mycobacterial pathogens. Following the widespread use of cART and implementation of guidelines for the prevention of opportunistic infections **(Table 93-10)**, the incidence of these secondary infections has decreased dramatically **(Fig. 93-34)**. Overall, the clinical spectrum of HIV disease is constantly changing as patients live longer and new and better approaches to treatment and prophylaxis are developed. In addition to the classic AIDS-defining illnesses, patients with HIV infection also have an increase in serious non-AIDS illnesses, including non-AIDS related cancers and, cardiovascular, renal and hepatic disease. Non-AIDS events dominate the disease burden for patients with HIV infection receiving cART (Table 93-3). Fewer than 50% of deaths among AIDS patients are as a direct result of an AIDS-defining illness. The physician providing care to a patient with HIV infection must be well versed in general internal medicine as well as HIV-related opportunistic diseases. In general, it should be stressed that a key element of treatment of symptomatic complications of HIV disease, whether they are primary or secondary, is achieving good control of HIV replication through the use of cART and instituting primary and secondary prophylaxis for opportunistic infections as indicated.

Diseases of the respiratory system

Acute bronchitis and sinusitis are prevalent during all stages of HIV infection. The most severe cases tend to occur in patients with lower CD4+ T cell counts. Sinusitis presents as fever, nasal congestion, and headache.

TABLE 93-10

NIH/CDC/IDSA 2009 GUIDELINES FOR THE PREVENTION OF OPPORTUNISTIC INFECTIONS IN PERSONS INFECTED WITH HIV

PATHOGEN	INDICATIONS	FIRST CHOICE(S)	ALTERNATIVES
Recommended as Standard of Care for Primary and Secondary Prophylaxis			
Pneumocystis jiroveci	CD4+ T cell count <200/μL *or* Oropharyngeal candidiasis *or* Prior bout of PCP May stop prophylaxis if CD4+ T cell count >200/μL for ≥3 months	Trimethoprim/sulfamethoxazole (TMP/SMX), 1 DS tablet qd PO *or* TMP/SMX, 1 SS tablet qd PO	Dapsone 50 mg bid PO or 100 mg/d PO *or* Dapsone 50 mg/d PO + Pyrimethamine 50 mg/week PO + Leucovorin 25 mg/week PO *or* (Dapsone 200 mg PO + Pyrimethamine 75 mg PO + Leucovorin 25 mg) weekly PO *or* Aerosolized pentamidine, 300 mg via Respirgard II nebulizer every month *or* Atovaquone 1500 mg/d PO *or* TMP/SMX 1 DS tablet 3×/week PO
Mycobacterium tuberculosis			
Isoniazid-sensitive	Skin test >5 mm *or* Prior positive test without treatment *or* Close contact with case of active pulmonary TB	(Isoniazid 300 mg PO + Pyridoxine 50 mg PO) qd × 9 months *or* Isoniazid 900 mg PO twice weekly + Pyridoxine 50 mg PO daily × 9 months	Rifabutin 300 mg or rifampin 600 mg PO qd × 4 months
Isoniazid-resistant	Same with high probability of exposure to isoniazid-resistant TB	(Rifabutin 300 mg or Rifampin 600 mg) PO qd × 4 months	
Multidrug-resistant	Same with high probability of exposure to multidrug-resistant TB	Consult local public health authorities	
Mycobacterium avium complex	CD4+ T cell count <50/μL	Azithromycin 1200 mg weekly PO *or* Clarithromycin 500 mg bid PO	Rifabutin 300 mg/d PO *or* Azithromycin 600 mg twice weekly PO
	Prior documented disseminated disease May stop prophylaxis if CD4+ T cell count >100/μL for ≥3 months	Clarithromycin 500 mg bid PO + Ethambutol 15 (mg/kg)/d PO ± Rifabutin 300 mg/d PO	Azithromycin 500 mg/d PO + Ethambutol 15 (mg/kg)/d PO ± Rifabutin 300 mg/d PO
Toxoplasma gondii	TOXO IgG antibody positive andCD4+ T cell count <100/μL	TMP/SMX 1 DS tablet PO qd	TMP/SMX 1 DS 3× weekly PO *or* TMP/SMX, 1 SS PO daily *or* Dapsone 50 mg/d PO + Pyrimethamine 50 mg weekly PO + Leucovorin 25 mg weekly PO *or* (Dapsone 200 mg PO + Pyrimethamine 75 mg PO + Leucovorin 25 mg PO) weekly *or* (Atovaquone 1500 mg PO ± Pyrimethamine 25 mg PO + Leucovorin 10 mg PO) daily

(*continued*)

TABLE 93-10

NIH/CDC/IDSA 2009 GUIDELINES FOR THE PREVENTION OF OPPORTUNISTIC INFECTIONS IN PERSONS INFECTED WITH HIV (*CONTINUED*)

PATHOGEN	INDICATIONS	FIRST CHOICE(S)	ALTERNATIVES
Recommended as Standard of Care for Primary and Secondary Prophylaxis (*continued*)			
	Prior toxoplasmic encephalitis and CD4+ T cell count <200/μL	Sulfadiazine 500–1000 mg qid PO + Pyrimethamine 25–50 mg/d PO + Leucovorin 10–25 mg/d PO	Clindamycin 600 mg q8h PO + Pyrimethamine 25–50 mg/d PO + Leucovorin 10–25 mg/d PO
	May stop prophylaxis if CD4+ T cell count >200/μL for ≥3 months		Atovaquone 750 mg PO q6–12 h ± Pyrimethamine 25 mg/d PO + Leucovorin 10 mg/d PO
Varicella-zoster virus	Significant exposure to chickenpox or shingles in a patient with no history of immunization or prior exposure to either	Varicella-zoster immune globulin, IM, within 96 h of exposure (1-800-843-7477)	Acyclovir 800 mg PO 5 × 1 day for 5 days
Cryptococcus neoformans	Prior documented disease May stop prophylaxis if CD4+ T cell count >200/μL for 6 months and no evidence of active infection	Fluconazole 200 mg/d PO	Itraconazole 200 mg/d PO
Histoplasma capsulatum	Prior documented disease or CD4+ T cell count <150/μL and high risk (endemic area or occupational exposure) May stop prophylaxis after 1 year if CD4+ T cell count >150/μL and patient on ARV therapy for ≥6 months	Itraconazole 200 mg bid PO	Fluconazole 800 mg/d PO
Coccidioides immitis	Prior documented disease *or* positive serology and CD4+ T cell count <250/μL if from a disease-endemic area (For this indication prophylaxis can be stopped if CD4+ T cell count is ≥250 for 6 months.)	Fluconazole 400 mg/d PO	Itraconazole 200 mg bid PO
Penicillium marneffei	Prior documented disease May stop secondary prophylaxis in patients on ARV therapy with CD4+ T cell count >100/μL for ≥6 months	Itraconazole 200 mg/d PO	
Salmonella species	Prior treament of bacteremia	Ciprofloxacin 500 mg bid PO for ≥6 months	
Bartonella species	Prior infection May stop if CD4+ T cell count >200/μL for >3 months	Doxycycline 200 mg/d *or* Azithromycin 1200 mg weekly PO *or* Clarithromycin 500 mg bid PO	
Cytomegalovirus	Prior end-organ disease May stop prophylaxis if CD4+ T cell count >100/μL for 6 months and no evidence of active CMV disease Restart if prior retinitis and CD4+ T cells <100/μL	Valganciclovir 900 mg bid PO *or* Ganciclovir sustained-release implant q6–9 months + Valganciclovir 900 mg bid PO	Cidofovir 5 mg/kg every other week IV +Probenecid *or* Fomivirsen 330 μg intravitreal q2–4 week *or* Foscarnet 90–120 (mg/kg)/d IV

(*continued*)

TABLE 93-10

NIH/CDC/IDSA 2009 GUIDELINES FOR THE PREVENTION OF OPPORTUNISTIC INFECTIONS IN PERSONS INFECTED WITH HIV (*CONTINUED*)

PATHOGEN	INDICATIONS	FIRST CHOICE(S)	ALTERNATIVES
Immunizations Generally Recommended			
Hepatitis B virus	All susceptible (anti-HBc- and anti-HBs-negative) patients	Hepatitis B vaccine: 3 doses	
Hepatitis A virus	All susceptible (anti-HAV-negative) patients	Hepatitis A vaccine: 2 doses	
Influenza virus	All patients annually	Inactivated trivalent influenza virus vaccine 1 dose yearly	Oseltamivir 75 mg PO qd *or* Rimantadine or amantadine 100 mg PO bid (influenza A only)
Streptococcus pneumoniae	All patients, preferably before CD4+ T cell count ≤200/μL	Pneumococcal vaccine 0.5 mL IM ×1 if CD4+ T cell count >200/μL Reimmunize patients initially immunized at a CD4+ T cell count <100/μL whose CD4+ T cell count then increases to >200/μL	
Human papillomavirus	All patients 9–26 years of age	HPV vaccine; 3 doses	
Recommended for Prevention of Severe or Frequent Recurrences			
Herpes simplex	Frequent/severe recurrences	Valacyclovir 500 mg bid PO *or* Acyclovir 400 mg bid PO *or* Famciclovir 500 mg bid PO	
Candida	Frequent/severe recurrences	Fluconazole 100–200 mg/d PO	Itraconazole solution 200 mg/d PO or posaconazole 400 mg bid PO

Abbreviations: ARV, antiretroviral; bid, twice daily; DS, double-strength; PCP, *Pneumocystis jiroveci* pneumonia; PO, by mouth; SS, single-strength; TB, tuberculosis.

The diagnosis is made by CT or MRI. The maxillary sinuses are most commonly involved; however, disease is also frequently seen in the ethmoid, sphenoid, and frontal sinuses. While some patients may improve without antibiotic therapy, radiographic improvement is quicker and more pronounced in patients who have received antimicrobial therapy. It is postulated that this high incidence of sinusitis results from an increased frequency of infection with encapsulated organisms such as *H. influenzae* and *Streptococcus pneumoniae*. In patients with low CD4+ T cell counts one may see mucormycosis infections of the sinuses. In contrast to the course of this infection in other patient populations, mucormycosis of the sinuses in patients with HIV infection may progress more slowly. In this setting aggressive, frequent local debridement in addition to local and systemic amphotericin B may result in effective treatment.

Pulmonary disease is one of the most frequent complications of HIV infection. The most common manifestation of pulmonary disease is pneumonia. Three of the 10 most common AIDS-defining illnesses are recurrent bacterial pneumonia, tuberculosis, and pneumonia due to the unicellular fungus *P. jiroveci*. Other major causes of pulmonary infiltrates include other mycobacterial infections, other fungal infections, nonspecific interstitial pneumonitis, KS, and lymphoma.

Bacterial pneumonia is seen with an increased frequency in patients with HIV infection, with 0.8–2.0 cases per 100 person-years. Patients with HIV infection are particularly prone to infections with encapsulated organisms. *S. pneumoniae* (Chap. 37) and *H. influenzae* (Chap. 50) are responsible for most cases of bacterial pneumonia in patients with AIDS. This may be a consequence of altered B cell function and/or defects in neutrophil function that may be secondary to HIV disease

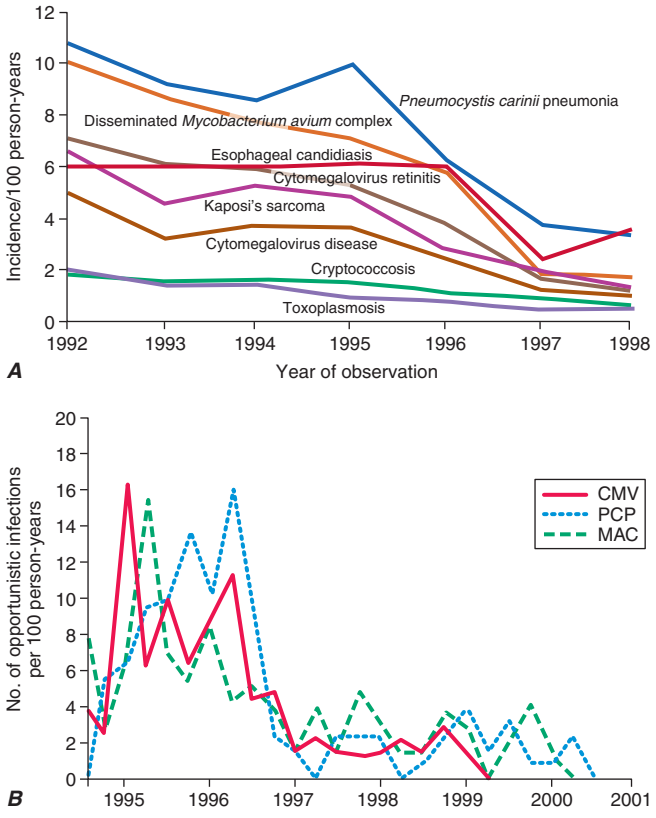


FIGURE 93-34

A. Decrease in the incidence of opportunistic infections and Kaposi's sarcoma in HIV-infected individuals with CD4+ T cell counts <100/μL from 1992 through 1998. (*Adapted and updated from FJ Palella et al: N Engl J Med 338:853, 1998, and JE Kaplan et al: Clin Infect Dis 30[S1]:S5, 2000, with permission.*) ***B.*** Quarterly incidence rates of cytomegalovirus (CMV), *Pneumocystis jiroveci* pneumonia (PCP), and *Mycobacterium avium* complex (MAC) from 1995 to 2001. (*From FJ Palella et al: AIDS 16:1617, 2002.*)

(see earlier). Pneumonias due to *S. aureus* (Chap. 38) and *P. aeruginosa* (Chap. 57) are also reported to occur with an increased frequency in patients with HIV infection. *S. pneumoniae* (pneumococcal) infection may be the earliest serious infection to occur in patients with HIV disease. This can present as pneumonia, sinusitis, and/or bacteremia. Patients with untreated HIV infection have a sixfold increase in the incidence of pneumococcal pneumonia and a 100-fold increase in the incidence of pneumococcal bacteremia. Pneumococcal disease may be seen in patients with relatively intact immune systems. In one study, the baseline CD4+ T cell count at the time of a first episode of pneumococcal pneumonia was ~300/μL. Of interest is the fact that the inflammatory response to pneumococcal infection appears proportional to the CD4+ T cell count. Due to this high risk of pneumococcal disease, immunization with pneumococcal polysaccharide is one of the generally recommended prophylactic measures for patients with HIV infection. This is likely most effective if given while the CD4+ T cell count is >200/μL and, if given to patients with lower CD4+ T cell counts, should be repeated once the count has been above 200 for 6 months. Although clear guidelines do not exist, it also makes sense to repeat immunization every 5 years. The incidence of bacterial pneumonia is cut in half when patients quit smoking.

Pneumocystis pneumonia (PCP), once the hallmark of AIDS, has dramatically declined in incidence following the development of effective prophylactic regimens and the widespread use of cART. It is, however, still the single most common cause of pneumonia in patients with HIV infection in the United States and can be identified as a likely etiologic agent in 25% of cases of pneumonia in patients with HIV infection, with an incidence in the range of 2–3 cases per 100 person-years. Approximately 50% of cases of HIV-associated PCP occur in patients who are unaware of their HIV status. The risk of PCP is greatest among those who have experienced a previous bout of PCP and those who have CD4+ T cell counts of <200/μL. Overall, 79% of patients with PCP have CD4+ T cell counts <100/μL and 95% of patients have CD4+ T cell counts <200/μL. Recurrent fever, night sweats, thrush, and unexplained weight loss are also associated with an increased incidence of PCP. For these reasons, it is strongly recommended that all patients with CD4+ T cell counts <200/μL (or a CD4 percentage <15) receive some form of PCP prophylaxis. The incidence of PCP is approaching zero in patients with known HIV infection receiving appropriate cART and prophylaxis. In the United States, primary PCP is now occurring at a median CD4+ T cell count of 36/μL, while secondary PCP is occurring at a median CD4+ T cell count of 10/μL. Patients with PCP generally present with fever and a cough that is usually nonproductive or productive of only scant amounts of white sputum. They may complain of a characteristic retrosternal chest pain that is worse on inspiration and is described as sharp or burning. HIV-associated PCP may have an indolent course characterized by weeks of vague symptoms and should be included in the differential diagnosis of fever, pulmonary complaints, or unexplained weight loss in any patient with HIV infection and <200 CD4+ T cells/μL. The most common finding on chest x-ray is either a normal film, if the disease is suspected early, or a faint bilateral interstitial infiltrate. The classic finding of a dense perihilar infiltrate is unusual in patients with AIDS. In patients with PCP who have been receiving aerosolized pentamidine for prophylaxis, one may see an x-ray picture of upper lobe cavitary disease, reminiscent of TB. Other less common findings on chest x-ray include lobar infiltrates and pleural effusions. Thin-section CT may demonstrate a patchy ground-glass appearance. Routine laboratory evaluation is usually of little help in the differential diagnosis of PCP. A mild leukocytosis is common, although this may not be obvious in patients with prior neutropenia. Elevation of lactate dehydrogenase is common. Arterial blood-gases may indicate hypoxemia with a decline in Pa_{O2} and an increase in the arterial-alveolar (a–A) gradient. Arterial blood-gas measurements not only aid in making the

diagnosis of PCP but also provide important information for staging the severity of the disease and directing treatment (see later). A definitive diagnosis of PCP requires demonstration of the organism in samples obtained from induced sputum, bronchoalveolar lavage, transbronchial biopsy, or open-lung biopsy. PCR has been used to detect specific DNA sequences for *P. jiroveci* in clinical specimens where histologic examinations have failed to make a diagnosis.

In addition to pneumonia, a number of other clinical problems have been reported in HIV-infected patients as a result of infection with *P. jiroveci*. Otic involvement may be seen as a primary infection, presenting as a polypoid mass involving the external auditory canal. In patients receiving aerosolized pentamidine for prophylaxis against PCP, one may see a variety of extrapulmonary manifestations of *P. jiroveci*. These include ophthalmic lesions of the choroid, a necrotizing vasculitis that resembles Burger's disease, bone marrow hypoplasia, and intestinal obstruction. Other organs that have been involved include lymph nodes, spleen, liver, kidney, pancreas, pericardium, heart, thyroid, and adrenals. Organ infection may be associated with cystic lesions that may appear calcified on CT or ultrasound.

The standard treatment for PCP or disseminated pneumocystosis is trimethoprim/sulfamethoxazole (TMP/SMX). A high (20–85%) incidence of side effects, particularly skin rash and bone marrow suppression, is seen with TMP/SMX in patients with HIV infection. Alternative treatments for mild to moderate PCP include dapsone/trimethoprim, clindamycin/primaquine, and atovaquone. IV pentamidine is the treatment of choice for severe disease in the patient unable to tolerate TMP/SMX. For patients with a Pa_{O2} <70 mmHg or with an a–A gradient >35 mmHg, adjunct glucocorticoid therapy should be used in addition to specific antimicrobials. Overall, treatment should be continued for 21 days and followed by secondary prophylaxis. Prophylaxis for PCP is indicated for any HIV-infected individual who has experienced a prior bout of PCP, any patient with a CD4+ T cell count of <200/μL or a CD4 percentage <15, any patient with unexplained fever for >2 weeks, and any patient with a history of oropharyngeal candidiasis. The preferred regimen for prophylaxis is TMP/SMX, one double-strength tablet daily. This regimen also provides protection against toxoplasmosis and some bacterial respiratory pathogens. For patients who cannot tolerate TMP/SMX, alternatives for prophylaxis include dapsone plus pyrimethamine plus leucovorin, aerosolized pentamidine administered by the Respirgard II nebulizer, and atovaquone. Primary or secondary prophylaxis for PCP can be discontinued in those patients treated with cART who maintain good suppression of HIV (<50 copies per milliliter) and CD4+ T cell counts >200/μL for 3–6 months.

M. tuberculosis, once thought to be on its way to extinction in the United States, experienced a resurgence associated with the HIV epidemic (Chap. 70). Worldwide, approximately one-third of all AIDS-related deaths are associated with TB, and TB is the primary cause of death for 10–15% of patients with HIV infection. In the United States ~5% of AIDS patients have active TB. Patients with HIV infection are more likely to have active TB by a factor of 100 when compared with an HIV-negative population. For an asymptomatic HIV-negative person with a positive purified protein derivative (PPD) skin test, the risk of reactivation TB is around 1% per year. For the patient with untreated HIV infection, a positive PPD skin test, and no signs or symptoms of TB, the rate of reactivation TB is 7–10% per year. Untreated TB can accelerate the course of HIV infection. Levels of plasma HIV RNA increase in the setting of active TB and decline in the setting of successful TB treatment. Active TB is most common in patients 25–44 years of age, in African Americans and Hispanics, in patients in New York City and Miami, and in patients in developing countries. In these demographic groups, 20–70% of the new cases of active TB are in patients with HIV infection. The epidemic of TB embedded in the epidemic of HIV infection probably represents the greatest health risk to the general public and the health care profession associated with the HIV epidemic. In contrast to infection with atypical mycobacteria such as MAC, active TB often develops relatively early in the course of HIV infection and may be an early clinical sign of HIV disease. In one study, the median CD4+ T cell count at presentation of TB was 326/μL. The clinical manifestations of TB in HIV-infected patients are quite varied and generally show different patterns as a function of the CD4+ T cell count. In patients with relatively high CD4+ T cell counts, the typical pattern of pulmonary reactivation occurs: patients present with fever, cough, dyspnea on exertion, weight loss, night sweats, and a chest x-ray revealing cavitary apical disease of the upper lobes. In patients with lower CD4+ T cell counts, disseminated disease is more common. In these patients the chest x-ray may reveal diffuse or lower lobe bilateral reticulonodular infiltrates consistent with miliary spread, pleural effusions, and hilar and/or mediastinal adenopathy. Infection may be present in bone, brain, meninges, GI tract, lymph nodes (particularly cervical lymph nodes), and viscera. Some patients with advanced HIV infection and active TB may have no symptoms of illness, and thus screening for TB should be part of the initial evaluation of every patient with HIV infection. Approximately 60–80% of HIV-infected patients with TB have pulmonary disease, and 30–40% have extrapulmonary disease. Respiratory isolation and a negative-pressure room should be used for patients in whom a diagnosis of pulmonary TB is being considered. This approach is critical to limit nosocomial and community spread of infection. Culture of the organism from an involved site provides a definitive diagnosis. Blood cultures are positive in 15% of patients. This figure is higher in patients with lower CD4+ T cell counts. In the setting of fulminant disease one cannot rely on the accuracy of a negative PPD skin test to rule out a diagnosis of TB. TB is one of the conditions associated with HIV infection for which cure is possible with appropriate therapy. Therapy for TB is

generally the same in the HIV-infected patient as in the HIV-negative patient (Chap. 70). Due to the possibility of multidrug-resistant or extensively drug-resistant TB, drug susceptibility testing should be performed to guide therapy. Due to pharmacokinetic interactions, adjusted doses of rifabutin should be substituted for rifampin in patients receiving the HIV protease inhibitors or nonnucleoside reverse transcriptase inhibitors. Treatment is most effective in programs that involve directly observed therapy. Initiation of cART and/or anti-TB therapy may be associated with clinical deterioration due to immune reconstitution inflammatory syndrome (IRIS) reactions. These are most common in patients initiating both treatments at the same time, may occur as early as 1 week after initiation of therapy, and are seen more frequently in patients with advanced HIV disease. For these reasons it is often recommended that initiation of cART be delayed in antiretroviral-naïve patients until 2–8 weeks following the initiation of treatment for TB. Effective prevention of active TB can be a reality if the health care professional is aggressive in looking for evidence of latent or active TB by making sure that all patients with HIV infection receive a PPD skin test or evaluation with an IFN-γ release assay. Anergy testing is not of value in this setting. Since these tests rely on the host mounting an immune response to *M. tuberculosis*, patients with CD4+ T cell counts <200 cells/μL should be retested if their CD4+ T cell counts rise to persistently above 200. Patients at risk of continued exposure to TB should be tested annually. HIV-infected individuals with a skin-test reaction of >5 mm, those with a positive IFN-γ release assay, or those who are close household contacts of persons with active TB should receive treatment with 9 months of isoniazid and pyridoxine.

Atypical mycobacterial infections are also seen with an increased frequency in patients with HIV infection. Infections with at least 12 different mycobacteria have been reported, including *M. bovis* and representatives of all four Runyon groups. The most common atypical mycobacterial infection is with *M. avium* or *M. intracellulare* species—the *Mycobacterium avium* complex (MAC). Infections with MAC are seen mainly in patients in the United States and are rare in Africa. It has been suggested that prior infection with *M. tuberculosis* decreases the risk of MAC infection. MAC infections probably arise from organisms that are ubiquitous in the environment, including both soil and water. There is little evidence for person-to-person transmission of MAC infection. The presumed portals of entry are the respiratory and GI tracts. MAC infection is a late complication of HIV infection, occurring predominantly in patients with CD4+ T cell counts of <50/μL. The average CD4+ T cell count at the time of diagnosis is 10/μL. The most common presentation is disseminated disease with fever, weight loss, and night sweats. At least 85% of patients with MAC infection are mycobacteremic, and large numbers of organisms can often be demonstrated on bone marrow biopsy. The chest x-ray is abnormal in ~25% of patients, with the most common pattern being that of a bilateral, lower lobe infiltrate suggestive of miliary spread. Alveolar or nodular infiltrates and hilar and/or mediastinal adenopathy can also occur. Other clinical findings include endobronchial lesions, abdominal pain, diarrhea, and lymphadenopathy. Anemia and elevated liver alkaline phosphatase are common. The diagnosis is made by the culture of blood or involved tissue. The finding of two consecutive sputum samples positive for MAC is highly suggestive of pulmonary infection. Cultures may take 2 weeks to turn positive. Therapy consists of a macrolide, usually clarithromycin, with ethambutol. Some physicians elect to add a third drug from among rifabutin, ciprofloxacin, or amikacin in patients with extensive disease. Therapy was generally for life; however, with the use of cART it is possible to discontinue therapy in patients with sustained suppression of HIV replication and CD4+ T cell counts >100/μL for 3–6 months. Primary prophylaxis for MAC is indicated in patients with HIV infection and CD4+ T cell counts <50/μL (Table 93-10). This may be discontinued in patients in whom cART induces a sustained suppression of viral replication and increases in CD4+ T cell counts to >100/μL for ≥3 months.

Rhodococcus equi is a gram-positive, pleomorphic, acid-fast, non-spore-forming bacillus that can cause pulmonary and/or disseminated infection in patients with advanced HIV infection. Fever and cough are the most common presenting signs. Radiographically one may see cavitary lesions and consolidation. Blood cultures are often positive. Treatment is based on antimicrobial sensitivity testing.

Fungal infections of the lung, in addition to PCP, can be seen in patients with AIDS. Patients with pulmonary cryptococcal disease present with fever, cough, dyspnea, and, in some cases, hemoptysis. A focal or diffuse interstitial infiltrate is seen on chest x-ray in >90% of patients. In addition, one may see lobar disease, cavitary disease, pleural effusions, and hilar or mediastinal adenopathy. More than half of patients are fungemic, and 90% of patients have concomitant CNS infection. *Coccidioides immitis* is a mold that is endemic in the southwest United States. It can cause a reactivation pulmonary syndrome in patients with HIV infection. Most patients with this condition will have CD4+ T cell counts <250/μL. Patients present with fever, weight loss, cough, and extensive, diffuse reticulonodular infiltrates on chest x-ray. One may also see nodules, cavities, pleural effusions, and hilar adenopathy. While serologic testing is of value in the immunocompetent host, serologies are negative in 25% of HIV-infected patients with coccidioidal infection. Invasive aspergillosis is not an AIDS-defining illness and is generally not seen in patients with AIDS in the absence of neutropenia or administration of glucocorticoids. When it does occur, *Aspergillus* infection may have an unusual presentation in the respiratory tract of patients with AIDS, where it gives the appearance of a pseudomembranous tracheobronchitis. Primary pulmonary infection of the lung

may be seen with *histoplasmosis*. The most common pulmonary manifestation of histoplasmosis, however, is in the setting of disseminated disease, presumably due to reactivation. In this setting respiratory symptoms are usually minimal, with cough and dyspnea occurring in 10–30% of patients. The chest x-ray is abnormal in ~50% of patients, showing either a diffuse interstitial infiltrate or diffuse small nodules.

Two forms of *idiopathic interstitial pneumonia* have been identified in patients with HIV infection: lymphoid interstitial pneumonitis (LIP) and nonspecific interstitial pneumonitis (NIP). LIP, a common finding in children, is seen in about 1% of adult patients with untreated HIV infection. This disorder is characterized by a benign infiltrate of the lung and is thought to be part of the polyclonal activation of lymphocytes seen in the context of HIV and EBV infections. Transbronchial biopsy is diagnostic in 50% of the cases, with an open-lung biopsy required for diagnosis in the remainder of cases. This condition is generally self-limited and no specific treatment is necessary. Severe cases have been managed with brief courses of glucocorticoids. Although rarely a clinical problem since the use of cART, evidence of NIP may be seen in up to half of all patients with untreated HIV infection. Histologically, interstitial infiltrates of lymphocytes and plasma cells in a perivascular and peribronchial distribution are present. When symptomatic, patients present with fever and nonproductive cough occasionally accompanied by mild chest discomfort. Chest x-ray is usually normal or may reveal a faint interstitial pattern. Similar to LIP, NIP is a self-limited process for which no therapy is indicated other than appropriate management of the underlying HIV infection. HIV-related pulmonary arterial hypertension (HIV-PAH) is seen in ~0.5% of HIV-infected individuals. Patients may present with an array of symptoms including shortness of breath, fatigue, syncope, chest pain, and signs of right-sided heart failure. Chest x-ray reveals dilated pulmonary vessels and right-sided cardiomegaly with right ventricular hypertrophy seen on electrocardiogram. cART does not appear to be of clear benefit, and the prognosis is quite poor with a median survival in the range of 2 years.

Neoplastic diseases of the lung including KS and lymphoma are discussed later in the section on neoplastic diseases.

Diseases of the cardiovascular system

Heart disease is a relatively common postmortem finding in HIV-infected patients (25–75% in autopsy series). The most common form of heart disease is coronary heart disease. In one large series the overall rate of myocardial infarction (MI) was 3.5/1000 patient-years, 28% of these events were fatal, and MI was responsible for 7% of all deaths in the cohort. In patients with HIV infection, cardiovascular disease may be associated with classic risk factors such as smoking, a direct consequence of HIV infection, or a complication of cART. Patients with HIV infection have higher levels of triglycerides, lower levels of high-density lipoprotein cholesterol, and a higher prevalence of smoking than cohorts of individuals without HIV infection. The finding that the rate of cardiovascular disease events was lower in patients on antiretroviral therapy than in those randomized to undergo a treatment interruption identified a clear association between HIV replication and risk of cardiovascular disease. In one study, a baseline CD4+ T cell count of <500/μL was found to be an independent risk factor for cardiovascular disease comparable in magnitude to that attributable to smoking. While the precise pathogenesis of this association remains unclear, it is likely related to the immune activation and increased propensity for coagulation seen as a consequence of HIV replication. Exposure to HIV protease inhibitors and certain reverse transcriptase inhibitors has been associated with increases in total cholesterol and/or risk of MI. Any increases in the risk of death from MI resulting from the use of certain antiretrovirals must be balanced against the marked increases in overall survival brought about by these drugs.

Another form of heart disease associated with HIV infection is a dilated cardiomyopathy associated with congestive heart failure (CHF) referred to as *HIV-associated cardiomyopathy*. This generally occurs as a late complication of HIV infection and, histologically, displays elements of myocarditis. For this reason some have advocated treatment with IV immunoglobulin (IVIg). HIV can be directly demonstrated in cardiac tissue in this setting, and there is debate over whether it plays a direct role in this condition. Patients present with typical findings of CHF including edema and shortness of breath. Patients with HIV infection may also develop cardiomyopathy as side effects of IFN-α or nucleoside analogue therapy. These are reversible once therapy is stopped. KS, cryptococcosis, Chagas' disease, and toxoplasmosis can involve the myocardium, leading to cardiomyopathy. In one series, most patients with HIV infection and a treatable myocarditis were found to have myocarditis associated with toxoplasmosis. Most of these patients also had evidence of CNS toxoplasmosis. Thus, MRI or double-dose contrast CT scan of the brain should be included in the workup of any patient with advanced HIV infection and cardiomyopathy.

A variety of other cardiovascular problems are found in patients with HIV infection. Pericardial effusions may be seen in the setting of advanced HIV infection. Predisposing factors include TB, CHF, mycobacterial infection, cryptococcal infection, pulmonary infection, lymphoma, and KS. While pericarditis is quite rare, in one series 5% of patients with HIV disease had pericardial effusions that were considered to be moderate or severe. Tamponade and death have occurred in association with pericardial KS, presumably owing to acute hemorrhage. Nonbacterial thrombotic endocarditis has been reported and should be considered in patients with unexplained embolic phenomena. Intravenous pentamidine,

when given rapidly, can result in hypotension as a consequence of cardiovascular collapse.

Diseases of the oropharynx and gastrointestinal system

Oropharyngeal and GI diseases are common features of HIV infection. They are most frequently due to secondary infections. In addition, oral and GI lesions may occur with KS and lymphoma.

Oral lesions, including *thrush*, *hairy leukoplakia*, and *aphthous ulcers* **(Fig. 93-35)**, are particularly common in patients with untreated HIV infection. Thrush, due to *Candida* infection, and oral hairy leukoplakia, presumed due to EBV, are usually indicative of fairly advanced immunologic decline; they generally occur in patients with CD4+ T cell counts of <300/μL. In one study, 59% of patients with oral candidiasis went on to develop AIDS in the next year. Thrush appears as a white, cheesy exudate, often on an erythematous mucosa in the posterior oropharynx. While most commonly seen on the soft palate, early lesions are often found along the gingival border. The diagnosis is made by direct examination of a scraping for pseudohyphal elements. Culturing is of no diagnostic value, as patients with HIV infection may have a positive throat culture for *Candida* in the absence of thrush. Oral hairy leukoplakia presents as white, frondlike lesions, generally along the lateral borders of the tongue and sometimes on the adjacent buccal mucosa (Fig. 93-35). Despite its name, oral hairy leukoplakia is not considered a premalignant condition. Lesions are associated with florid

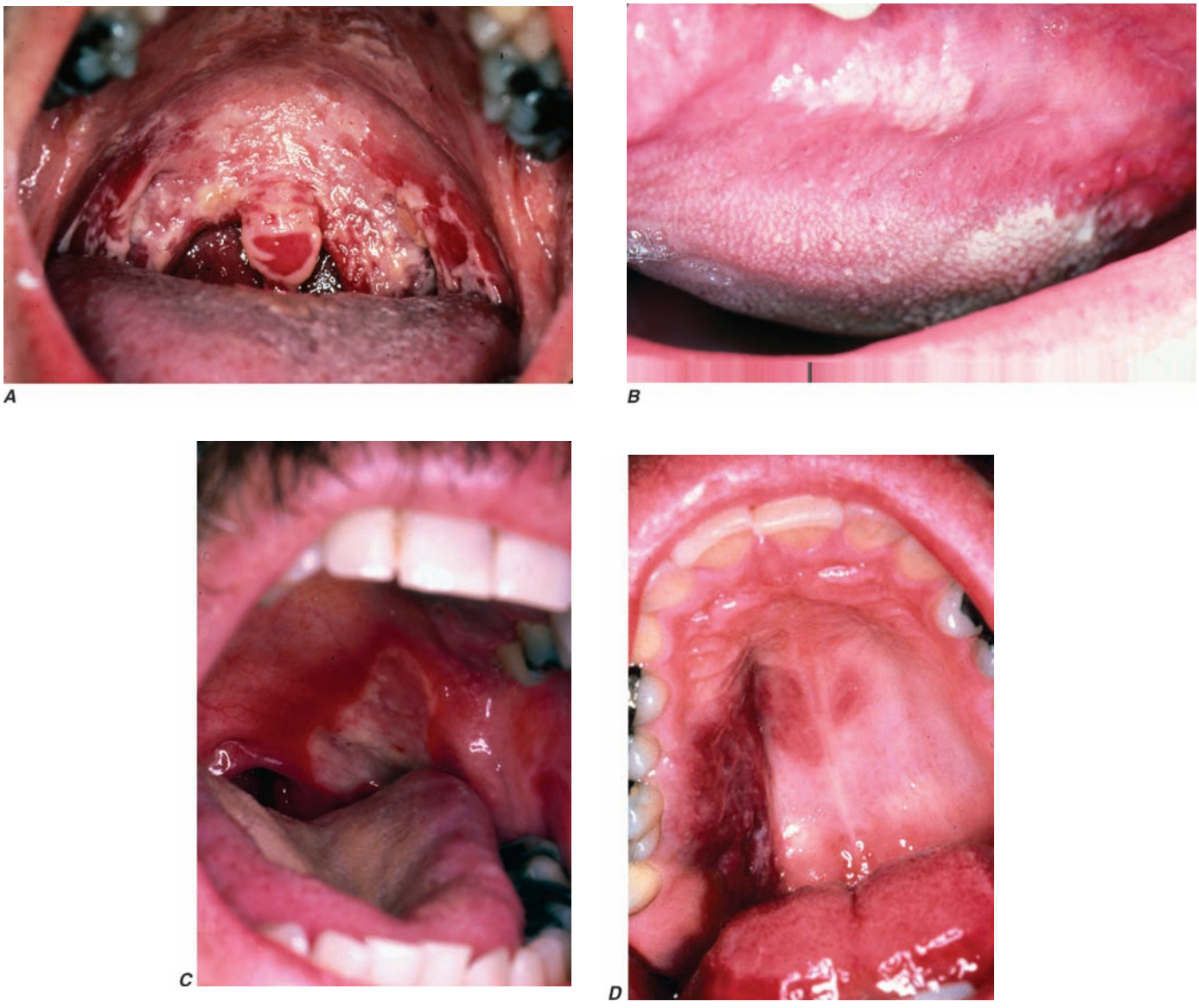


FIGURE 93-35
Various oral lesions in HIV-infected individuals. *A.* Thrush. ***B.*** Hairy leukoplakia. ***C.*** Aphthous ulcer. ***D.*** Kaposi's sarcoma.

replication of EBV. While usually more disconcerting as a sign of HIV-associated immunodeficiency than a clinical problem in need of treatment, severe cases have been reported to respond to topical podophyllin or systemic therapy with anti-herpesvirus agents. Aphthous ulcers of the posterior oropharynx are also seen with regularity in patients with HIV infection (Fig. 93-35). These lesions are of unknown etiology and can be quite painful and interfere with swallowing. Topical anesthetics provide immediate symptomatic relief of short duration. The fact that thalidomide is an effective treatment for this condition suggests that the pathogenesis may involve the action of tissue-destructive cytokines. Palatal, glossal, or gingival ulcers may also result from cryptococcal disease or histoplasmosis.

Esophagitis **(Fig. 93-36)** may present with odynophagia and retrosternal pain. Upper endoscopy is generally required to make an accurate diagnosis. Esophagitis may be due to *Candida*, CMV, or HSV. While CMV tends to be associated with a single large ulcer, HSV infection is more often associated with multiple small ulcers. The esophagus may also be the site of KS and lymphoma. Like the oral mucosa, the esophageal mucosa may have large, painful ulcers of unclear etiology that may respond to thalidomide. While achlorhydria is a common problem in patients with HIV infection, other gastric problems are generally rare. Among the neoplastic conditions involving the stomach are KS and lymphoma.

Infections of the small and large intestine leading to diarrhea, abdominal pain, and occasionally fever are among the most significant GI problems in HIV-infected patients. They include infections with bacteria, protozoa, and viruses.

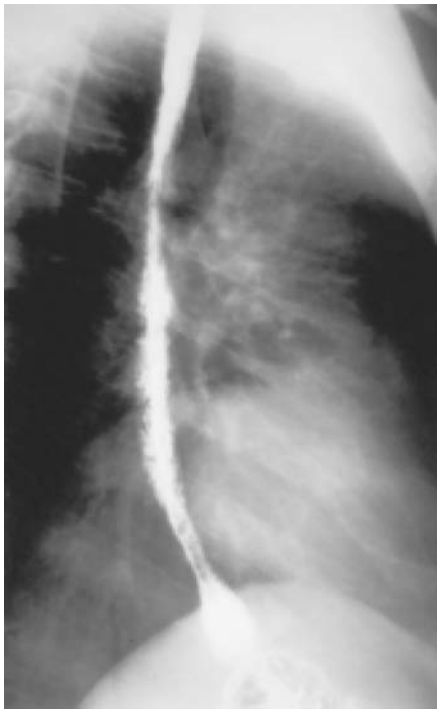


FIGURE 93-36
Barium swallow of a patient with *Candida* esophagitis. The flow of barium along the mucosal surface is grossly irregular.

Bacteria may be responsible for secondary infections of the GI tract. Infections with enteric pathogens such as *Salmonella*, *Shigella*, and *Campylobacter* are more common in homosexual men and are often more severe and more apt to relapse in patients with HIV infection. Patients with untreated HIV have approximately a 20-fold increased risk of infection with *S. typhimurium*. They may present with a variety of nonspecific symptoms including fever, anorexia, fatigue, and malaise of several weeks' duration. Diarrhea is common but may be absent. Diagnosis is made by culture of blood and stool. Long-term therapy with ciprofloxacin is the recommended treatment. HIV-infected patients also have an increased incidence of *S. typhi* infection in areas of the world where typhoid is a problem. *Shigella* spp., particularly *S. flexneri*, can cause severe intestinal disease in HIV-infected individuals. Up to 50% of patients will develop bacteremia. *Campylobacter* infections occur with an increased frequency in patients with HIV infection. While *C. jejuni* is the strain most frequently isolated, infections with many other strains have been reported. Patients usually present with crampy abdominal pain, fever, and bloody diarrhea. Infection may also present as proctitis. Stool examination reveals the presence of fecal leukocytes. Systemic infection can occur, with up to 10% of infected patients exhibiting bacteremia. Most strains are sensitive to erythromycin. Abdominal pain and diarrhea may be seen with MAC infection.

Fungal infections may also be a cause of diarrhea in patients with HIV infection. Histoplasmosis, coccidioidomycosis, and penicilliosis have all been identified as a cause of fever and diarrhea in patients with HIV infection. Peritonitis has been seen with *C. immitis*.

Cryptosporidia, microsporidia, and *Isospora belli* (Chap. 125) are the most common opportunistic protozoa that infect the GI tract and cause diarrhea in HIV-infected patients. Cryptosporidial infection may present in a variety of ways, ranging from a self-limited or intermittent diarrheal illness in patients in the early stages of HIV infection to a severe, life-threatening diarrhea in severely immunodeficient individuals. In patients with untreated HIV infection and CD4+ T cell counts of <300/μL, the incidence of cryptosporidiosis is ~1% per year. In 75% of cases the diarrhea is accompanied by crampy abdominal pain, and 25% of patients have nausea and/or vomiting. Cryptosporidia may also cause biliary tract disease in the HIV-infected patient, leading to cholecystitis with or without accompanying cholangitis and pancreatitis secondary to papillary stenosis. The diagnosis of cryptosporidial diarrhea is made by stool examination or biopsy of the small intestine. The diarrhea is noninflammatory, and the characteristic finding is the presence of oocysts that stain with acid-fast dyes. Therapy is predominantly supportive, and marked improvements have been reported in the setting of effective cART. Treatment with up to 2000 mg/d of nitazoxanide (NTZ) is associated with improvement in symptoms or a decrease in shedding of organisms in about half

of patients. Its overall role in the management of this condition remains unclear. Patients can minimize their risk of developing cryptosporidiosis by avoiding contact with human and animal feces, by not drinking untreated water from lakes or rivers, and by not eating raw shellfish.

Microsporidia are small, unicellular, obligate intracellular parasites that reside in the cytoplasm of enteric cells (Chap. 125). The main species causing disease in humans is *Enterocytozoon bieneusi*. The clinical manifestations are similar to those described for cryptosporidia and include abdominal pain, malabsorption, diarrhea, and cholangitis. The small size of the organism may make it difficult to detect; however, with the use of chromotrope-based stains, organisms can be identified in stool samples by light microscopy. Definitive diagnosis generally depends on electron-microscopic examination of a stool specimen, intestinal aspirate, or intestinal biopsy specimen. In contrast to cryptosporidia, microsporidia have been noted in a variety of extraintestinal locations, including the eye, brain, sinuses, muscle, and liver, and they have been associated with conjunctivitis and hepatitis. The most effective way to deal with microsporia in a patient with HIV infection is to restore the immune system by treating the HIV infection with cART. Albendazole, 400 mg bid, has been reported to be of benefit in some patients.

I. belli is a coccidian parasite (Chap. 125) most commonly found as a cause of diarrhea in patients from tropical and subtropical regions. Its cysts appear in the stool as large, acid-fast structures that can be differentiated from those of cryptosporidia on the basis of size, shape, and number of sporocysts. The clinical syndromes of *Isospora* infection are identical to those caused by cryptosporidia. The important distinction is that infection with *Isospora* is generally relatively easy to treat with TMP/SMX. While relapses are common, a thrice-weekly regimen of TMP/SMX appears adequate to prevent recurrence.

CMV colitis was once seen as a consequence of advanced immunodeficiency in 5–10% of patients with AIDS. It is much less common with the advent of cART. CMV colitis presents as diarrhea, abdominal pain, weight loss, and anorexia. The diarrhea is usually nonbloody, and the diagnosis is achieved through endoscopy and biopsy. Multiple mucosal ulcerations are seen at endoscopy, and biopsies reveal characteristic intranuclear and cytoplasmic inclusion bodies. Secondary bacteremias may result as a consequence of thinning of the bowel wall. Treatment is with either ganciclovir or foscarnet for 3–6 weeks. Relapses are common, and maintenance therapy is typically necessary in patients whose HIV infection is poorly controlled. Patients with CMV disease of the GI tract should be carefully monitored for evidence of CMV retinitis.

In addition to disease caused by specific secondary infections, patients with HIV infection may also experience a chronic diarrheal syndrome for which no etiologic agent other than HIV can be identified. This entity is referred to as *AIDS enteropathy* or *HIV enteropathy*. It is most likely a direct result of HIV infection in the GI tract. Histologic examination of the small bowel in these patients reveals low-grade mucosal atrophy with a decrease in mitotic figures, suggesting a hyporegenerative state. Patients often have decreased or absent small-bowel lactase and malabsorption with accompanying weight loss.

The initial evaluation of a patient with HIV infection and diarrhea should include a set of stool examinations, including culture, examination for ova and parasites, and examination for *Clostridium difficile* toxin. Approximately 50% of the time this workup will demonstrate infection with pathogenic bacteria, mycobacteria, or protozoa. If the initial stool examinations are negative, additional evaluation, including upper and/or lower endoscopy with biopsy, will yield a diagnosis of microsporidial or mycobacterial infection of the small intestine ~30% of the time. In patients for whom this diagnostic evaluation is nonrevealing, a presumptive diagnosis of HIV enteropathy can be made if the diarrhea has persisted for >1 month. An algorithm for the evaluation of diarrhea in patients with HIV infection is given in **Fig. 93-37**.

Rectal lesions are common in HIV-infected patients, particularly the perirectal ulcers and erosions due to the reactivation of HSV **(Fig. 93-38)**. These lesions may appear quite atypical, as denuded skin without vesicles, and they respond well to treatment with acyclovir, famciclovir, or foscarnet. Other rectal lesions encountered in patients with HIV infection include condylomata acuminata, KS, and intraepithelial neoplasia (see later).

Hepatobiliary diseases

Diseases of the hepatobiliary system are a major problem in patients with HIV infection. It has been

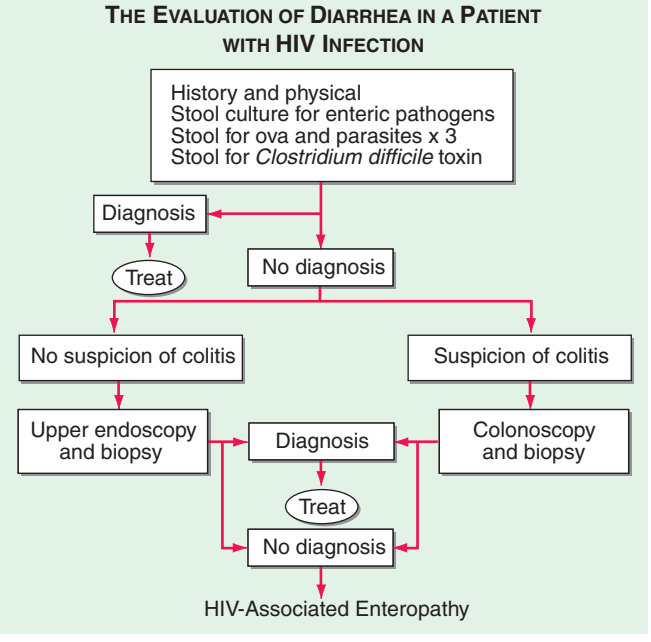


FIGURE 93-37
Algorithm for the evaluation of diarrhea in a patient with HIV infection. HIV-associated enteropathy is a diagnosis of exclusion and can be made only after other, generally treatable forms of diarrheal illness have been ruled out.

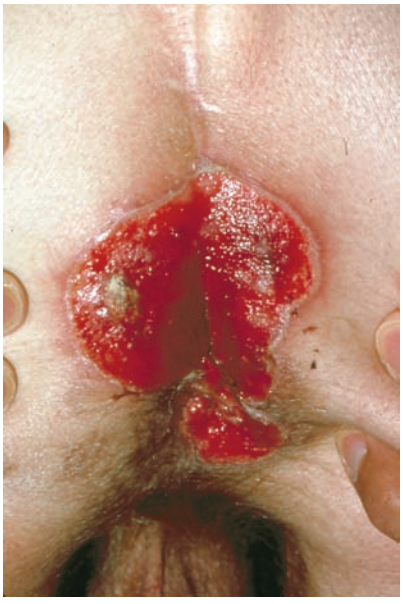


FIGURE 93-38
Severe, erosive perirectal herpes simplex in a patient with AIDS.

estimated that approximately one-third of the deaths of patients with HIV infection are in some way related to liver disease. While this is predominantly a reflection of the problems encountered in the setting of co-infection with hepatitis B or C, it is also a reflection of the hepatic injury, ranging from hepatic steatosis to hypersensitivity reactions to immune reconstitution, that can be seen in the context of cART.

The prevalence of co-infection with HIV and hepatitis viruses varies by geographic region. In the United States, ~90% of HIV-infected individuals have evidence of infection with HBV; 6–14% have chronic HBV infection; 5–50% of current or past patients are co-infected with HCV; and co-infection with hepatitis D, E, and/or G viruses is common. Among IV drug users with HIV infection, rates of HCV infection range from 70 to 95%. HIV infection has a significant impact on the course of hepatitis virus infection. It is associated with approximately a threefold increase in the development of persistent hepatitis B surface antigenemia. Patients infected with both HBV and HIV have decreased evidence of inflammatory liver disease. The presumption that this is due to the immunosuppressive effects of HIV infection is supported by the observations that this situation can be reversed, and one may see the development of more severe hepatitis following the initiation of effective cART. In studies of the impact of HIV on HBV infection, four- to tenfold increases in liver-related mortality rates have been noted in patients with HIV and active HBV infection compared to rates in patients with either infection alone. There is, however, only a slight increase in overall mortality rate in HIV-infected individuals who are also hepatitis B surface antigen (HBsAg)–positive. IFN-α is less successful as a treatment of HBV in patients with HIV co-infection. Lamivudine, emtricitabine, adefovir/tenofovir/entecavir, and telbivudine alone or in combination are useful in the treatment of hepatitis B in patients with HIV infection. It is important to remember that all the drugs mentioned earlier also have activity against HIV and should not be used alone in patients with HIV infection in order to avoid the emergence of quasispecies of HIV resistant to these drugs. For this reason, the need to treat hepatitis B infection in a patient with HIV infection is an indication to treat HIV infection in that same patient, regardless of CD4+ T cell count. HCV infection is more severe in the patient with HIV infection; it does not appear to affect overall mortality rate in HIV-infected individuals when other variables such as age, baseline CD4+ T cell count, and use of cART are taken into account. In the setting of HIV and HCV co-infection, levels of HCV are approximately tenfold higher than in the HIV-negative patient with HCV infection and there is a tenfold increased risk of death due to liver disease in co-infected patients. Treatment for HCV infection consists of pegylated IFN-α and ribavirin with an array of experimental therapies currently in clinical trials. If a 2-log drop in levels of HCV RNA is not seen within 12 weeks, it is unlikely that therapy will be of value. Hepatitis A virus infection is not seen with an increased frequency in patients with HIV infection. It is recommended that all patients with HIV infection who have not experienced natural infection be immunized with hepatitis A and/or hepatitis B vaccines. Infection with hepatitis G virus, also known as GB virus C, is seen in ~50% of patients with HIV infection. For reasons that are currently unclear, there are data to suggest that patients with HIV infection co-infected with this virus have a decreased rate of progression to AIDS.

A variety of other infections may also involve the liver. Granulomatous hepatitis may be seen as a consequence of mycobacterial or fungal infections, particularly MAC infection. Hepatic masses may be seen in the context of TB, peliosis hepatis, or fungal infection. Among the fungal opportunistic infections, *C. immitis* and *Histoplasma capsulatum* are those most likely to involve the liver. Biliary tract disease in the form of papillary stenosis or sclerosing cholangitis has been reported in the context of cryptosporidiosis, CMV infection, and KS.

Many of the drugs used to treat HIV infection are metabolized by the liver and can cause liver injury. Fatal hepatic reactions have been reported with a wide array of antiretrovirals, including nucleoside analogues, nonnucleoside analogues, and protease inhibitors. Nucleoside analogues work by inhibiting DNA synthesis. This can result in toxicity to mitochondria, which can lead to disturbances in oxidative metabolism. This may manifest as hepatic steatosis and, in severe cases, lactic acidosis and fulminant liver failure. It is important to be aware of this condition and to watch for it in patients with HIV infection receiving nucleoside analogues. It is reversible if diagnosed early and the offending agent(s) discontinued. Nevirapine has been associated with sometimes fatal fulminant and cholestatic hepatitis, hepatic

necrosis, and hepatic failure. Indinavir may cause mild to moderate elevations in serum bilirubin in 10–15% of patients in a syndrome similar to Gilbert's syndrome. A similar pattern of hepatic injury may be seen with atazanavir. In the patient receiving cART with an unexplained increase in hepatic transaminases, strong consideration should be given to drug toxicity. *Pancreatic injury* is most commonly a consequence of drug toxicity, notably that secondary to pentamidine or dideoxynucleosides. While up to half of patients in some series have biochemical evidence of pancreatic injury, <5% of patients show any clinical evidence of pancreatitis that is not linked to a drug toxicity.

Diseases of the kidney and genitourinary tract

Diseases of the kidney or genitourinary tract may be a direct consequence of HIV infection, due to an opportunistic infection or neoplasm, or related to drug toxicity. Overall, microalbuminuria is seen in ~20% of untreated HIV-infected patients; significant proteinuria is seen in closer to 2%. The presence of microalbuminuria has been associated with an increase in all-cause mortality rate. *HIV-associated nephropathy* (HIVAN) was first described in IDUs and was initially thought to be IDU nephropathy in patients with HIV infection; it is now recognized as a true direct complication of HIV infection. Although the majority of patients have CD4+ T cell counts <200/μL, HIV-associated nephropathy can be an early manifestation of HIV infection and is also seen in children. Over 90% of reported cases have been in African-American or Hispanic individuals; the disease is not only more prevalent in these populations but also more severe and is the third leading cause of end-stage renal failure among African Americans age 20–64 in the United States. Proteinuria is the hallmark of this disorder. Edema and hypertension are rare. Ultrasound examination reveals enlarged, hyperechogenic kidneys. A definitive diagnosis is obtained through renal biopsy. Histologically, focal segmental glomerulosclerosis is present in 80%, and mesangial proliferation in 10–15% of cases. Prior to effective antiretroviral therapy, this disease was characterized by relatively rapid progression to end-stage renal disease. Patients with HIV-associated nephropathy should be treated for their HIV infection regardless of CD4+ T cell count. Treatment with angiotensin-converting enzyme (ACE) inhibitors and/or prednisone, 60 mg/d, has also been reported to be of benefit in some cases. The incidence of this disease in patients receiving adequate cART has not been well defined; however, the impression is that it has decreased in frequency and severity. It is the leading cause of end-stage renal disease in patients with HIV infection.

Among the drugs commonly associated with renal damage in patients with HIV disease are pentamidine, amphotericin, adefovir, cidofovir, tenofovir, and foscarnet. TMP/SMX may compete for tubular secretion with creatinine and cause an increase in the serum creatinine level. Sulfadiazine may crystallize in the kidney and result in an easily reversible form of renal shutdown, while indinavir may form renal calculi. Adequate hydration is the mainstay of treatment and prevention for these latter two conditions.

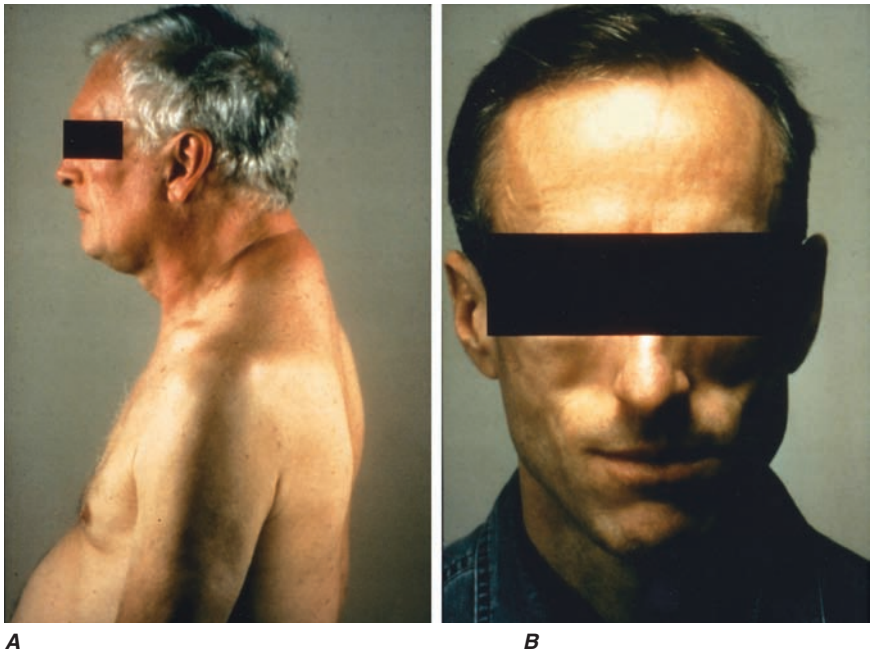
Genitourinary tract infections are seen with a high frequency in patients with HIV infection; they present with skin lesions, dysuria, hematuria, and/or pyuria and are managed in the same fashion as in patients without HIV infection. Infections with HSV are covered later ("Dermatologic Diseases"). Infections with *T. pallidum*, the etiologic agent of *syphilis*, play an important role in the HIV epidemic. In HIV-negative individuals, genital syphilitic ulcers as well as the ulcers of chancroid are major predisposing factors for heterosexual transmission of HIV infection. While most HIV-infected individuals with syphilis have a typical presentation, a variety of formerly rare clinical problems may be encountered in the setting of dual infection. Among them are *lues maligna*, an ulcerating lesion of the skin due to a necrotizing vasculitis; unexplained fever; nephrotic syndrome; and neurosyphilis. The most common presentation of syphilis in the HIV-infected patient is that of *condylomata lata*, a form of secondary syphilis. Neurosyphilis may be asymptomatic or may present as acute meningitis, neuroretinitis, deafness, or stroke. The rate of neurosyphilis may be as high as 1% in patients with HIV infection, and one should consider a lumbar puncture to look for neurosyphilis in all patients with HIV infection and secondary syphilis. As a consequence of the immunologic abnormalities seen in the setting of HIV infection, diagnosis of syphilis through standard serologic testing may be challenging. On the one hand, a significant number of patients have false-positive Venereal Disease Research Laboratory (VDRL) tests due to polyclonal B cell activation. On the other hand, the development of a new positive VDRL may be delayed in patients with new infections, and the anti–fluorescent treponemal antibody (anti-FTA) test may be negative due to immunodeficiency. Thus, dark-field examination of appropriate specimens should be performed in any patient in whom syphilis is suspected, even if the patient has a negative VDRL. Similarly, any patient with a positive serum VDRL test, neurologic findings, and an abnormal spinal fluid examination should be considered to have neurosyphilis and treated accordingly, regardless of the CSF VDRL result. In any setting, patients treated for syphilis need to be carefully monitored to ensure adequate therapy. Approximately one-third of patients with HIV infection will experience a Jarisch-Herxheimer reaction upon initiation of therapy for syphilis.

Vulvovaginal candidiasis is a common problem in women with HIV infection. Symptoms include pruritus, discomfort, dyspareunia, and dysuria. Vulvar infection may present as a morbilliform rash that may extend to the thighs. Vaginal infection is usually associated with a white discharge, and plaques may be seen along an erythematous vaginal wall. Diagnosis is made by microscopic examination of the discharge for pseudohyphal elements in a 10% potassium hydroxide solution. Mild disease can be treated with topical therapy.

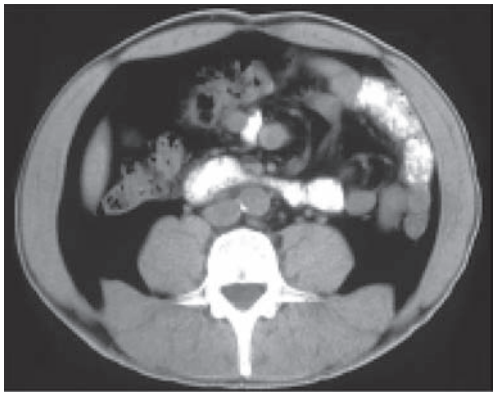
More serious disease can be treated with fluconazole. Other causes of vaginitis include *Trichomonas* and mixed bacteria.

Diseases of the endocrine system and metabolic disorders

A variety of endocrine and metabolic disorders are seen in the context of HIV infection. These may be a direct consequence of HIV infection, secondary to opportunistic infections or neoplasms, or related to medication side effects. Between 33% and 75% of patients with HIV infection receiving cART develop a syndrome often referred to as *lipodystrophy*, consisting of elevations in plasma triglycerides, total cholesterol, and apolipoprotein B as well as hyperinsulinemia and hyperglycemia. Many of the patients have been noted to have a characteristic set of body habitus changes associated with fat redistribution, consisting of truncal obesity coupled with peripheral wasting **(Fig. 93-39)**. Truncal obesity is apparent as an increase in abdominal girth related to increases in mesenteric fat, a dorsocervical fat pad ("buffalo hump") reminiscent of patients with Cushing's syndrome, and enlargement of the breasts. The peripheral wasting, or lipoatrophy, is particularly noticeable in the face and buttocks and by the prominence of the veins in the legs. These changes may develop at any time ranging from ~6 weeks to several years following the initiation of cART. Approximately 20% of the patients with HIV-associated lipodystrophy meet the criteria for the *metabolic syndrome* as defined by The International Diabetes Federation or The U.S. National Cholesterol Education Program Adult Treatment Panel III. The lipodystrophy syndrome has been reported in association with regimens containing a variety of different drugs, and while initially reported in the setting of



A **B**



C

FIGURE 93-39
Characteristics of lipodystrophy. *A.* Truncal obesity and buffalo hump. ***B.*** Facial wasting. ***C.*** Accumulation of intraabdominal fat on CT scan.

protease inhibitor therapy, it appears that similar changes can also be induced by potent protease-sparing regimens. It has been suggested that the lipoatrophy changes are particularly severe in patients receiving the thymidine analogues stavudine and zidovudine. National Cholesterol Education Program (NCEP) guidelines should be followed in the management of these lipid abnormalities. Due to concerns regarding drug interactions, the most commonly utilized lipid-lowering agents in this setting are gemfibrozil and atorvastatin.

In addition to these abnormalities, patients with HIV infection treated with cART have been found to have an increased incidence of osteonecrosis or avascular necrosis of the hip and shoulders. In a study of asymptomatic patients, 4.4% were found to have evidence of osteonecrosis on MRI. This complication has been associated with the use of lipid-lowering agents, systemic glucocorticoids, or testosterone; bodybuilding exercise; alcohol consumption; and the presence of anticardiolipin antibodies. Osteoporosis has been reported in 7% of women with HIV infection, with 41% of women demonstrating some degree of osteopenia. In addition, lactic acidosis is associated with cART. This is most commonly seen with nucleoside analogue reverse transcriptase inhibitors and can be fatal (see later).

Patients with advanced HIV disease may develop hyponatremia due to the syndrome of inappropriate antidiuretic hormone (vasopressin) secretion (SIADH) as a consequence of increased free-water intake and decreased free-water excretion. SIADH is usually seen in conjunction with pulmonary or CNS disease. Low serum sodium may also be due to adrenal insufficiency; a concomitant high serum potassium should alert one to this possibility. Hyperkalemia may be secondary to adrenal insufficiency; HIV nephropathy; or medications, particularly trimethoprim and pentamidine. Hypokalemia may be seen in the setting of tenofovir therapy. Adrenal gland disease may be due to mycobacterial infections, CMV disease, cryptococcal disease, histoplasmosis, or ketoconazole toxicity. Iatrogenic Cushing's syndrome with suppression of the hypothalamic-pituitary-adrenal axis may be seen with the use of local glucocorticoids (injected or inhaled) in patients receiving ritonavir. This is due to inhibition of the hepatic enzyme CYP3A4 by ritonavir leading to prolongation of the glucocorticoid half-life.

Thyroid function may be altered in 10–15% of patients with HIV infection. Both hypo- and hyperthyroidism may be seen. The predominant abnormality is subclinical hypothyroidism. In the setting of cART, up to 10% of patients have been noted to have elevated thyroid-stimulating hormone levels, suggesting that this may be a manifestation of immune reconstitution. Immune-reconstitution Graves' disease may occur as a late (9–48 months) complication of cART. In advanced HIV disease, infection of the thyroid gland may occur with opportunistic pathogens, including *P. jiroveci*, CMV, mycobacteria, *Toxoplasma gondii*, and *Cryptococcus neoformans*. These infections are generally associated with a nontender, diffuse enlargement of the thyroid gland. Thyroid function is usually normal. Diagnosis is made by fine-needle aspirate or open biopsy.

Depending on the severity of disease, HIV infection is associated with *hypogonadism* in 20–50% of men. While this is generally a complication of underlying illness, testicular dysfunction may also be a side effect of ganciclovir therapy. In some surveys, up to two-thirds of patients report decreased libido and one-third complain of erectile dysfunction. Androgen-replacement therapy should be considered in patients with symptomatic hypogonadism. HIV infection does not seem to have a significant effect on the menstrual cycle outside the setting of advanced disease.

Immunologic and rheumatologic diseases

Immunologic and rheumatologic disorders are common in patients with HIV infection and range from excessive immediate-type hypersensitivity reactions to an increase in the incidence of reactive arthritis to conditions characterized by a diffuse infiltrative lymphocytosis. The occurrence of these phenomena is an apparent paradox in the setting of the profound immunodeficiency and immunosuppression that characterizes HIV infection and reflects the complex nature of the immune system and its regulatory mechanisms.

Drug allergies are the most significant allergic reactions occurring in HIV-infected patients and appear to become more common as the disease progresses. They occur in up to 65% of patients who receive therapy with TMP/SMX for PCP. In general, these drug reactions are characterized by erythematous, morbilliform eruptions that are pruritic, tend to coalesce, and are often associated with fever. Nonetheless, ~33% of patients can be maintained on the offending therapy, and thus these reactions are not an immediate indication to stop the drug. Anaphylaxis is extremely rare in patients with HIV infection, and patients who have a cutaneous reaction during a single course of therapy can still be considered candidates for future treatment or prophylaxis with the same agent. The one exception to this is the nucleoside analogue abacavir, where fatal hypersensitivity reactions have been reported with rechallenge. This hypersensitivity is strongly associated with the HLA-B5701 haplotype, and a hypersensitivity reaction to abacavir is an absolute contraindication to future therapy. For other agents, including TMP/SMX, desensitization regimens are moderately successful. While the mechanisms underlying these allergic-type reactions remain unknown, patients with HIV infection have been noted to have elevated IgE levels that increase as the CD4+ T cell count declines. The numerous examples of patients with multiple drug reactions suggest that a common pathway is involved.

HIV infection shares many similarities with a variety of autoimmune diseases, including a substantial polyclonal B cell activation that is associated with a high incidence of antiphospholipid antibodies, such as anticardiolipin antibodies, VDRL antibodies, and lupus-like anticoagulants. In addition, HIV-infected individuals

have an increased incidence of antinuclear antibodies. Despite these serologic findings, there is no evidence that HIV-infected individuals have an increase in two of the more common autoimmune diseases, i.e., systemic lupus erythematosus and rheumatoid arthritis. In fact, it has been observed that these diseases may be somewhat ameliorated by the concomitant presence of HIV infection, suggesting that an intact CD4+ T cell limb of the immune response plays an integral role in the pathogenesis of these conditions. Similarly, there are anecdotal reports of patients with common variable immunodeficiency, characterized by hypogammaglobulinemia, who have had a normalization of Ig levels following the development of HIV infection, suggesting a possible role for overactive CD4+ T cell immunity in certain forms of that syndrome. The one autoimmune disease that may occur with an increased frequency in patients with HIV infection is a variant of primary Sjögren's syndrome. Patients with HIV infection may develop a syndrome consisting of parotid gland enlargement, dry eyes, and dry mouth that is associated with lymphocytic infiltrates of the salivary gland and lung. One also can see peripheral neuropathy, polymyositis, renal tubular acidosis, and hepatitis. In contrast to Sjögren's syndrome, in which the lymphocytic infiltrates are composed predominantly of CD4+ T cells, in patients with HIV infection the infiltrates are composed predominantly of CD8+ T cells. In addition, while patients with Sjögren's syndrome are mainly women who have autoantibodies to Ro and La and who frequently have HLA-DR3 or -B8 MHC haplotypes, HIV-infected individuals with this syndrome are usually African-American men who do not have anti-Ro or anti-La and who most often are HLA-DR5. This syndrome appears to be less common with the increased use of effective cART. The term *diffuse infiltrative lymphocytosis syndrome* (DILS) is used to describe this entity and to distinguish it from Sjögren's syndrome.

Approximately one-third of HIV-infected individuals experience arthralgias; furthermore, 5–10% are diagnosed as having some form of reactive arthritis, such as Reiter's syndrome or psoriatic arthritis as well as undifferentiated spondyloarthropathy. These syndromes occur with increasing frequency as the competency of the immune system declines. This association may be related to an increase in the number of infections with organisms that may trigger a reactive arthritis with progressive immunodeficiency or to a loss of important regulatory T cells. Reactive arthritides in HIV-infected individuals generally respond well to standard treatment; however, therapy with methotrexate has been associated with an increase in the incidence of opportunistic infections and should be used with caution and only in severe cases.

HIV-infected individuals also experience a variety of joint problems without obvious cause that are referred to generically as *HIV-* or *AIDS-associated arthropathy*. This syndrome is characterized by subacute oligoarticular arthritis developing over a period of 1–6 weeks and lasting 6 weeks to 6 months. It generally involves the large joints, predominantly the knees and ankles, and is nonerosive with only a mild inflammatory response. X-rays of the joint are nonrevealing. Nonsteroidal anti-inflammatory drugs are only marginally helpful; however, relief has been noted with the use of intraarticular glucocorticoids. A second form of arthritis also thought to be secondary to HIV infection is called *painful articular syndrome*. This condition, reported as occurring in as many as 10% of AIDS patients, presents as an acute, severe, sharp pain in the affected joint. It affects primarily the knees, elbows, and shoulders; lasts 2–24 h; and may be severe enough to require narcotic analgesics. The cause of this arthropathy is unclear; however, it is thought to result from a direct effect of HIV on the joint. This condition is reminiscent of the fact that other lentiviruses, in particular the caprine arthritis-encephalitis virus, are capable of directly causing arthritis.

A variety of other immunologic or rheumatologic diseases have been reported in HIV-infected individuals, either de novo or in association with opportunistic infections or drugs. Using the criteria of widespread musculoskeletal pain of at least 3 months' duration and the presence of at least 11 of 18 possible tender points by digital palpation, 11% of an HIV-infected cohort containing 55% IDUs were diagnosed as having *fibromyalgia*. While the incidence of frank arthritis was lower in this population than in other studied populations that consisted predominantly of men who have sex with men, these data support the occurrence of musculoskeletal problems as a direct result of HIV infection. In addition there have been reports of leukocytoclastic vasculitis in the setting of zidovudine therapy. CNS angiitis and polymyositis have also been reported in HIV-infected individuals. Septic arthritis is surprisingly rare, especially given the increased incidence of staphylococcal bacteremias seen in this population. When septic arthritis has been reported, it has usually been due to *Staphylococcus aureus*; to systemic fungal infection with *C. neoformans*, *Sporothrix schenckii*, or *H. capsulatum*; or to systemic mycobacterial infection with *M. tuberculosis*, *M. haemophilum*, *M. avium*, or *M. kansasii*.

As noted earlier, 4.4% of patients with HIV infection were found to have some evidence of osteonecrosis by MRI during systematic screening of asymptomatic patients. The percentage of patients with symptomatic osteonecrosis has been estimated to be as high as 1%. While this problem was first recognized in the setting of cART, it has been difficult to establish a cause-and-effect relationship. Alcohol consumption and a history of glucocorticoid use have been particularly associated with this condition in patients with HIV infection.

Immune reconstitution inflammatory syndrome (IRIS)

Following the initiation of effective cART, a paradoxical worsening of preexisting, untreated, or partially treated opportunistic infections may be noted. One may also see exacerbations of pre-existing or the development of new

TABLE 93-11

CHARACTERISTICS OF IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME (IRIS)

- Paradoxical worsening of clinical condition is seen following the initiation of antiretroviral therapy
- Occurs weeks to months following the initiation of antiretroviral therapy
- Is most common in patients starting therapy with a CD4+ T cell count under 50/μL who experience a precipitous drop in viral load
- Is frequently seen in the setting of tuberculosis
- Can be fatal

TABLE 93-12

CAUSES OF BONE MARROW SUPPRESSION IN PATIENTS WITH HIV INFECTION

HIV infection	Medications
Mycobacterial infections	Zidovudine
Fungal infections	Dapsone
B19 parvovirus infection	Trimethoprim/ sulfamethoxazole
Lymphoma	Pyrimethamine
	5-Flucytosine
	Ganciclovir
	Interferon α
	Trimetrexate
	Foscarnet

autoimmune conditions following the initiation of antiretrovirals (Table 93-11). IRIS related to a pre-existing infection is often referred to as immune reconstitution disease (IRD) to distinguish it from the autoimmune manifestations of IRIS. IRD is particularly common in patients with underlying untreated mycobacterial or fungal infections. IRIS is seen in anywhere from 10 to 30% of patients, depending on the clinical setting, and is most common in patients starting therapy with CD4+ T cell counts <50 cells/μL who have a precipitous drop in HIV RNA levels following the initiation of cART. Signs and symptoms may appear anywhere from 2 weeks to 2 years after the initiation of cART and can include localized lymphadenitis, prolonged fever, pulmonary infiltrates, increased intracranial pressure, uveitis, sarcoidosis, and Graves' disease. The clinical course can be protracted and severe cases can be fatal. The underlying mechanism appears to be related to a phenomenon similar to type IV hypersensitivity reactions and reflects the immediate improvements in immune function that occur as levels of HIV RNA drop and the immunosuppressive effects of HIV infection are controlled. In severe cases, the use of immunosuppressive drugs such as glucocorticoids may be required to blunt the inflammatory component of these reactions while specific antimicrobial therapy takes effect.

Diseases of the hematopoietic system

Disorders of the hematopoietic system, including lymphadenopathy, anemia, leukopenia, and/or thrombocytopenia, are common throughout the course of HIV infection and may be the direct result of HIV, manifestations of secondary infections and neoplasms, or side effects of therapy (Table 93-12). Direct histologic examination and culture of lymph node or bone marrow tissue are often diagnostic. A significant percentage of bone marrow aspirates from patients with HIV infection have been reported to contain lymphoid aggregates, the precise significance of which is unknown. Initiation of cART will lead to reversal of most hematologic complications that are the direct result of HIV infection.

Some patients, otherwise asymptomatic, may develop *persistent generalized lymphadenopathy* as an early clinical manifestation of HIV infection. This condition is defined as the presence of enlarged lymph nodes (>1 cm) in two or more extrainguinal sites for >3 months without an obvious cause. The lymphadenopathy is due to marked follicular hyperplasia in the node in response to HIV infection. The nodes are generally discrete and freely movable. This feature of HIV disease may be seen at any point in the spectrum of immune dysfunction and is not associated with an increased likelihood of developing AIDS. Paradoxically, a loss in lymphadenopathy or a decrease in lymph node size outside the setting of cART may be a prognostic marker of disease progression. In patients with CD4+ T cell counts >200/μL, the differential diagnosis of lymphadenopathy includes KS, TB, Castleman's disease, and lymphoma. In patients with more advanced disease, lymphadenopathy may also be due to atypical mycobacterial infection, toxoplasmosis, systemic fungal infection, or bacillary angiomatosis. While indicated in patients with CD4+ T cell counts <200/μL, lymph node biopsy is not indicated in patients with early-stage disease unless there are signs and symptoms of systemic illness, such as fever and weight loss, or unless the nodes begin to enlarge, become fixed, or coalesce. Monoclonal gammopathy of unknown significance (MGUS), defined as the presence of a serum monoclonal IgG, IgA, or IgM in the absence of a clear cause, has been reported in 3% of patients with HIV infection. The overall clinical significance of this finding in patients with HIV infection is unclear, although it has been associated with other viral infections, non-Hodgkin's lymphoma, and plasma cell malignancy.

Anemia is the most common hematologic abnormality in HIV-infected patients and, in the absence of a specific treatable cause, is independently associated with a poor prognosis. While generally mild, anemia can be quite severe and require chronic blood transfusions. Among the specific reversible causes of anemia in the setting of HIV infection are drug toxicity, systemic fungal and mycobacterial infections, nutritional deficiencies, and parvovirus B19 infections. Zidovudine may block erythroid maturation prior to its effects on other marrow elements. A characteristic feature of zidovudine therapy is an elevated mean corpuscular volume (MCV).

Another drug used in patients with HIV infection that has a selective effect on the erythroid series is dapsone. This drug can cause a serious hemolytic anemia in patients who are deficient in glucose-6-phosphate dehydrogenase and can create a functional anemia in others through induction of methemoglobinemia. Folate levels are usually normal in HIV-infected individuals; however, vitamin B_{12} levels may be depressed as a consequence of achlorhydria or malabsorption. True autoimmune hemolytic anemia is rare, although ~20% of patients with HIV infection may have a positive direct antiglobulin test as a consequence of polyclonal B cell activation. Infection with parvovirus B19 may also cause anemia. It is important to recognize this possibility given the fact that it responds well to treatment with IVIg. Erythropoietin levels in patients with HIV infection and anemia are generally lower than expected given the degree of anemia. Treatment with erythropoietin may result in an increase in hemoglobin levels. An exception to this is a subset of patients with zidovudine-associated anemia in whom erythropoietin levels may be quite high.

During the course of HIV infection, neutropenia may be seen in approximately half of patients. In most instances it is mild; however, it can be severe and can put patients at risk of spontaneous bacterial infections. This is most frequently seen in patients with severely advanced HIV disease and in patients receiving any of a number of potentially myelosuppressive therapies. In the setting of neutropenia, diseases that are not commonly seen in HIV-infected patients, such as aspergillosis or mucormycosis, may occur. Both granulocyte colony-stimulating factor (G-CSF) and GM-CSF increase neutrophil counts in patients with HIV infection regardless of the cause of the neutropenia. Earlier concerns about the potential of these agents to also increase levels of HIV were not confirmed in controlled clinical trials.

Thrombocytopenia may be an early consequence of HIV infection. Approximately 3% of patients with untreated HIV infection and CD4+ T cell counts ≥400/μL have platelet counts <150,000/μL. For untreated patients with CD4+ T cell counts <400/μL, this incidence increases to 10%. In patients receiving antiretrovirals, thrombocytopenia is associated with hepatitis C, cirrhosis, and ongoing high-level HIV replication. Thrombocytopenia is rarely a serious clinical problem in patients with HIV infection and generally responds well to successful cART. Clinically, it resembles the thrombocytopenia seen in patients with idiopathic thrombocytopenic purpura. Immune complexes containing anti-gp120 antibodies and anti-anti-gp120 antibodies have been noted in the circulation and on the surface of platelets in patients with HIV infection. Patients with HIV infection have also been noted to have a platelet-specific antibody directed toward a 25-kDa component of the surface of the platelet. Other data suggest that the thrombocytopenia in patients with HIV infection may be due to a direct effect of HIV on megakaryocytes. Whatever the cause, it is very clear that the most effective medical approach to this problem has been the use of cART. For patients with platelet counts <20,000/μL, a more aggressive approach combining IVIg or anti-Rh Ig for an immediate response with cART for a more lasting response is appropriate. Rituximab has been used with some success in otherwise refractory cases. Splenectomy is a rarely needed option and is reserved for patients refractory to medical management. Because of the risk of serious infection with encapsulated organisms, all patients with HIV infection about to undergo splenectomy should be immunized with pneumococcal polysaccharide. It should be noted that, in addition to causing an increase in the platelet count, removal of the spleen will result in an increase in the peripheral blood lymphocyte count, making CD4+ T cell counts unreliable markers of immunocompetence. In this setting, the clinician should rely on the CD4+ T cell percent for making diagnostic decisions with respect to the likelihood of opportunistic infections. A CD4+ T cell percent of 15 is approximately equivalent to a CD4+ T cell count of 200/μL. In patients with early HIV infection, thrombocytopenia has also been reported as a consequence of classic thrombotic thrombocytopenic purpura. This clinical syndrome, consisting of fever, thrombocytopenia, hemolytic anemia, and neurologic and renal dysfunction, is a rare complication of early HIV infection. As in other settings, the appropriate management is the use of salicylates and plasma exchange. Other causes of thrombocytopenia include lymphoma, mycobacterial infections, and fungal infections.

The incidence of venous thromboembolic disease such as deep-vein thrombosis or pulmonary embolus is approximately 1% per year in patients with HIV infection. This is approximately 10 times higher than that seen in an age-matched population. Among the factors associated with clinical thrombosis are age over 45, history of an opportunistic infection, lower CD4 count, and estrogen use. Abnormalities of the coagulation cascade including decreased protein S activity, increases in factor VIII, anticardiolipin antibodies, or lupus-like anticoagulant have been reported in more than 50% of patients with HIV infection. The clinical significance of this increased propensity toward thromboembolic disease is likely reflected in the observation that elevations in D-dimer are strongly associated with all-cause mortality in patients with HIV infection (Table 93-8).

Dermatologic diseases

Dermatologic problems occur in >90% of patients with HIV infection. From the macular, roseola-like rash seen with the acute seroconversion syndrome to extensive end-stage KS, cutaneous manifestations of HIV disease can be seen throughout the course of HIV infection. Among the more common nonneoplastic problems are seborrheic dermatitis, folliculitis, and opportunistic infections. Extrapulmonary pneumocystosis may cause a necrotizing vasculitis. Neoplastic conditions are covered later.

Seborrheic dermatitis occurs in 3% of the general population and in up to 50% of patients with HIV infection.

Seborrheic dermatitis increases in prevalence and severity as the CD4+ T cell count declines. In HIV-infected patients, seborrheic dermatitis may be aggravated by concomitant infection with *Pityrosporum*, a yeastlike fungus; use of topical antifungal agents has been recommended in cases refractory to standard topical treatment.

Folliculitis is among the most prevalent dermatologic disorders in patients with HIV infection and is seen in ~20% of patients. It is more common in patients with CD4+ T cell counts <200 cells/μL. Pruritic papular eruption is one of the most common pruritic rashes in patients with HIV infection. It appears as multiple papules on the face, trunk, and extensor surfaces and may improve with cART. *Eosinophilic pustular folliculitis* is a rare form of folliculitis that is seen with increased frequency in patients with HIV infection. It presents as multiple, urticarial perifollicular papules that may coalesce into plaquelike lesions. Skin biopsy reveals an eosinophilic infiltrate of the hair follicle, which in certain cases has been associated with the presence of a mite. Patients typically have an elevated serum IgE level and may respond to treatment with topical anthelmintics. Pruritus is a common symptom in patients with HIV infection and can lead to prurigo nodularis. Patients with HIV infection have also been reported to develop a severe form of *Norwegian scabies* with hyperkeratotic psoriasiform lesions.

Both *psoriasis* and *ichthyosis*, although they are not reported to be increased in frequency, may be particularly severe when they occur in patients with HIV infection. Preexisting psoriasis may become guttate in appearance and more refractory to treatment in the setting of HIV infection.

Reactivation herpes zoster (*shingles*) is seen in 10–20% of patients with HIV infection. This reactivation syndrome of varicella-zoster virus indicates a modest decline in immune function and may be the first indication of clinical immunodeficiency. In one series, patients who developed shingles did so an average of 5 years after HIV infection. In a cohort of patients with HIV infection and localized zoster, the subsequent rate of the development of AIDS was 1% per month. In that study, AIDS was more likely to develop if the outbreak of zoster was associated with severe pain, extensive skin involvement, or involvement of cranial or cervical dermatomes. The clinical manifestations of reactivation zoster in HIV-infected patients, although indicative of immunologic compromise, are not as severe as those seen in other immunodeficient conditions. Thus, while lesions may extend over several dermatomes, involve the spinal cord, and/or be associated with frank cutaneous dissemination, visceral involvement has not been reported. In contrast to patients without a known underlying immunodeficiency state, patients with HIV infection tend to have recurrences of zoster with a relapse rate of ~20%. Valacyclovir, acyclovir or famciclovir is the treatment of choice. Foscarnet may be of value in patients with acyclovir-resistant virus.

Infection with *herpes simplex virus* in HIV-infected individuals is associated with recurrent orolabial, genital, and perianal lesions as part of recurrent reactivation syndromes (Chap. 84). As HIV disease progresses and the CD4+ T cell count declines, these infections become more frequent and severe. Lesions often appear as beefy red, are exquisitely painful, and have a tendency to occur high in the gluteal cleft (Fig. 93-38). Perirectal HSV may be associated with proctitis and anal fissures. HSV should be high in the differential diagnosis of any HIV-infected patient with a poorly healing, painful perirectal lesion. In addition to recurrent mucosal ulcers, recurrent HSV infection in the form of *herpetic whitlow* can be a problem in patients with HIV infection, presenting with painful vesicles or extensive cutaneous erosion. Valacyclovir, acyclovir or famciclovir is the treatment of choice in these settings. Of note is the fact that even subclinical reactivation of herpes simplex may be associated with increases in plasma HIV RNA levels.

Diffuse skin eruptions due to *Molluscum contagiosum* may be seen in patients with advanced HIV infection. These flesh-colored, umbilicated lesions may be treated with local agents. They tend to regress with effective cART. Similarly, *condyloma acuminatum* lesions may be more severe and more widely distributed in patients with low CD4+ T cell counts. Imiquimod cream may be helpful in some cases. Atypical mycobacterial infections may present as erythematous cutaneous nodules, as may fungal infections, *Bartonella*, *Acanthamoeba*, and KS.

The skin of patients with HIV infection is often a target organ for drug reactions. Although most skin reactions are mild and not necessarily an indication to discontinue therapy, patients may have particularly severe cutaneous reactions, including erythroderma, *Stevens-Johnson syndrome*, and toxic epidermal necrolysis, as a reaction to drugs—particularly sulfa drugs, the nonnucleoside reverse transcriptase inhibitors, abacavir, amprenavir, darunavir, fosamprenavir, and tipranavir. Similarly, patients with HIV infection are often quite photosensitive and burn easily following exposure to sunlight or as a side effect of radiation therapy.

HIV infection and its treatment may be accompanied by cosmetic changes of the skin that are not of great clinical importance but may be troubling to patients. Yellowing of the nails and straightening of the hair, particularly in African-American patients, have been reported as a consequence of HIV infection. Zidovudine therapy has been associated with elongation of the eyelashes and the development of a bluish discoloration to the nails, again more common in African-American patients. Therapy with clofazimine may cause a yellow-orange discoloration of the skin and urine.

Neurologic diseases

Clinical disease of the nervous system accounts for a significant degree of morbidity in a high percentage of patients with HIV infection **(Table 93-13)**. The neurologic problems that occur in HIV-infected individuals may be either primary to the pathogenic processes of HIV infection or secondary to opportunistic infections or neoplasms (see earlier). Among the more frequent

TABLE 93-13

NEUROLOGIC DISEASES IN PATIENTS WITH HIV INFECTION

- Opportunistic infections
  - Toxoplasmosis
  - Cryptococcosis
  - Progressive multifocal leukoencephalopathy
  - Cytomegalovirus
  - Syphilis
  - *Mycobacterium tuberculosis*
  - HTLV-I infection
  - Amebiasis
- Neoplasms
  - Primary CNS lymphoma
  - Kaposi's sarcoma
- Result of HIV-1 infection
  - Aseptic meningitis
  - HIV-associated neurocognitive disorders, including HIV encephalopathy/AIDS dementia complex
- Result of HIV-1 infection (con't)
  - Myelopathy
    - Vacuolar myelopathy
    - Pure sensory ataxia
    - Paresthesia/dysesthesia
  - Peripheral neuropathy
    - Acute inflammatory demyelinating polyneuropathy (Guillain-Barré syndrome)
    - Chronic inflammatory demyelinating polyneuropathy (CIDP)
    - Mononeuritis multiplex
    - Distal symmetric polyneuropathy
  - Myopathy

opportunistic diseases that involve the CNS are toxoplasmosis, cryptococcosis, progressive multifocal leukoencephalopathy, and primary CNS lymphoma. Other less common problems include mycobacterial infections; syphilis; and infection with CMV, HTLV-I, *Trypanosoma cruzi*, or *Acanthamoeba*. Overall, secondary diseases of the CNS have been reported to occur in approximately one-third of patients with AIDS. These data antedate the widespread use of cART, and this frequency is considerably lower in patients receiving effective antiretroviral drugs. Primary processes related to HIV infection of the nervous system are reminiscent of those seen with other lentiviruses, such as the Visna-Maedi virus of sheep.

Neurologic problems directly attributable to HIV occur throughout the course of infection and may be inflammatory, demyelinating, or degenerative in nature. The term *HIV-associated neurocognitive disorders* (HAND) is used to describe a spectrum of disorders that range from asymptomatic neurocognitive impairment (ANI) to minor neurocognitive disorder (MND) to clinically severe dementia. The most severe form, *HIV-associated dementia* (HAD), also referred to as the *AIDS dementia complex*, or *HIV encephalopathy*, is considered an AIDS-defining illness. Most HIV-infected patients have some neurologic problem during the course of their disease. Even in the setting of suppressive cART, approximately 50% of HIV-infected individuals can be shown to have mild to moderate neurocognitive impairment using sensitive neuropsychiatric testing. As noted in the section on pathogenesis, damage to the CNS may be a direct result of viral infection of the CNS macrophages or glial cells or may be secondary to the release of neurotoxins and potentially toxic cytokines such as IL-1β, TNF-α, IL-6, and TGF-β. It has been reported that HIV-infected individuals with the E4 allele for apo E are at increased risk for AIDS encephalopathy and peripheral neuropathy. Virtually all patients with HIV infection have some degree of nervous system involvement with the virus. This is evidenced by the fact that CSF findings are abnormal in ~90% of patients, even during the asymptomatic phase of HIV infection. CSF abnormalities include pleocytosis (50–65% of patients), detection of viral RNA (~75%), elevated CSF protein (35%), and evidence of intrathecal synthesis of anti-HIV antibodies (90%). It is important to point out that evidence of infection of the CNS with HIV does not imply impairment of cognitive function. The neurologic function of an HIV-infected individual should be considered normal unless clinical signs and symptoms suggest otherwise.

Aseptic meningitis may be seen in any but the very late stages of HIV infection. In the setting of acute primary infection, patients may experience a syndrome of headache, photophobia, and meningismus. Rarely, an acute encephalopathy due to encephalitis may occur. Cranial nerve involvement may be seen, predominantly cranial nerve VII but occasionally V and/or VIII. CSF findings include a lymphocytic pleocytosis, elevated protein level, and normal glucose level. This syndrome, which cannot be clinically differentiated from other viral meningitides (Chap. 32), usually resolves spontaneously within 2–4 weeks; however, in some patients, signs and symptoms may become chronic. Aseptic meningitis may occur any time in the course of HIV infection; however, it is rare following the development of AIDS. This fact suggests that clinical aseptic meningitis in the context of HIV infection is an immune-mediated disease.

C. neoformans is the leading infectious cause of meningitis in patients with AIDS (Chap. 109). It is the initial AIDS-defining illness in ~2% of patients and generally occurs in patients with CD4+ T cell counts <100/μL. Cryptococcal meningitis is particularly common in untreated patients with AIDS in Africa, occurring in ~5% of patients. Most patients present with a picture of subacute meningoencephalitis with fever, nausea, vomiting, altered mental status, headache, and meningeal signs. The incidence of seizures and focal neurologic deficits is low. The CSF profile may be normal or may show only modest elevations in WBC or protein levels and decreases in glucose. The opening pressure in the CSF is usually elevated. In addition to meningitis, patients may develop cryptococcomas and cranial nerve involvement. Approximately one-third of patients also have pulmonary disease. Uncommon manifestations of cryptococcal infection include skin lesions that resemble *molluscum contagiosum*, lymphadenopathy, palatal and glossal ulcers, arthritis, gastroenteritis, myocarditis, and prostatitis. The prostate gland may serve as a reservoir for smoldering cryptococcal infection. The diagnosis of cryptococcal meningitis is made by identification of organisms in spinal fluid with india ink examination or by the detection of cryptococcal antigen. Blood cultures for fungus are often positive. A biopsy may be needed to make a diagnosis of CNS cryptococcoma. Treatment is

with IV amphotericin B 0.7 mg/kg daily, or liposomal amphotericin 4–6 mg/kg daily, with flucytosine 25 mg/kg qid for at least 2 weeks and, if possible, until the CSF culture turns negative. This is followed by fluconazole 400 mg/d PO for 8 weeks, and then fluconazole 200 mg/d until the CD4+ T cell count has increased to >200 cells/μL for 6 months in response to cART. Repeated lumbar puncture may be required to manage increased intracranial pressure. Symptoms may recur with initiation of cART as an immune reconstitution syndrome (see earlier). Other fungi that may cause meningitis in patients with HIV infection are *C. immitis* and *H. capsulatum*. Meningoencephalitis has also been reported due to *Acanthamoeba* or *Naegleria*.

HIV-associated dementia consists of a constellation of signs and symptoms of CNS disease. While this is generally a late complication of HIV infection that progresses slowly over months, it can be seen in patients with CD4+ T cell counts >350 cells/μL. A major feature of this entity is the development of dementia, defined as a decline in cognitive ability from a previous level. It may present as impaired ability to concentrate, increased forgetfulness, difficulty reading, or increased difficulty performing complex tasks. Initially these symptoms may be indistinguishable from findings of situational depression or fatigue. In contrast to "cortical" dementia (such as Alzheimer's disease), aphasia, apraxia, and agnosia are uncommon, leading some investigators to classify HIV encephalopathy as a "subcortical dementia" characterized by defects in short-term memory and executive function (see later). In addition to dementia, patients with HIV encephalopathy may also have motor and behavioral abnormalities. Among the motor problems are unsteady gait, poor balance, tremor, and difficulty with rapid alternating movements. Increased tone and deep tendon reflexes may be found in patients with spinal cord involvement. Late stages may be complicated by bowel and/or bladder incontinence. Behavioral problems include apathy, irritability, and lack of initiative, with progression to a vegetative state in some instances. Some patients develop a state of agitation or mild mania. These changes usually occur without significant changes in level of alertness. This is in contrast to the finding of somnolence in patients with dementia due to toxic/metabolic encephalopathies.

HIV-associated dementia is the initial AIDS-defining illness in ~3% of patients with HIV infection and thus only rarely precedes clinical evidence of immunodeficiency. Clinically significant encephalopathy eventually develops in ~25% of untreated patients with AIDS. As immunologic function declines, the risk and severity of HIV-associated dementia increases. Autopsy series suggest that 80–90% of patients with HIV infection have histologic evidence of CNS involvement. Several classification schemes have been developed for grading HIV encephalopathy; a commonly used clinical staging system is outlined in **Table 93-14**.

The precise cause of HIV-associated dementia remains unclear, although the condition is thought to be a result of a combination of direct effects of HIV on the CNS and associated immune activation. HIV has been found in the brains of patients with HIV encephalopathy by Southern blot, in situ hybridization, PCR, and electron microscopy. Multinucleated giant cells, macrophages, and microglial cells appear to be the main cell types harboring virus in the CNS. Histologically, the major changes are seen in the subcortical areas of the brain and include pallor and gliosis, multinucleated giant cell encephalitis, and vacuolar myelopathy. Less commonly, diffuse or focal spongiform changes occur in the white matter. Areas of the brain involved in motor, language, and judgment are most severely affected.

TABLE 93-14

CLINICAL STAGING OF HIV ENCEPHALOPATHY (AIDS DEMENTIA COMPLEX)

STAGE	DEFINITION
0 (Normal)	Normal mental and motor function.
0.5 (Equivocal/ subclinical)	Absent, minimal, or equivocal symptoms without impairment of work or capacity to perform activities of daily living. Mild signs (snout response, slowed ocular or extremity movements) may be present. Gait and strength are normal.
1 (Mild)	Able to perform all but the more demanding aspects of work or activities of daily living but with unequivocal evidence (signs or symptoms that may include performance on neuropsychological testing) of functional, intellectual, or motor impairment. Can walk without assistance.
2 (Moderate)	Able to perform basic activities of self-care but cannot work or maintain the more demanding aspects of daily life. Ambulatory, but may require a single prop.
3 (Severe)	Major intellectual incapacity (cannot follow news or personal events, cannot sustain complex conversation, considerable slowing of all output) or motor disability (cannot walk unassisted, usually with slowing and clumsiness of arms as well).
4 (End-stage)	Nearly vegetative. Intellectual and social comprehension and output are at a rudimentary level. Nearly or absolutely mute. Paraparetic or paraplegic with urinary and fecal incontinence.

Source: Adapted from JJ Sidtis, RW Price: Neurology 40:197, 1990.

There are no specific criteria for a diagnosis of HIV-associated dementia, and this syndrome must be differentiated from a number of other diseases that affect the CNS of HIV-infected patients (Table 93-13). The diagnosis of dementia depends on demonstrating a decline in cognitive function. This can be accomplished objectively with the use of a Mini-Mental Status Examination (MMSE) in patients for whom prior scores are available. For this reason, it is advisable for all patients with a diagnosis of HIV infection to have a baseline MMSE. However, changes in MMSE scores may be absent in patients with mild HIV encephalopathy. Imaging studies of the CNS, by either MRI or CT, often demonstrate evidence of cerebral atrophy **(Fig. 93-40)**. MRI may also reveal small areas of increased density on T2-weighted images. Lumbar puncture is an important element of the evaluation of patients with HIV infection and neurologic abnormalities. It is generally most helpful in ruling out or making a diagnosis of opportunistic infections. In HIV encephalopathy, patients may have the nonspecific findings of an increase in CSF cells and protein level. While HIV RNA can often be detected in the spinal fluid and HIV can be cultured from the CSF, this finding is not specific for HIV encephalopathy. There appears to be no correlation between the presence of HIV in the CSF and the presence of HIV encephalopathy. Elevated levels of macrophage chemoattractant protein (MCP-1), β_2-microglobulin, neopterin, and quinolinic acid (a metabolite of tryptophan reported to cause CNS injury) have been noted in the CSF of patients with HIV encephalopathy. These findings suggest that these factors as well as inflammatory cytokines may be involved in the pathogenesis of this syndrome.

Combination antiretroviral therapy is of benefit in patients with HIV-associated dementia. Improvement in neuropsychiatric test scores has been noted for both adult and pediatric patients treated with antiretrovirals. The rapid improvement in cognitive function noted with the initiation of cART suggests that at least some component of this problem is quickly reversible, again supporting at least a partial role of soluble mediators in the pathogenesis. It should also be noted that these patients have an increased sensitivity to the side effects of neuroleptic drugs. The use of these drugs for symptomatic treatment is associated with an increased risk of extrapyramidal side effects; therefore, patients with HIV encephalopathy who receive these agents must be monitored carefully. It is felt by many physicians that the decrease in the prevalence of severe cases of HAND brought about by cART has resulted in an increase in the prevalence of milder forms of this disorder.

Seizures may be a consequence of opportunistic infections, neoplasms, or HIV encephalopathy **(Table 93-15)**. The seizure threshold is often lower than normal in patients with advanced HIV infection due to the frequent presence of electrolyte abnormalities. Seizures are seen in 15–40% of patients with cerebral toxoplasmosis, 15–35% of patients with primary CNS lymphoma, 8% of patients with cryptococcal meningitis, and 7–50% of patients with HIV encephalopathy. Seizures may also be seen in patients with CNS tuberculosis, aseptic meningitis, and progressive multifocal leukoencephalopathy. Seizures may be the presenting clinical symptom of HIV disease. In one study of 100 patients with HIV infection presenting with a first seizure, cerebral mass lesions were the most common cause, responsible for 32 of the 100 new-onset seizures.

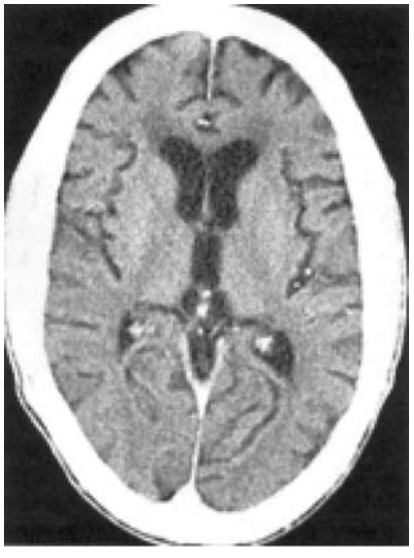


FIGURE 93-40
AIDS dementia complex. Postcontrast CT scan through the lateral ventricles of a 47-year-old man with AIDS, altered mental status, and dementia. The lateral and third ventricles and the cerebral sulci are abnormally prominent. Mild white matter hypodensity is also seen adjacent to the frontal horns of the lateral ventricles.

TABLE 93-15
CAUSES OF SEIZURES IN PATIENTS WITH HIV INFECTION

DISEASE	OVERALL CONTRIBUTION TO FIRST SEIZURE, %	FRACTION OF PATIENTS WHO HAVE SEIZURES, %
HIV encephalopathy	24–47	7–50
Cerebral toxoplasmosis	28	15–40
Cryptococcal meningitis	13	8
Primary central nervous system lymphoma	4	15–30
Progressive multifocal leukoencephalopathy	1	

Source: From DM Holtzman et al: Am J Med 87:173, 1989.

Of these 32 cases, 28 were due to toxoplasmosis and 4 to lymphoma. HIV encephalopathy accounted for an additional 24 new-onset seizures. Cryptococcal meningitis was the third most common diagnosis, responsible for 13 of the 100 seizures. In 23 cases, no cause could be found, and it is possible that these cases represent a subcategory of HIV encephalopathy. Of these 23 cases, 16 (70%) had two or more seizures, suggesting that anticonvulsant therapy is indicated in all patients with HIV infection and seizures unless a rapidly correctable cause is found. While phenytoin remains the initial treatment of choice, hypersensitivity reactions to this drug have been reported in >10% of patients with AIDS, and therefore the use of phenobarbital or valproic acid must be considered as alternatives. Due to a variety of drug-drug interactions between antiseizure medications and antiretrovirals, drug levels need to be monitored carefully.

Patients with HIV infection may present with *focal neurologic deficits* from a variety of causes. The most common causes are toxoplasmosis, progressive multifocal leukoencephalopathy, and CNS lymphoma. Other causes include cryptococcal infections (discussed earlier; also Chap. 109), stroke, and reactivation of Chagas' disease.

Toxoplasmosis has been one of the most common causes of secondary CNS infections in patients with AIDS, but its incidence is decreasing in the era of cART. It is most common in patients from the Caribbean and from France, where the seroprevalence of *T. gondii* is around 50%. This figure is closer to 15% in the United States. Toxoplasmosis is generally a late complication of HIV infection and usually occurs in patients with CD4+ T cell counts <200/μL. Cerebral toxoplasmosis is thought to represent a reactivation of latent tissue cysts. It is 10 times more common in patients with antibodies to the organism than in patients who are seronegative. Patients diagnosed with HIV infection should be screened for IgG antibodies to *T. gondii* during the time of their initial workup. Those who are seronegative should be counseled about ways to minimize the risk of primary infection, including avoiding the consumption of undercooked meat and careful hand washing after contact with soil or changing the cat litter box. The most common clinical presentation of cerebral toxoplasmosis in patients with HIV infection is fever, headache, and focal neurologic deficits. Patients may present with seizure, hemiparesis, or aphasia as a manifestation of these focal deficits or with a picture more influenced by the accompanying cerebral edema and characterized by confusion, dementia, and lethargy, which can progress to coma. The diagnosis is usually suspected on the basis of MRI findings of multiple lesions in multiple locations, although in some cases only a single lesion is seen. Pathologically, these lesions generally exhibit inflammation and central necrosis and, as a result, demonstrate ring enhancement on contrast MRI **(Fig. 93-41)** or, if MRI is unavailable or contraindicated, on double-dose contrast CT. There is usually evidence of surrounding edema. In addition to toxoplasmosis, the differential diagnosis of single or multiple enhancing mass lesions in the HIV-infected patient includes primary CNS lymphoma and, less commonly, TB or fungal or bacterial abscesses. The definitive diagnostic procedure is brain biopsy. However, given the morbidity rate that can accompany this procedure, it is usually reserved for the patient who has failed 2–4 weeks of empiric therapy. If the patient is seronegative for *T. gondii*, the likelihood that a mass lesion is due to toxoplasmosis is <10%. In that setting, one may choose to be more aggressive and perform a brain biopsy sooner. Standard treatment is sulfadiazine and pyrimethamine with leucovorin as needed for a minimum of 4–6 weeks. Alternative therapeutic regimens include clindamycin in combination with pyrimethamine; atovaquone plus pyrimethamine; and azithromycin plus pyrimethamine plus rifabutin. Relapses are common, and it is recommended that patients with a history of prior toxoplasmic encephalitis receive maintenance therapy with sulfadiazine, pyrimethamine, and leucovorin as long as their CD4+ T cell counts remain <200 cells/μL. Patients with CD4+ T cell counts <100/μL and IgG antibody to *Toxoplasma* should receive primary prophylaxis for toxoplasmosis. Fortunately, the same daily regimen of a single double-strength tablet of TMP/SMX used for *P. jiroveci* prophylaxis provides adequate primary protection against toxoplasmosis. Secondary prophylaxis/maintenance therapy for toxoplasmosis may be discontinued in the setting of effective cART and increases in CD4+ T cell counts to >200/μL for 6 months.

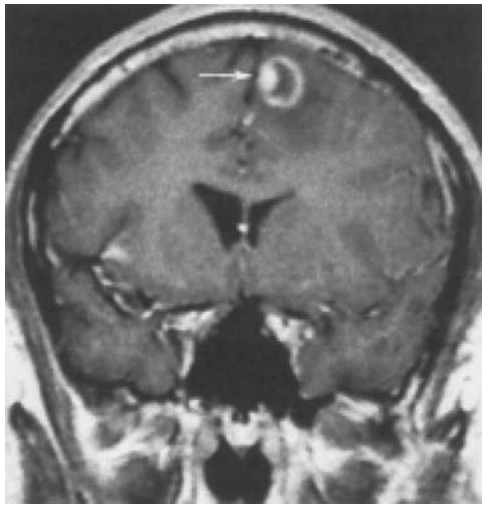


FIGURE 93-41
Central nervous system toxoplasmosis. A coronal post-contrast T1-weighted MRI scan demonstrates a peripheral enhancing lesion in the left frontal lobe, associated with an eccentric nodular area of enhancement (*arrow*); this so-called eccentric target sign is typical of toxoplasmosis.

JC virus, a human polyomavirus that is the etiologic agent of *progressive multifocal leukoencephalopathy* (PML), is an important opportunistic pathogen in patients with AIDS (Chap. 31). While ~80% of the general adult population has antibodies to JC virus, indicative of prior infection, <10% of healthy adults show any evidence of ongoing viral replication. PML is the only known

clinical manifestation of JC virus infection. It is a late manifestation of AIDS and is seen in ~4% of patients with AIDS. The lesions of PML begin as small foci of demyelination in subcortical white matter that eventually coalesce. The cerebral hemispheres, cerebellum, and brainstem may all be involved. Patients typically have a protracted course with multifocal neurologic deficits, with or without changes in mental status. Approximately 20% of patients experience seizures. Ataxia, hemiparesis, visual field defects, aphasia, and sensory defects may occur. Headache, fever, nausea, and vomiting are rarely seen. Their presence should suggest another diagnosis. MRI typically reveals multiple, nonenhancing white matter lesions that may coalesce and have a predilection for the occipital and parietal lobes. The lesions show signal hyperintensity on T2-weighted images and diminished signal on T1-weighted images. The measurement of JC virus DNA levels in CSF has a diagnostic sensitivity of 76% and a specificity of close to 100%. Prior to the availability of cART, the majority of patients with PML died within 3–6 months of the onset of symptoms. Paradoxical worsening of PML has been seen with initiation of cART as an immune reconstitution syndrome. There is no specific treatment for PML; however, a median survival of 2 years and survival of >15 years have been reported in patients with PML treated with cART for their HIV disease. Despite having a significant impact on survival, only ~50% of patients with HIV infection and PML show neurologic improvement with cART. Studies with other antiviral agents such as cidofovir have failed to show clear benefit. Factors influencing a favorable prognosis for PML in the setting of HIV infection include a CD4+ T cell count >100/μL at baseline and the ability to maintain an HIV viral load of <500 copies per milliliter. Baseline HIV-1 viral load does not have independent predictive value of survival. PML is one of the few opportunistic infections that continues to occur with some frequency despite the widespread use of cART.

Reactivation American trypanosomiasis may present as acute meningoencephalitis with focal neurologic signs, fever, headache, vomiting, and seizures. Accompanying cardiac disease in the form of arrhythmias or heart failure should increase the index of suspicion. The presence of antibodies to *T. cruzi* supports the diagnosis. In South America, reactivation of *Chagas' disease* is considered to be an AIDS-defining condition and may be the initial AIDS-defining condition. The majority of cases occur in patients with CD4+ T cell counts <200 cells/μL. Lesions appear radiographically as single or multiple hypodense areas, typically with ring enhancement and edema. They are found predominantly in the subcortical areas, a feature that differentiates them from the deeper lesions of toxoplasmosis. *T. cruzi* amastigotes, or trypanosomes, can be identified from biopsy specimens or CSF. Other CSF findings include elevated protein and a mild (<100 cells/μL) lymphocytic pleocytosis. Organisms can also be identified by direct examination of the blood. Treatment consists of benzimidazole (2.5 mg/kg bid) or nifurtimox (2 mg/kg qid) for at least 60 days, followed by maintenance therapy for the duration of immunodeficiency with either drug at a dose of 5 mg/kg three times a week. As is the case with cerebral toxoplasmosis, successful therapy with antiretrovirals may allow discontinuation of therapy for Chagas' disease.

Stroke may occur in patients with HIV infection. In contrast to the other causes of focal neurologic deficits in patients with HIV infection, the symptoms of a stroke are sudden in onset. Patients with HIV infection have an increased prevalence of many classic risk factors associated with stroke, including smoking and diabetes. It also appears that HIV infection itself can lead to an increase in carotid artery stiffness. Among the secondary infectious diseases in patients with HIV infection that may be associated with stroke are vasculitis due to cerebral varicella zoster or neurosyphilis and septic embolism in association with fungal infection. Other elements of the differential diagnosis of stroke in the patient with HIV infection include atherosclerotic cerebral vascular disease, thrombotic thrombocytopenic purpura, and cocaine or amphetamine use.

Primary CNS lymphoma is discussed later in the section on neoplastic diseases.

Spinal cord disease, or myelopathy, is present in ~20% of patients with AIDS, often as part of HIV-associated neurocognitive disorder. In fact, 90% of the patients with HIV-associated myelopathy have some evidence of dementia, suggesting that similar pathologic processes may be responsible for both conditions. Three main types of spinal cord disease are seen in patients with AIDS. The first of these is a vacuolar myelopathy, as mentioned earlier. This condition is pathologically similar to subacute combined degeneration of the cord, such as that occurring with pernicious anemia. Although vitamin B_{12} deficiency can be seen in patients with AIDS as a primary complication of HIV infection, it does not appear to be responsible for the myelopathy seen in the majority of patients. Vacuolar myelopathy is characterized by a subacute onset and often presents with gait disturbances, predominantly ataxia and spasticity; it may progress to include bladder and bowel dysfunction. Physical findings include evidence of increased deep tendon reflexes and extensor plantar responses. The second form of spinal cord disease involves the dorsal columns and presents as a pure sensory ataxia. The third form is also sensory in nature and presents with paresthesias and dysesthesias of the lower extremities. In contrast to the cognitive problems seen in patients with HIV encephalopathy, these spinal cord syndromes do not respond well to antiretroviral drugs, and therapy is mainly supportive.

One important disease of the spinal cord that also involves the peripheral nerves is a *myelopathy* and *polyradiculopathy* seen in association with CMV infection. This entity is generally seen late in the course of HIV infection and is fulminant in onset, with lower-extremity and sacral paresthesias, difficulty in walking, areflexia, ascending sensory loss, and urinary retention. The clinical course is rapidly progressive over a period of weeks. CSF examination reveals a predominantly neutrophilic pleocytosis, and CMV DNA can be detected by CSF PCR. Therapy with ganciclovir or

foscarnet can lead to rapid improvement, and prompt initiation of foscarnet or ganciclovir therapy is important in minimizing the degree of permanent neurologic damage. Combination therapy with both drugs should be considered in patients who have been previously treated for CMV disease. Other diseases involving the spinal cord in patients with HIV infection include HTLV-I-associated myelopathy (HAM), neurosyphilis (Chap. 74), infection with herpes simplex (Chap. 84) or varicella-zoster (Chap. 85), TB (Chap. 70), and lymphoma.

Peripheral neuropathies are common in patients with HIV infection. They occur at all stages of illness and take a variety of forms. Early in the course of HIV infection, an acute inflammatory demyelinating polyneuropathy resembling Guillain-Barré syndrome may occur. In other patients, a progressive or relapsing-remitting inflammatory neuropathy resembling chronic inflammatory demyelinating polyneuropathy (CIDP) has been noted. Patients commonly present with progressive weakness, areflexia, and minimal sensory changes. CSF examination often reveals a mononuclear pleocytosis, and peripheral nerve biopsy demonstrates a perivascular infiltrate suggesting an autoimmune etiology. Plasma exchange or IVIg has been tried with variable success. Because of the immunosuppressive effects of glucocorticoids, they should be reserved for severe cases of CIDP refractory to other measures. Another autoimmune peripheral neuropathy seen in patients with AIDS is mononeuritis multiplex due to a necrotizing arteritis of peripheral nerves. The most common peripheral neuropathy in patients with HIV infection is a *distal sensory polyneuropathy* (DSPN) also referred to as painful sensory neuropathy (HIV-SN), predominantly sensory neuropathy, or distal symmetric peripheral neuropathy. This condition may be a direct consequence of HIV infection or a side effect of dideoxynucleoside therapy. It is more common in taller individuals, older individuals, and those with lower CD4 counts. Two-thirds of patients with AIDS may be shown by electrophysiologic studies to have some evidence of peripheral nerve disease. Presenting symptoms are usually painful burning sensations in the feet and lower extremities. Findings on examination include a stocking-type sensory loss to pinprick, temperature, and touch sensation and a loss of ankle reflexes. Motor changes are mild and are usually limited to weakness of the intrinsic foot muscles. Response of this condition to antiretrovirals has been variable, perhaps because antiretrovirals are responsible for the problem in some instances. When due to dideoxynucleoside therapy, lower-extremity peripheral neuropathy may cause patients to complain of a sensation that they are walking on ice. Other entities in the differential diagnosis of peripheral neuropathy include diabetes mellitus, vitamin B_{12} deficiency, and side effects from metronidazole or dapsone. For distal symmetric polyneuropathy that fails to resolve following the discontinuation of dideoxynucleosides, therapy is symptomatic; gabapentin, carbamazepine, tricyclics, or analgesics may be effective for dysesthesias. Treatment-naïve patients may respond to cART.

Myopathy may complicate the course of HIV infection; causes include HIV infection itself, zidovudine, and the generalized wasting syndrome. HIV-associated myopathy may range in severity from an asymptomatic elevation in creatine kinase levels to a subacute syndrome characterized by proximal muscle weakness and myalgias. Quite pronounced elevations in creatine kinase may occur in asymptomatic patients, particularly after exercise. The clinical significance of this as an isolated laboratory finding is unclear. A variety of both inflammatory and noninflammatory pathologic processes have been noted in patients with more severe myopathy, including myofiber necrosis with inflammatory cells, nemaline rod bodies, cytoplasmic bodies, and mitochondrial abnormalities. Profound muscle wasting, often with muscle pain, may be seen after prolonged zidovudine therapy. This toxic side effect of the drug is dose-dependent and is related to its ability to interfere with the function of mitochondrial polymerases. It is reversible following discontinuation of the drug. Red ragged fibers are a histologic hallmark of zidovudine-induced myopathy.

Ophthalmologic diseases

Ophthalmologic problems occur in ~50% of patients with advanced HIV infection. The most common abnormal findings on funduscopic examination are cotton-wool spots. These are hard white spots that appear on the surface of the retina and often have an irregular edge. They represent areas of retinal ischemia secondary to microvascular disease. At times they are associated with small areas of hemorrhage and thus can be difficult to distinguish from CMV retinitis. In contrast to CMV retinitis, however, these lesions are not associated with visual loss and tend to remain stable or improve over time.

One of the most devastating consequences of HIV infection is CMV retinitis. Patients at high risk of CMV retinitis (CD4+ T cell count $<100/\mu L$) should undergo an ophthalmologic examination every 3–6 months. The majority of cases of CMV retinitis occur in patients with a CD4+ T cell count $<50/\mu L$. Prior to the availability of cART, this CMV reactivation syndrome was seen in 25–30% of patients with AIDS. CMV retinitis usually presents as a painless, progressive loss of vision. Patients may also complain of blurred vision, "floaters," and scintillations. The disease is usually bilateral, although typically it affects one eye more than the other. The diagnosis is made on clinical grounds by an experienced ophthalmologist. The characteristic retinal appearance is that of perivascular hemorrhage and exudate. In situations where the diagnosis is in doubt due to an atypical presentation or an unexpected lack of response to therapy, vitreous or aqueous humor sampling with molecular diagnostic techniques may be of value. CMV infection of the retina results in a necrotic inflammatory process, and the visual loss that develops is irreversible. CMV retinitis may be complicated by rhegmatogenous retinal detachment as a consequence of retinal atrophy in areas of

prior inflammation. Therapy for CMV retinitis consists of oral valganciclovir, IV ganciclovir, or IV foscarnet, with cidofovir as an alternative. Combination therapy with ganciclovir and foscarnet has been shown to be slightly more effective than either ganciclovir or foscarnet alone in the patient with relapsed CMV retinitis. A 3-week induction course is followed by maintenance therapy with oral valganciclovir. If CMV disease is limited to the eye, a ganciclovir-releasing intraocular implant, periodic injections of the antisense nucleic acid preparation fomivirsen (no longer available in the United States), or intravitreal injections of ganciclovir or foscarnet may be considered; some choose to combine intraocular implants with oral valganciclovir. Intravitreal injections of cidofovir are generally avoided due to the increased risk of uveitis and hypotony. Maintenance therapy is continued until the CD4+ T cell count remains >100–150/μL for >6 months. The majority of patients with HIV infection and CMV disease develop some degree of uveitis with the initiation of cART. The etiology of this is unknown; however, it has been suggested that this may be due to the generation of an enhanced immune response to CMV as an IRIS (see earlier). In some instances this has required the use of topical glucocorticoids.

Both HSV and varicella-zoster virus can cause a rapidly progressing, bilateral necrotizing retinitis referred to as the *acute retinal necrosis syndrome*, or *progressive outer retinal necrosis* (PORN). This syndrome, in contrast to CMV retinitis, is associated with pain, keratitis, and iritis. It is often associated with orolabial HSV or trigeminal zoster. Ophthalmologic examination reveals widespread pale gray peripheral lesions. This condition is often complicated by retinal detachment. It is important to recognize and treat this condition with IV acyclovir as quickly as possible to minimize the loss of vision.

Several other secondary infections may cause ocular problems in HIV-infected patients. *P. jiroveci* can cause a lesion of the choroid that may be detected as an incidental finding on ophthalmologic examination. These lesions are typically bilateral, are from half to twice the disc diameter in size, and appear as slightly elevated yellow-white plaques. They are usually asymptomatic and may be confused with cotton-wool spots. Chorioretinitis due to toxoplasmosis can be seen alone or, more commonly, in association with CNS toxoplasmosis. KS may involve the eyelid or conjunctiva, while lymphoma may involve the retina. Syphilis may lead to a uveitis that is highly associated with the presence of neurosyphilis.

Additional disseminated infections and wasting syndrome

Infections with species of the small, gram-negative, *Rickettsia*-like organism *Bartonella* (Chap. 65) are seen with increased frequency in patients with HIV infection. While it is not considered an AIDS-defining illness by the CDC, many experts view infection with *Bartonella* as indicative of a severe defect in cell-mediated immunity. It is usually seen in patients with CD4+ T cell counts <100/μL and is a significant cause of unexplained fever in patients with advanced HIV infection. Among the clinical manifestations of *Bartonella* infection are bacillary angiomatosis, cat-scratch disease, and trench fever. *Bacillary angiomatosis* is usually due to infection with *B. henselae* and is linked to exposure to flea-infested cats. It is characterized by a vascular proliferation that leads to a variety of skin lesions that have been confused with the skin lesions of KS. In contrast to the lesions of KS, the lesions of bacillary angiomatosis generally blanch, are painful, and typically occur in the setting of systemic symptoms. Infection can extend to the lymph nodes, liver (peliosis hepatis), spleen, bone, heart, CNS, respiratory tract, and GI tract. *Cat-scratch disease* is also due to *B. henselae* and generally begins with a papule at the site of inoculation. This is followed several weeks later by the development of regional adenopathy and malaise. Infection with *B. quintana* is transmitted by lice and has been associated with case reports of trench fever, endocarditis, adenopathy, and bacillary angiomatosis. The organism is quite difficult to culture, and diagnosis often relies on identifying the organism in biopsy specimens using the Warthin-Starry or similar stains. Treatment is with either doxycycline or erythromycin for at least 3 months.

Histoplasmosis is an opportunistic infection that is seen most frequently in patients in the Mississippi and Ohio River valleys, Puerto Rico, the Dominican Republic, and South America. These are all areas in which infection with *H. capsulatum* is endemic (Chap. 106). Because of this limited geographic distribution, the percentage of AIDS cases in the United States with histoplasmosis is only ~0.5. Histoplasmosis is generally a late manifestation of HIV infection; however, it may be the initial AIDS-defining condition. In one study, the median CD4+ T cell count for patients with histoplasmosis and AIDS was 33/μL. While disease due to *H. capsulatum* may present as a primary infection of the lung, disseminated disease, presumably due to reactivation, is the most common presentation in HIV-infected patients. Patients usually present with a 4- to 8-week history of fever and weight loss. Hepatosplenomegaly and lymphadenopathy are each seen in about 25% of patients. CNS disease, either meningitis or a mass lesion, is seen in 15% of patients. Bone marrow involvement is common, with thrombocytopenia, neutropenia, and anemia occurring in 33% of patients. Approximately 7% of patients have mucocutaneous lesions consisting of a maculopapular rash and skin or oral ulcers. Respiratory symptoms are usually mild, with chest x-ray showing a diffuse infiltrate or diffuse small nodules in ~50% of cases. Diagnosis is made by culturing the organisms from blood, bone marrow, or tissue or by detecting antigen in blood or urine. Treatment is typically with liposomal amphotericin B followed by maintenance therapy with oral itraconazole until the serum *Histoplasma* antigen is <2 units, the patient has been on antiretrovirals for at least 6 months, and the CD4 count is >150 cells/μL. In the setting of mild infection, it may be appropriate to initiate therapy with itraconazole alone.

Following the spread of HIV infection to southeast Asia, disseminated infection with the fungus *Penicillium*

marneffei was recognized as a complication of HIV infection and is considered an AIDS-defining condition in those parts of the world where it occurs. *P. marneffei* is the third most common AIDS-defining illness in Thailand, following TB and cryptococcosis. It is more frequently diagnosed in the rainy than the dry season. Clinical features include fever, generalized lymphadenopathy, hepatosplenomegaly, anemia, thrombocytopenia, and papular skin lesions with central umbilication. Treatment is with amphotericin B followed by itraconazole until the CD4+ T cell count is >100 cells/μL for at least 6 months.

Visceral leishmaniasis (Chap. 122) is recognized with increasing frequency in patients with HIV infection who live in or travel to areas endemic for this protozoal infection transmitted by sandflies. The clinical presentation is one of hepatosplenomegaly, fever, and hematologic abnormalities. Lymphadenopathy and other constitutional symptoms may be present. A chronic, relapsing course is seen in two-thirds of co-infected patients. Organisms can be isolated from cultures of bone marrow aspirates. Histologic stains may be negative, and antibody titers are of little help. Patients with HIV infection usually respond well initially to standard therapy with amphotericin B or pentavalent antimony compounds. Eradication of the organism is difficult, however, and relapses are common.

Patients with HIV infection are at a slightly increased risk of clinical malaria. This is particularly true for patients from nonendemic areas with presumed primary infection and in patients with lower CD4+ T cell counts. HIV-positive individuals with CD4+ T cell counts <300 cells/μL have a poorer response to malaria treatment than others. Co-infection with malaria is associated with a modest increase in HIV viral load. The risk of malaria may be decreased with TMP/SMX prophylaxis.

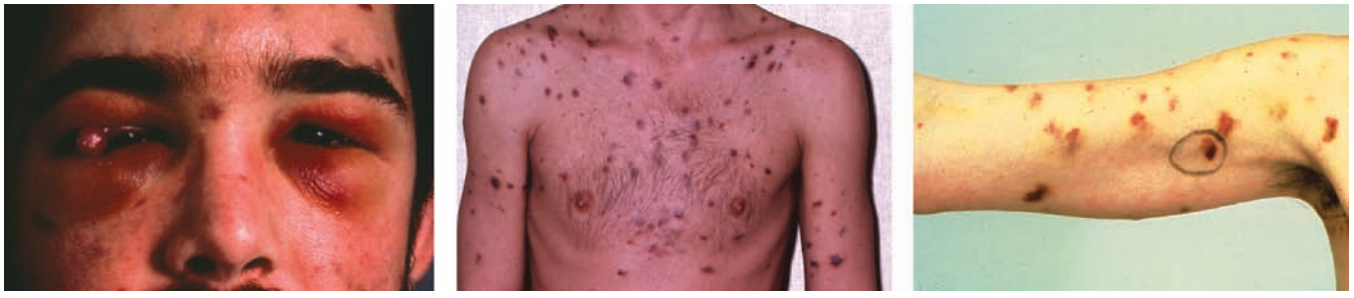
Generalized wasting is an AIDS-defining condition; it is defined as involuntary weight loss of >10% associated with intermittent or constant fever and chronic diarrhea or fatigue lasting >30 days in the absence of a defined cause other than HIV infection. Prior to the widespread use of cART it was the initial AIDS-defining condition in ~10% of patients with AIDS in the United States and is an indication for initiation of cART. Generalized wasting is rarely seen today with the earlier initiation of antiretrovirals. A constant feature of this syndrome is severe muscle wasting with scattered myofiber degeneration and occasional evidence of myositis. Glucocorticoids may be of some benefit; however, this approach must be carefully weighed against the risk of compounding the immunodeficiency of HIV infection. Androgenic steroids, growth hormone, and total parenteral nutrition have been used as therapeutic interventions with variable success.

Neoplastic diseases

The neoplastic diseases considered to be AIDS-defining conditions are Kaposi's sarcoma, non-Hodgkin's lymphoma, and invasive cervical carcinoma. In addition, there is also an increase in the incidence of a variety of non-AIDS-defining malignancies including Hodgkin's disease; multiple myeloma; leukemia; melanoma; and cervical, brain, testicular, oral, lung, gastric, liver, renal, and anal cancers. Since the introduction of potent cART, there has been a marked reduction in the incidence of KS (Fig. 93-34) and CNS lymphoma, such that the non-AIDS-defining malignancies now account for more morbidity and mortality in patients with HIV infection than the AIDS-defining malignancies. Rates of non-Hodgkin's lymphoma have declined as well; however, this decline has not been as dramatic as the decline in rates of KS. In contrast, cART has had little effect on human papillomavirus (HPV)-associated malignancies. As patients with HIV infection live longer, a wider array of cancers is seen in this population. While some may only reflect known risk factors (e.g., smoking, alcohol consumption, co-infection with other viruses such as hepatitis B) that are increased in patients with HIV infection, some may be a direct consequence of HIV and are clearly increased in patients with lower CD4+ T cell counts.

Kaposi's sarcoma is a multicentric neoplasm consisting of multiple vascular nodules appearing in the skin, mucous membranes, and viscera. The course ranges from indolent, with only minor skin or lymph node involvement, to fulminant, with extensive cutaneous and visceral involvement. In the initial period of the AIDS epidemic, KS was a prominent clinical feature of the first cases of AIDS, occurring in 79% of the patients diagnosed in 1981. By 1989 it was seen in only 25% of cases, by 1992 the number had decreased to 9%, and by 1997 the number was <1%. HHV-8 or KSHV has been strongly implicated as a viral cofactor in the pathogenesis of KS.

Clinically, KS has varied presentations and may be seen at any stage of HIV infection, even in the presence of a normal CD4+ T cell count. The initial lesion may be a small, raised reddish-purple nodule on the skin **(Fig. 93-42)**, a discoloration on the oral mucosa (Fig. 93-35*D*), or a swollen lymph node. Lesions often appear in sun-exposed areas, particularly the tip of the nose, and have a propensity to occur in areas of trauma (Koebner phenomenon). Because of the vascular nature of the tumors and the presence of extravasated red blood cells in the lesions, their colors range from reddish to purple to brown and often take the appearance of a bruise, with yellowish discoloration and tattooing. Lesions range in size from a few millimeters to several centimeters in diameter and may be either discrete or confluent. KS lesions most commonly appear as raised macules; however, they can also be papular, particularly in patients with higher CD4+ T cell counts. Confluent lesions may give rise to surrounding lymphedema and may be disfiguring when they involve the face and disabling when they involve the lower extremities or the surfaces of joints. Apart from skin, the lymph nodes, GI tract, and lung are the organ systems most commonly affected by KS. Lesions have been reported in virtually every organ, including the heart and the CNS. In contrast to most malignancies, in which lymph node involvement implies metastatic spread and a poor prognosis, lymph node involvement may be seen very early in KS and is of no special clinical significance. In fact,



A B C

FIGURE 93-42
Kaposi's sarcoma in three patients with AIDS demonstrating ***(A)*** periorbital edema and bruising; ***(B)*** classic truncal distribution of lesions; and ***(C)*** upper-extremity lesions.

some patients may present with disease limited to the lymph nodes. These are generally patients with relatively intact immune function and thus the patients with the best prognosis. Pulmonary involvement with KS generally presents with shortness of breath. Some 80% of patients with pulmonary KS also have cutaneous lesions. The chest x-ray characteristically shows bilateral lower lobe infiltrates that obscure the margins of the mediastinum and diaphragm **(Fig. 93-43)**. Pleural effusions are seen in 70% of cases of pulmonary KS, a fact that is often helpful in the differential diagnosis. GI involvement is seen in 50% of patients with KS and usually takes one of two forms: (1) mucosal involvement, which may lead to bleeding that can be severe; these patients sometimes also develop symptoms of GI obstruction if lesions become large; and (2) biliary tract involvement. KS lesions may infiltrate the gallbladder and biliary tree, leading to a clinical picture of obstructive jaundice similar to that seen with sclerosing cholangitis. Several staging systems have been proposed for KS. One in common use was developed by the National Institute of Allergy and Infectious Diseases AIDS Clinical Trials Group; it distinguishes patients on the basis of tumor extent, immunologic function, and presence or absence of systemic disease **(Table 93-16)**.

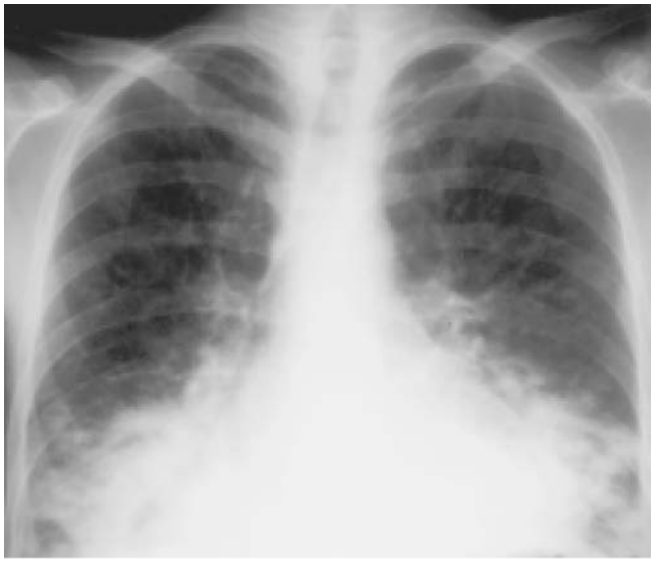


FIGURE 93-43
Chest x-ray of a patient with AIDS and pulmonary Kaposi's sarcoma. The characteristic findings include dense bilateral lower-lobe infiltrates obscuring the heart borders and pleural effusions.

TABLE 93-16
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES AIDS CLINICAL TRIALS GROUP TIS STAGING SYSTEM FOR KAPOSI'S SARCOMA

PARAMETER	GOOD RISK (STAGE 0): ALL OF THE FOLLOWING	POOR RISK (STAGE 1): ANY OF THE FOLLOWING
Tumor (T)	Confined to skin and/or lymph nodes and/or minimal oral disease	Tumor-associated edema or ulceration Extensive oral lesions GI lesions Nonnodal visceral lesions
Immune system (I)	CD4+ T cell count ≥200/μL	CD4+ T cell count <200/μL
Systemic illness (S)	No B symptoms[a] Karnofsky performance status ≥70 No history of opportunistic infection, neurologic disease, lymphoma, or thrush	B symptoms[a] present Karnofsky performance status <70 History of opportunistic infection, neurologic disease, lymphoma, or thrush

[a]Defined as unexplained fever, night sweats, >10% involuntary weight loss, or diarrhea persisting for more than 2 weeks.

A diagnosis of KS is based on biopsy of a suspicious lesion. Histologically one sees a proliferation of spindle cells and endothelial cells, extravasation of red blood cells, hemosiderin-laden macrophages, and, in early cases, an inflammatory cell infiltrate. Included in the differential diagnosis are lymphoma (particularly for oral lesions), bacillary angiomatosis, and cutaneous mycobacterial infections.

Management of KS **(Table 93-17)** should be carried out in consultation with an expert since definitive treatment guidelines do not exist. In the majority of cases, effective cART will go a long way in achieving control. Antiretroviral therapy has been associated with the spontaneous regression of KS lesions. Paradoxically, it has also been associated with the initial appearance of KS as a form of IRIS. For patients in whom tumor persists or in whom control of HIV replication is not possible, a variety of options exist. In some cases, lesions remain quite indolent, and many of these patients can be managed with no specific treatment. Fewer than 10% of AIDS patients with KS die as a consequence of their malignancy, and death from secondary infections is considerably more common. Thus, whenever possible one should avoid treatment regimens that may further suppress the immune system and increase susceptibility to opportunistic infections. Treatment is indicated under two main circumstances. The first is when a single lesion or a limited number of lesions are causing significant discomfort or cosmetic problems, such as with prominent facial lesions, lesions overlying a joint, or lesions in the oropharynx that interfere with swallowing or breathing. Under these circumstances, treatment with localized radiation, intralesional vinblastine, topical 9-*cis*-retinoic acid, or cryotherapy may be helpful. It should be noted that patients with HIV infection are particularly sensitive to the side effects of radiation therapy. This is especially true with respect to the development of radiation-induced mucositis; doses of radiation directed at mucosal surfaces, particularly in the head and neck region, should be adjusted accordingly. The use of systemic therapy, either IFN-α or chemotherapy, should be considered in patients with a large number of lesions or in patients with visceral involvement. The single most important determinant of response appears to be the CD4+ T cell count. This relationship between response rate and baseline CD4+ T cell count is particularly true for IFN-α. The response rate for patients with CD4+ T cell counts >600/μL is ~80%, while the response rate for patients with counts <150/μL is <10%. In contrast to the other systemic therapies, IFN-α provides an added advantage of having antiretroviral activity; thus, it may be the appropriate first choice for single-agent systemic therapy for early patients with disseminated disease. A variety of chemotherapeutic agents have also been shown to have activity against KS. Three of them: liposomal daunorubicin, liposomal doxorubicin, and paclitaxel, have been approved by the FDA for this indication. Liposomal daunorubicin is approved as first-line therapy for patients with advanced KS. It has fewer side effects than conventional chemotherapy. In contrast, liposomal doxorubicin and paclitaxel are approved only for KS patients who have failed standard chemotherapy. Response rates vary from 23% to 88%, appear to be comparable to what had been achieved earlier with combination chemotherapy regimens, and are greatly influenced by CD4+ T cell count.

TABLE 93-17

MANAGEMENT OF AIDS-ASSOCIATED KAPOSI'S SARCOMA

Observation and optimization of antiretroviral therapy
Single or limited number of lesions
Radiation
Intralesional vinblastine
Cryotherapy
Extensive disease
Initial therapy
Interferon α (if CD4+ T cells >150/ L)
Liposomal daunorubicin
Subsequent therapy
Liposomal doxorubicin
Paclitaxel
Combination chemotherapy with low-dose doxorubicin, bleomycin, and vinblastine (ABV)
Targeted radiation

Lymphomas occur with an increased frequency in patients with congenital or acquired T cell immunodeficiencies. AIDS is no exception; at least 6% of all patients with AIDS develop lymphoma at some time during the course of their illness. This is a 120-fold increase in incidence compared with the general population. In comparison to the situation with KS, primary CNS lymphoma, and most opportunistic infections, the incidence of AIDS-associated systemic lymphomas has not experienced as dramatic a decrease as a consequence of the widespread use of effective cART. Lymphoma occurs in all risk groups, with the highest incidence in patients with hemophilia and the lowest incidence in patients from the Caribbean or Africa with heterosexually acquired infection. Lymphoma is a late manifestation of HIV infection, generally occurring in patients with CD4+ T cell counts <200/μL. As HIV disease progresses, the risk of lymphoma increases. The attack rate for lymphoma increases exponentially with increasing duration of HIV infection and decreasing level of immunologic function. At 3 years following a diagnosis of HIV infection, the risk of lymphoma is 0.8% per year; by 8 years after infection, it is 2.6% per year. As individuals with HIV infection live longer as a consequence of improved cART and better treatment and prophylaxis of opportunistic infections, it is anticipated that the incidence of lymphomas may increase.

Three main categories of lymphoma are seen in patients with HIV infection: grade III or IV immunoblastic lymphoma, Burkitt's lymphoma, and primary CNS lymphoma. Approximately 90% of these lymphomas are B cell in phenotype; more than half contain EBV DNA. Some are associated with KSHV. These tumors may be either monoclonal or oligoclonal in nature and are probably in some way related to the

pronounced polyclonal B cell activation seen in patients with AIDS.

Immunoblastic lymphomas account for ~60% of the cases of lymphoma in patients with AIDS. The majority of these are diffuse large B cell lymphomas (DLBCL). They are generally high grade and would have been classified as diffuse histiocytic lymphomas in earlier classification schemes. This tumor is more common in older patients, increasing in incidence from 0% in HIV-infected individuals <1 year old to >3% in those >50. Two variants of immunoblastic lymphoma that are seen primarily in HIV-infected patients are primary effusion lymphoma (PEL) and its solid variant, plasmacytic lymphoma of the oral cavity. PEL, also referred to as body cavity lymphoma, presents with lymphomatous pleural, pericardial, and/or peritoneal effusions in the absence of discrete nodal or extranodal masses. The tumor cells do not express surface markers for B cells or T cells and are felt to represent a preplasmacytic stage of differentiation. While both HHV-8 and EBV DNA sequences have been found in the genomes of the malignant cells from patients with body cavity lymphoma, KSHV is felt to be the driving force behind the oncogenesis (see earlier).

Small noncleaved cell lymphoma (*Burkitt's lymphoma*) accounts for ~20% of the cases of lymphoma in patients with AIDS. It is most frequent in patients 10–19 years old and usually demonstrates characteristic c-*myc* translocations from chromosome 8 to chromosomes 14 or 22. Burkitt's lymphoma is not commonly seen in the setting of immunodeficiency other than HIV-associated immunodeficiency, and the incidence of this particular tumor is more than 1000-fold higher in the setting of HIV infection than in the general population. In contrast to African Burkitt's lymphoma, where 97% of the cases contain EBV genome, only 50% of HIV-associated Burkitt's lymphomas are EBV-positive.

Primary CNS lymphoma accounts for ~20% of the cases of lymphoma in patients with HIV infection. In contrast to HIV-associated Burkitt's lymphoma, primary CNS lymphomas are usually positive for EBV. In one study, the incidence of Epstein-Barr positivity was 100%. This malignancy does not have a predilection for any particular age group. The median CD4+ T cell count at the time of diagnosis is ~50/μL. Thus, CNS lymphoma generally presents at a later stage of HIV infection than does systemic lymphoma. This may explain, at least in part, the poorer prognosis for this subset of patients.

The clinical presentation of lymphoma in patients with HIV infection is quite varied, ranging from focal seizures to rapidly growing mass lesions in the oral mucosa **(Fig. 93-44)** to persistent unexplained fever. At least 80% of patients present with extranodal disease, and a similar percentage have B-type symptoms of fever, night sweats, or weight loss. Virtually any site in the body may be involved. The most common extranodal site is the CNS, which is involved in approximately one-third of all patients with lymphoma. Approximately 60% of these cases are primary CNS lymphoma. Primary CNS lymphoma generally presents with focal neurologic deficits, including cranial nerve findings, headaches, and/or seizures. MRI or CT generally reveals a limited number (one to three) of 3- to 5-cm lesions **(Fig. 93-45)**. The lesions often show ring enhancement on contrast administration and may occur in any location. Contrast enhancement is usually less pronounced than that seen with toxoplasmosis. Locations that are most commonly involved with CNS lymphoma are deep in the white matter. The main diseases in the differential diagnosis are cerebral toxoplasmosis and cerebral Chagas' disease. In addition to the 20% of lymphomas in HIV-infected individuals that are primary CNS lymphomas, CNS disease is also seen in HIV-infected patients with systemic lymphoma. Approximately 20% of patients with systemic lymphoma have CNS disease in the form of leptomeningeal

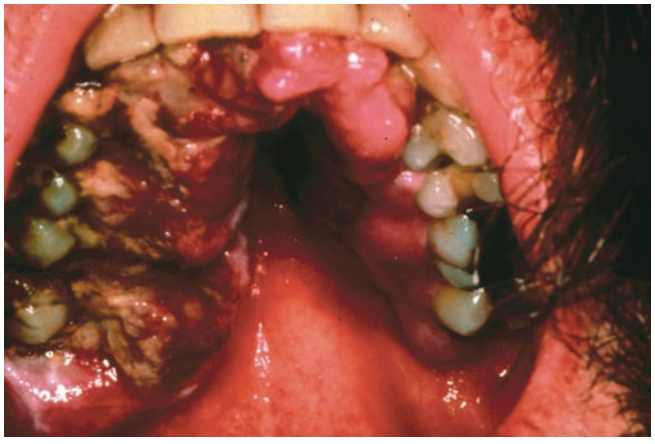


FIGURE 93-44
Immunoblastic lymphoma involving the hard palate of a patient with AIDS.

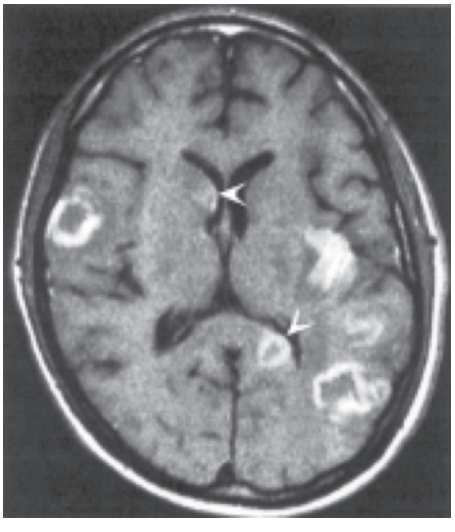


FIGURE 93-45
Central nervous system lymphoma. Postcontrast T1-weighted MRI scan in a patient with AIDS, an altered mental status, and hemiparesis. Multiple enhancing lesions, some ring-enhancing, are present. The left sylvian lesion shows gyral and subcortical enhancement, and the lesions in the caudate and splenium (*arrowheads*) show enhancement of adjacent ependymal surfaces.

involvement. This fact underscores the importance of lumbar puncture in the staging evaluation of patients with systemic lymphoma.

Systemic lymphoma is seen at earlier stages of HIV infection than primary CNS lymphoma. In one series the mean CD4+ T cell count was 189/μL. In addition to lymph node involvement, systemic lymphoma may commonly involve the GI tract, bone marrow, liver, and lung. GI tract involvement is seen in ~25% of patients. Any site in the GI tract may be involved, and patients may complain of difficulty swallowing or abdominal pain. The diagnosis is usually suspected on the basis of CT or MRI of the abdomen. Bone marrow involvement is seen in ~20% of patients and may lead to pancytopenia. Liver and lung involvement are each seen in ~10% of patients. Pulmonary disease may present as a mass lesion, multiple nodules, or an interstitial infiltrate.

Both conventional and unconventional approaches have been employed in an attempt to treat HIV-related lymphomas. Systemic lymphoma is generally treated by the oncologist with combination chemotherapy. Earlier disappointing figures are being replaced with more optimistic results for the treatment of systemic lymphoma following the availability of more effective cART and the use of rituximab in CD20+ tumors. While there is controversy regarding the use of antiretrovirals during chemotherapy, there is no question that their use overall in patients with HIV lymphoma has improved survival. As in most situations in patients with HIV disease, those with the higher CD4+ T cell counts tend to fare better. Response rates as high as 72% with a median survival of 33 months and disease-free intervals up to 9 years have been reported. Treatment of primary CNS lymphoma remains a significant challenge. Treatment is complicated by the fact that this illness usually occurs in patients with advanced HIV disease. Palliative measures such as radiation therapy provide some relief. The prognosis remains poor in this group, with a 2-year survival rate of 29%.

Multicentric Castleman's disease is a KSHV-associated lymphoproliferative disorder that is seen with an increased frequency in patients with HIV infection. While not a true malignancy, it shares many features with lymphoma, including generalized lymphadenopathy, hepatosplenomegaly, and systemic symptoms of fever, fatigue, and weight loss. Pulmonary symptoms may be seen in ~50% of patients. KS is present in 75–82% of cases. Lymph node biopsies reveal a predominance of interfollicular plasma cells and/or germinal centers with vascularization and an "onionskin" (hyaline vascular) appearance. Prior to the availability of cART, HIV-infected patients with multicentric Castleman's disease had a 15-fold increased risk of developing non-Hodgkin's lymphoma compared with HIV-infected patients in general. Treatment typically involves chemotherapy. Anecdotal reports of success with rituximab suggest that more specific treatment may be successful, although in one series treatment with rituximab was associated with worsening of coexisting KS. The median survival of patients with treated multicentric Castleman's disease pre-cART was 14 months. This has increased to a 2-year survival rate of more than 90% in the era of cART.

Evidence of infection with *human papillomavirus* (HPV), associated with *intraepithelial dysplasia of the cervix* or *anus*, is approximately twice as common in HIV-infected individuals as in the general population and can lead to intraepithelial neoplasia and eventually invasive cancer. In a series of studies, HIV-infected men were examined for evidence of anal dysplasia, and Papanicolaou (Pap) smears were found to be abnormal in 20–80%. These changes tend to persist and are generally not affected by cART, raising the possibility of a subsequent transition to a more malignant condition. While the incidence of an abnormal Pap smear of the cervix is ~5% in otherwise healthy women, the incidence of abnormal cervical smears in women with HIV infection is 30–60%, and *invasive cervical cancer* is included as an AIDS-defining condition. Thus far, however, only small increases in the incidence of cervical or anal cancer have been seen as a consequence of HIV infection. However, given this high rate of dysplasia, a comprehensive gynecologic and rectal examination, including Pap smear, is indicated at the initial evaluation and 6 months later for all patients with HIV infection. If these examinations are negative at both time points, the patient should be followed with yearly evaluations. If an initial or repeat Pap smear shows evidence of severe inflammation with reactive squamous changes, the next Pap smear should be performed at 3 months. If, at any time, a Pap smear shows evidence of squamous intraepithelial lesions, colposcopic examination with biopsies as indicated should be performed. The 2-year survival rate for HIV-infected patients with invasive cervical cancer is 64% compared with 79% in non-HIV-infected patients. The most common HPV genotypes in the general population and the genotypes upon which current HPV vaccines are based are 16 and 18. This is not the case in the HIV-infected population, where other genotypes such as 56 and 53 predominate. This raises concerns as to the potential effectiveness of the current HPV vaccines for HIV-infected patients.

IDIOPATHIC CD4+ T LYMPHOCYTOPENIA

A syndrome was recognized in 1992 that was characterized by an absolute CD4+ T cell count of <300/μL or <20% of total T cells on a minimum of two occasions at least 6 weeks apart; no evidence of HIV-1, HIV-2, HTLV-I, or HTLV-II on testing; and the absence of any defined immunodeficiency or therapy associated with decreased levels of CD4+ T cells. By mid-1993, ~100 patients had been described. After extensive multicenter investigations, a series of reports were published in early 1993, which together allowed a number of conclusions. Idiopathic CD4+ lymphocytopenia (ICL) is a very rare syndrome, as determined by studies of blood donors and cohorts of HIV-seronegative men who have sex with men. Cases were clearly identified as early as 1983 and were remarkably similar to the clinical features of ICL

that had been identified decades earlier. The definition of ICL based on CD4+ T cell counts coincided with the ready availability of testing for CD4+ T cells in patients suspected of being immunodeficient. Although, as a result of immune deficiency, certain patients with ICL develop some of the opportunistic diseases (particularly cryptococcosis, nontuberculous mycobacterial infections, and cervical dysplasia) seen in HIV-infected patients, the syndrome is demographically, clinically, and immunologically unlike HIV infection and AIDS. Fewer than half of the reported ICL patients had risk factors for HIV infection, and there were wide geographic and age distributions. The fact that a significant proportion of patients did have risk factors probably reflects a selection bias, in that physicians who take care of HIV-infected patients are more likely to monitor CD4+ T cells. Approximately half of the patients are women, compared with approximately one-third among HIV-infected individuals in the United States. Many patients with ICL remained clinically stable, and their condition did not deteriorate progressively as is common with seriously immunodeficient HIV-infected patients. Approximately 15% of patients with ICL experience spontaneous reversal of the CD4+ T lymphocytopenia. Immunologic abnormalities in ICL are somewhat different from those of HIV infection. ICL patients often have increases in CD4+ T cell activation with decreases in CD8+ T cells and B cells. Furthermore, immunoglobulin levels are either normal or, more commonly, decreased in patients with ICL, compared with the usual hypergammaglobulinemia of HIV-infected individuals. Virologic studies of these patients have revealed no evidence of HIV-1, HIV-2, HTLV-I, or HTLV-II or of any other mononuclear cell–tropic virus. Furthermore, there has been no epidemiologic evidence to suggest that a transmissible microbe was involved. The cases of ICL have been widely dispersed, with no clustering. Close contacts and sexual partners who were studied were clinically well and were serologically, immunologically, and virologically negative for HIV. ICL is a heterogeneous syndrome, and it is highly likely that there is no common cause; however, there may be common causes among subgroups of patients that are currently unrecognized.

Patients who present with laboratory data consistent with ICL should be worked up for underlying diseases that could be responsible for the immune deficiency. If no underlying cause is detected, no specific therapy should be initiated. However, if opportunistic diseases occur, they should be treated appropriately (see earlier). Depending on the level of the CD4+ T cell count, patients should receive prophylaxis for the commonly encountered opportunistic infections.

TREATMENT AIDS and Related Disorders

GENERAL PRINCIPLES OF PATIENT MANAGEMENT The CDC guidelines call for the testing for HIV infection to be a part of routine medical care. It is recommended that the patient be informed of the intention to test, as is the case with other routine laboratory determinations, and be given the opportunity to "opt out." Such an approach is critical to the goal of identifying as many infected individuals as possible since ~21% of the >1 million individuals in the United States who are HIV-infected are not aware of their status. Under these circumstances of routine testing, although it is desirable, pretest counseling may not always be built into the testing process. However, no matter how well prepared a patient is for adversity, the discovery of a diagnosis of HIV infection is a devastating event. Thus, physicians should be sensitive to this fact and, where possible, execute some degree of pretest counseling to at least partially prepare the patient should the results demonstrate the presence of HIV infection. Following a diagnosis of HIV infection, the health care provider should be prepared to immediately activate support systems for the newly diagnosed patient. These should include an experienced social worker or nurse who can spend time talking to the person and ensuring that he or she is emotionally stable. Most communities have HIV support centers that can be of great help in these difficult situations.

The treatment of patients with HIV infection requires not only a comprehensive knowledge of the possible disease processes that may occur and up-to-date knowledge of and experience with cART, but also the ability to deal with the problems of a chronic, potentially life-threatening illness. A comprehensive knowledge of internal medicine is required to deal with the changing spectrum of illness associated with HIV infection. Great advances have been made in the treatment of patients with HIV infection. The appropriate use of potent cART and other treatment and prophylactic interventions is of critical importance in providing each patient with the best opportunity to live a long and healthy life despite the presence of HIV infection. In contrast to the earlier days of this epidemic, a diagnosis of HIV infection need no longer be equated with having an inevitably fatal disease. In addition to medical interventions, the health care provider has a responsibility to provide each patient with appropriate counseling and education concerning their disease as part of a comprehensive care plan. Patients must be educated about the potential transmissibility of their infection and about the fact that while health care providers may refer to levels of the virus as "undetectable," this is more a reflection of the sensitivity of the assay being used to measure the virus than a comment on the presence or absence of the virus. It is important for patients to be aware that the virus is still present and capable of being transmitted at all stages of HIV disease. Thus, there must be frank discussions concerning sexual practices and the sharing of syringes and other paraphernalia used in illicit drug use. The treating physician not only must be aware of the latest medications available for patients with HIV infection but also must educate patients concerning the natural history of their illness and listen and be sensitive to their fears and concerns. As with other diseases, therapeutic decisions

should be made in consultation with the patient, when possible, and with the patient's proxy if the patient is incapable of making decisions. In this regard, it is recommended that all patients with HIV infection, and in particular those with CD4+ T cell counts <200/μL, designate a trusted individual with durable power of attorney to make medical decisions on their behalf, if necessary.

Following a diagnosis of HIV infection, there are several examinations and laboratory studies that should be performed to help determine the extent of disease and provide baseline standards for future reference (Table 93-18). In addition to routine chemistry, fasting lipid profile, aspartate aminotransferase, alanine aminotransferase, total and direct bilirubin, fasting glucose and hematology screening panels, Pap smear, urinalysis, and chest x-ray, one should also obtain a CD4+ T cell count, two separate plasma HIV RNA levels, an HIV resistance test, a rapid plasma reagin or VDRL test, an anti-*Toxoplasma* antibody titer, and serologies for hepatitis A, B, and C. A PPD test should be done and an MMSE performed and recorded. A pregnancy test should be done in women in whom the drug efavirenz is being considered, and HLA-B5701 testing should be done in all patients in whom the drug abacavir is being considered. Patients should be immunized with pneumococcal polysaccharide, with annual influenza shots, and, if seronegative for these viruses, with hepatitis A and hepatitis B vaccines. The status of hepatitis C infection should be determined. In addition, patients should be counseled with regard to sexual practices and needle sharing, and counseling should be offered to those whom the patient knows or suspects may also be infected. Once these baseline activities are performed, short- and long-term medical management strategies should be developed based on the most recent information available and modified as new information becomes available. The field of HIV medicine is changing rapidly, and it is difficult to remain fully up to date. Fortunately, there are a series of excellent sites on the Internet that are frequently updated, and they provide the most recent information on a variety of topics, including consensus panel reports on treatment (Table 93-19).

TABLE 93-18

INITIAL EVALUATION OF THE PATIENT WITH HIV INFECTION
History and physical examination
Routine chemistry and hematology
AST, ALT, direct and indirect bilirubin
Lipid profile and fasting glucose
CD4+ T lymphocyte count
Two plasma HIV RNA levels
HIV resistance testing
HLA-B5701 screening
RPR or VDRL test
Anti-*Toxoplasma* antibody titer
PPD skin test
Mini-Mental Status Examination
Serologies for hepatitis A, hepatitis B, and hepatitis C
Immunization with pneumococcal polysaccharide; influenza as indicated
Immunization against hepatitis A and hepatitis B if seronegative
Counseling regarding natural history and transmission
Help contacting others who might be infected

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; PPD, purified protein derivative; RPR, rapid plasma reagin; VDRL, Venereal Disease Research Laboratory.

ANTIRETROVIRAL THERAPY Combination antiretroviral therapy (cART), also referred to as highly active antiretroviral therapy (HAART), is the cornerstone of management of patients with HIV infection. Following the initiation of widespread use of cART in the United States in 1995–1996, marked declines were noted in the incidence of most AIDS-defining conditions (Fig. 93-34). Suppression of HIV replication is an important component in prolonging life as well as in improving the quality of life in patients with HIV infection. Adequate suppression requires strict adherence to prescribed regimens of antiretroviral drugs. This has been facilitated by the coformulations of antiretrovirals and the development of once-daily regimens. Unfortunately, many of the most important questions related to the treatment of HIV disease currently lack definitive answers. Among them are the questions of when therapy should be started, what the best initial regimen is, when a given regimen should be changed, and what it should be changed to when a change is made. Notwithstanding these uncertainties, the physician and patient must come to a mutually agreeable plan based on the best available data. In an effort to facilitate this process, the U.S. Department of Health and Human Services makes available on the Internet (*www.aidsinfo.nih.gov*) a series of periodically updated guidelines, including "*Principles of Therapy of HIV Infection*," "*Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents*," and "*Guidelines for the Prevention of Opportunistic Infections in Persons Infected with Human Immunodeficiency Virus*." At present, an extensive clinical trials network, involving both clinical investigators and patient advocates, is in place

TABLE 93-19

RESOURCES AVAILABLE ON THE WORLD WIDE WEB ON HIV DISEASE	
aidsinfo.nih.gov	AIDSinfo, a service of the U.S. Department of Health and Human Services, posts federally approved treatment guidelines for HIV and AIDS; provides information on federally funded and privately funded clinical trials and CDC publications and data
www.cdcnpin.org	Updates on epidemiologic data and prevention information from the CDC

Note: CDC, Centers for Disease Control and Prevention.

attempting to develop improved approaches to therapy. Consortia comprising representatives of academia, industry, independent foundations, and the federal government are involved in the process of drug development, including a wide-ranging series of clinical trials. As a result, new therapies and new therapeutic strategies are continually emerging. New drugs are often available through expanded access programs prior to official licensure. Given the complexity of this field, decisions regarding cART are best made in consultation with experts.

Currently available drugs for the treatment of HIV infection fall into four categories: those that inhibit the viral reverse transcriptase enzyme (nucleoside and nucleotide reverse transcriptase inhibitors; nonnucleoside reverse transcriptase inhibitors), those that inhibit the viral protease enzyme (protease inhibitors), those that inhibit the viral integrase enzyme (integrase inhibitors), and those that interfere with viral entry (fusion inhibitors; CCR5 antagonists) **(Table 93-20; Fig. 93-46)**.

The FDA-approved reverse transcriptase inhibitors include the *nucleoside analogues* zidovudine, didanosine, zalcitabine, stavudine, lamivudine, abacavir, and emtricitabine; the *nucleotide analogue* tenofovir; and the *nonnucleoside reverse transcriptase inhibitors* nevirapine, delavirdine, efavirenz, and etravirine (Fig. 93-46; Table 93-20). These represent the first class of drugs licensed for the treatment of HIV infection. They are indicated for this use as part of combination regimens. It should be stressed that none of these drugs should be used as monotherapy for HIV infection due to the relative ease with which drug resistance may develop under such circumstances. Thus, when lamivudine, emtricitabine, or tenofovir is used to treat hepatitis B infection in the setting of HIV infection, one should ensure that the patient is also on additional antiretroviral medication. The reverse transcriptase inhibitors block the HIV replication cycle at the point of RNA-dependent DNA synthesis, the reverse transcription step. While the nonnucleoside reverse transcriptase inhibitors are quite selective for the HIV-1 reverse transcriptase, the nucleoside and nucleotide analogues inhibit a variety of DNA polymerases in addition to those of the HIV-1 reverse transcriptase. For this reason, serious side effects are more varied with the nucleoside analogues and include mitochondrial damage that can lead to hepatic steatosis and lactic acidosis as well as peripheral neuropathy and pancreatitis. The use of either of the thymidine analogues zidovudine and stavudine has been associated with a syndrome of hyperlipidemia, glucose intolerance/insulin resistance, and fat redistribution often referred to as *lipodystrophy syndrome* (discussed earlier in "Diseases of the Endocrine System and Metabolic Disorders,").

Zidovudine (AZT; 3′-azido-2′,3′-dideoxythymidine) was the first drug approved for the treatment of HIV infection and is the prototype nucleoside analogue. These compounds, in which the hydroxyl group in the 3′ position of the ribose moiety is substituted with a hydrogen or other chemical group, act as DNA chain terminators owing to their inability to form a 3′–5′ phosphodiester linkage with another nucleoside. They bind much more avidly to the active site of the RNA-dependent DNA polymerase of HIV (reverse transcriptase) than to the active site of mammalian cell DNA polymerases; this explains their selective effect on HIV replication. Zidovudine also has a relatively high avidity for the DNA polymerase γ of human mitochondria. This may contribute to the development of the fatty liver and myopathy sometimes observed in patients taking zidovudine. As with all the nucleoside analogues, the active form of zidovudine is the triphosphate, and the rate of phosphorylation, a thymidine kinase–dependent pathway, may be different in different cells. This may explain why zidovudine is more effective at inhibiting HIV replication in some cells than in others. The clinical benefit of zidovudine was clearly established in 1986 in a phase II, randomized, placebo-controlled trial in patients with advanced HIV disease. However, while treatment of patients with early stages of HIV infection with zidovudine monotherapy was associated with increases in CD4+ T cell count, it was not associated with a better overall outcome than waiting until later to treat. Subsequent trials established the ability of this drug to dramatically decrease the incidence of perinatal transmission of HIV from infected mother to infant. Eventually a series of studies demonstrated the superiority of cART regimens over zidovudine alone, and combination therapy (discussed later) remains the standard of treatment today. Among the side effects of zidovudine at the initiation of therapy are fatigue, malaise, nausea, and headache. These side effects often subside over time. Patients on zidovudine may develop a macrocytic anemia, neutropenia, myopathy, cardiomyopathy, and lactic acidosis associated with fatty infiltration of the liver. As with every antiretroviral drug, HIV has the ability to develop resistance to zidovudine. Zidovudine resistance has been reported to occur ~6 months following the initiation of zidovudine monotherapy. More recently, zidovudine-resistant viruses have been noted in patients with acute infection prior to the initiation of therapy, implying that zidovudine-resistant viruses can be transmitted from person to person. Resistance emerges more rapidly in late-stage patients, presumably as a consequence of a greater degree of viral replication and thus a greater opportunity for mutation. A variety of amino acid changes, including substitutions, insertions, and deletions, have been reported to confer zidovudine resistance **(Fig. 93-47)**. One combination preparation, Combivir, consists of zidovudine and lamivudine, while another, Trizivir, consists of zidovudine, lamivudine, and abacavir.

Didanosine (ddI; 2′,3′-dideoxyinosine) was the second drug licensed for the treatment of HIV infection, followed shortly thereafter by zalcitabine. Didanosine is metabolized to dideoxyadenosine in vivo. It is best absorbed on an empty stomach at a high pH. The toxicity profile of didanosine is quite different from that of zidovudine. The most common toxicity is a painful sensory peripheral neuropathy that occurs in ~30% of

TABLE 93-20

ANTIRETROVIRAL DRUGS USED IN THE TREATMENT OF HIV INFECTION

DRUG	STATUS	INDICATION	DOSE IN COMBINATION	SUPPORTING DATA	TOXICITY
Nucleoside or Neucleotide Reverse Transcriptase Inhibitors					
Zidovudine (AZT, azidothymidine, Retrovir, 3′azido-3′-deoxythymidine)	Licensed	Treatment of HIV infection in combination with other antiretroviral agents	200 mg q8h or 300 mg bid	19 vs 1 death in original placebo-controlled trial in 281 patients with AIDS or ARC	Anemia, granulocytopenia, myopathy, lactic acidosis, hepatomegaly with steatosis, headache, nausea, nail pigmentation, lipid abnormalities, lipoatrophy, hyperglycemia
		Prevention of maternal-fetal HIV transmission		In pregnant women with CD4+ T cell count ≥200/μL, AZT PO beginning at weeks 14–34 of gestation plus IV drug during labor and delivery plus PO AZT to infant for 6 weeks decreased transmission of HIV by 67.5% (from 25.5% to 8.3%), *n* = 363	
Didanosine (Videx, Videx EC, ddI, dideoxyinosine, 2′, 3′-dideoxyinosine)	Licensed	For treatment of HIV infection in combination with other antiretroviral agents	Buffered: Requires 2 tablets to achieve adequate buffering of stomach acid; should be administered on an empty stomach ≥60 kg: 200 mg bid <60 kg: 125 mg bid Enteric coated: ≥60 kg: 400 mg qd < 60 kg: 250 mg qd	Clinically superior to AZT as monotherapy in 913 patients with prior AZT therapy; clinically superior to AZT and comparable to AZT + ddI and AZT + ddC in 1067 AZT-naïve patients with CD4+ T cell counts of 200–500/μL	Pancreatitis, peripheral neuropathy, abnormalities on liver function tests, lactic acidosis, hepatomegaly with steatosis, optic neuritis, nausea, hyperglycemia
Zalcitabine (ddC, HIVID, 2′3′-dideoxycytidine)	Licensed Discontinued in 2006	In combination with other antiretroviral agents for the treatment of HIV infection	0.75 mg tid	Clinically inferior to AZT monotherapy as initial treatment; clinically as good as ddI in advanced patients intolerant to AZT; in combination with AZT, was clinically superior to AZT alone in patients with AIDS or CD4+ T cell count <350/μL	Peripheral neuropathy, pancreatitis, lactic acidosis, hepatomegaly with steatosis, oral ulcers
Stavudine (d4T, Zerit, 2′3′-didehydro-3′-dideoxythymidine)	Licensed	Treatment of HIV-infected patients in combination with other antiretroviral agents	≥60 kg: 40 mg bid <60 kg: 30 mg bid	Superior to AZT with respect to changes in CD4+ T cell counts in 359 patients who had received ≥24 weeks of AZT; following 12 weeks of randomization, the CD4+ T cell count had decreased in AZT-treated controls by a mean of 22/μL, while in stavudine-treated patients, it had increased by a mean of 22/μL	Peripheral neuropathy, pancreatitis, lactic acidosis, hepatomegaly with steatosis, ascending neuromuscular weakness, lipodystrophy, lipid abnormalities, hyperglycemia

(*continued*)

TABLE 93-20

ANTIRETROVIRAL DRUGS USED IN THE TREATMENT OF HIV INFECTION (*CONTINUED*)

DRUG	STATUS	INDICATION	DOSE IN COMBINATION	SUPPORTING DATA	TOXICITY
Nucleoside or Neucleotide Reverse Transcriptase Inhibitors (*continued*)					
Lamivudine (Epivir, 2′3′-dideoxy-3′-thiacytidine, 3TC)	Licensed	In combination with other antiretroviral agents for the treatment of HIV infection	150 mg bid 300 mg qd	In combination with AZT, superior to AZT alone with respect to changes in CD4+ T cell counts in 495 patients who were zidovudine-naïve and 477 patients who were zidovudine-experienced; overall CD4+ T cell counts for the zidovudine group were at baseline by 24 weeks, while in the group treated with zidovudine plus lamivudine, they were 10–50 cells/μL above baseline; 54% decrease in progression to AIDS/death compared with AZT alone	Flare of hepatitis in HBV-co-infected patients who discontinue drug
Emtricitabine (FTC, Emtriva)	Licensed	In combination with other antiretroviral agents for the treatment of HIV infection	200 mg qd	Comparable to d4T in combination with ddI and efavirenz in 571 treatment-naïve patients; similar to 3TC in combination with AZT or d4T + NNRTI or PI in 440 patients doing well for ≥12 weeks on a 3TC regimen	Hepatotoxicity in HBV-co-infected patients who discontinue drug, skin discoloration
Abacavir (Ziagen)	Licensed	For treatment of HIV infection in combination with other antiretroviral agents	300 mg bid	Abacavir + AZT + 3TC equivalent to indinavir + AZT + 3TC with regard to viral load suppression (~60% in each group with <400 HIV RNA copies/mL plasma) and CD4+ T cell increase (~100/μL in each group) at 24 weeks	Hypersensitivity reaction In HLA-B5701+ individuals (can be fatal); fever, rash, nausea, vomiting, malaise or fatigue, and loss of appetite
Tenofovir (Viread)	Licensed	For use in combination with other antiretroviral agents when treatment is indicated	300 mg qd	Reduction of ~0.6 log in HIV-1 RNA levels when added to background regimen in treatment-experienced patients	Renal osteomalacia, flare of hepatitis in HBV-co-infected patients who discontinue drug
Nonnucleoside Reverse Transcriptase Inhibitors					
Delavirdine (Rescriptor)	Licensed	For use in combination with appropriate antiretrovirals when treatment is warranted	400 mg tid	Delavirdine + AZT superior to AZT alone with regard to viral load suppression at 52 weeks	Skin rash, abnormalities in liver function tests
Nevirapine (Viramune)	Licensed	In combination with other antiretroviral agents for treatment of progressive HIV infection	200 mg/d × 14 days, then 200 mg bid *or* 400 mg extended-release qd	Increase in CD4+ T cell count, decrease in HIV RNA when used in combination with nucleosides	Skin rash, hepatotoxicity

(*continued*)

TABLE 93-20

ANTIRETROVIRAL DRUGS USED IN THE TREATMENT OF HIV INFECTION (*CONTINUED*)

DRUG	STATUS	INDICATION	DOSE IN COMBINATION	SUPPORTING DATA	TOXICITY
Nonnucleoside Reverse Transcriptase Inhibitors (*continued*)					
Efavirenz (Sustiva)	Licensed	For treatment of HIV infection in combination with other antiretroviral agents	600 mg qhs	Efavirenz + AZT + 3TC comparable to indinavir + AZT + 3TC with regard to viral load suppression (a higher percentage of the efavirenz group achieved viral load <50 copies/mL, but the discontinuation rate in the indinavir group was unexpectedly high, accounting for most treatment "failures"); CD4 cell increase (~140/μL in each group) at 24 weeks	Rash, dysphoria, elevated liver function tests, drowsiness, abnormal dreams, depression, lipid abnormalities, potentially teratogenic
Etravirine (Intelence)	Licensed	In combination with other antiretroviral agents in treatment-experienced patients whose HIV is resistant to nonnucleoside reverse transcriptase inhibitors and other antiretroviral medications	200 mg bid	Higher rates of HIV RNA suppression to <50 copies/mL (56% vs 39%); greater increases in CD4+ T cell count (89 vs 64 cells) compared to placebo when given in combination with an optimized background regimen	Rash, nausea, hypersensitivity reactions
Rilpivirine (Edurant)	Licensed	In combination with other drugs in previously untreated patients when treatment is indicated	25 mg qd	Non-inferior to efavirenz with respect to suppression at week 48 in 1368 treatment-naive individuals	Nausea, dizziness, somnolence, vertigo, less CNS toxicity and rash than efavirenz
Protease Inhibitors					
Saquinavir mesylate (Invirase—hard-gel capsule)	Licensed	In combination with other antiretroviral agents when therapy is warranted	1000 mg + 100 mg ritonavir bid	Increases in CD4+ T cell counts, reduction in HIV RNA most pronounced in combination therapy with ddC; 50% reduction in first AIDS-defining event or death in combination with ddC compared with either agent alone	Diarrhea, nausea, headaches, hyperglycemia, fat redistribution, lipid abnormalities, PR and QT interval prolongation
(Fortovase—soft-gel capsule)	Licensed Discontinued 2006	For use in combination with other antiretroviral agents when treatment is warranted	1200 mg tid	Reduction in the mortality rate and AIDS-defining events for patients who received hard-gel formulation in combination with ddC	Diarrhea, nausea, abdominal pain, headaches, hyperglycemia, fat redistribution, lipid abnormalities

(*continued*)

TABLE 93-20

ANTIRETROVIRAL DRUGS USED IN THE TREATMENT OF HIV INFECTION (*CONTINUED*)

DRUG	STATUS	INDICATION	DOSE IN COMBINATION	SUPPORTING DATA	TOXICITY
Protease Inhibitors (*continued*)					
Ritonavir (Norvir)	Licensed	In combination with other antiretroviral agents for treatment of HIV infection when treatment is warranted	600 mg bid (also used in lower doses as pharmacokinetic booster)	Reduction in the cumulative incidence of clinical progression or death from 34 to 17% in patients with CD4+ T cell count <100/μL treated for a median of 6 months	Nausea, abdominal pain, hyperglycemia, fat redistribution, lipid abnormalities; may alter levels of many other drugs, including saquinavir; paresthesias, hepatitis
Indinavir sulfate (Crixivan)	Licensed	For treatment of HIV infection in combination with other antiretroviral agents when antiretroviral treatment is warranted	800 mg q8h or 800 mg + 100 mg ritonavir bid or 1000 mg q8h when used with efavirenz or nevirapine	Increase in CD4+ T cell count by 100/μL and 2-log decrease in HIV RNA levels when given in combination with zidovudine and lamivudine; decrease of 50% in risk of progression to AIDS or death when given with zidovudine and lamivudine compared with zidovudine and lamivudine alone	Nephrolithiasis, indirect hyperbilirubinemia, hyperglycemia, fat redistribution, lipid abnormalities, nausea, transaminase elevations, headache
Nelfinavir mesylate (Viracept)	Licensed	For treatment of HIV infection in combination with other antiretroviral agents when antiretroviral therapy is warranted	750 mg tid or 1250 mg bid	2.0-log decline in HIV RNA when given in combination with stavudine	Diarrhea, loose stools, hyperglycemia, fat redistribution, lipid abnormalities, transaminase elevations
Amprenavir (Agenerase)	Licensed	In combination with other antiretroviral agents for treatment of HIV infection	Amprenavir: 1200 mg bid or 600 mg + 100 mg ritonavir bid or 1200 mg + 200 mg ritonavir qd	In treatment-naïve patients, amprenavir + AZT + 3TC superior to AZT + 3TC with regard to viral load suppression (53% vs 11% with <400 HIV RNA copies/mL plasma at 24 weeks); CD4+ T cell responses similar between treatment groups; in treatment-experienced patients, amprenavir + NRTIs similar to indinavir + NRTIs with regard to viral load suppression (43% vs 53% with <400 HIV RNA copies/mL plasma at 24 weeks); CD4+ T cell responses superior in the indinavir + NRTI group	Nausea, vomiting, diarrhea, rash, oral paresthesias, elevated liver function tests, hyperglycemia, fat redistribution, lipid abnormalities, headache, nephrolithiasis
Fosamprenavir (Lexiva)	Licensed		Fosamprenavir: 1400 mg bid or 700 mg + 100 mg ritonavir bid or 1400 mg + 200 mg ritonavir qd		

(*continued*)

TABLE 93-20

ANTIRETROVIRAL DRUGS USED IN THE TREATMENT OF HIV INFECTION (*CONTINUED*)

DRUG	STATUS	INDICATION	DOSE IN COMBINATION	SUPPORTING DATA	TOXICITY
Protease Inhibitors (*continued*)					
Lopinavir/ritonavir (Kaletra)	Licensed	For treatment of HIV infection in combination with other antiretroviral agents	400 mg/100 mg bid	In treatment-naïve patients, lopinavir/ritonavir + d4T + 3TC superior to nelfinavir + d4T + 3TC with regard to viral load suppression (79% vs 64% with <400 HIV RNA copies/mL at 40 weeks); CD4+ T cell increases similar in both groups	Diarrhea, hyperglycemia, fat redistribution, lipid abnormalities, nausea, pancreatitis, elevated liver function tests, PR and QT interval prolongations
Atazanavir (Reyataz)	Licensed	For treatment of HIV infection in combination with other antiretroviral agents	400 mg qd or 300 mg qd + ritonavir 100 mg qd when given with efavirenz	Comparable to efavirenz when given in combination with AZT + 3TC in a study of 810 treatment-naïve patients; comparable to nelfinavir when given in combination with d4T + 3TC in a study of 467 treatment-naïve patients	Hyperbilirubinemia, PR prolongation, nausea, vomiting, hyperglycemia, fat maldistribution, rash, transaminase elevations
Tipranavir (Aptivus)	Licensed	In combination with 200 mg ritonavir for combination therapy in treatment-experienced adults	500 mg + 200 mg ritonavir twice daily	At 24 weeks, patients with prior extensive exposure to ARV therapy showed a –0.8 log change in HIV RNA levels and a 34-cell increase in CD4+ T cells compared with –0.25 log and 4 cells in the control arm; inferior to lopinavir/ritonavir in a randomized, controlled trial in naïve patients	Diarrhea, nausea, fatigue, headache, skin rash, hepatotoxicity, intracranial hemorrhage, hyperglycemia, lipid abnormalities, fat redistribution
Darunavir (Prezista)	Licensed	In combination with 100 mg ritonavir for combination therapy in treatment-experienced adults	600 mg + 100 mg ritonavir twice daily with food	At 24 weeks, patients with prior extensive exposure to antiretrovirals treated with a new combination including darunavir showed a –1.89 log change in HIV RNA levels and a 92-cell increase in CD4+ T cells compared with –0.48 log and 17 cells in the control arm	Diarrhea, nausea, headache, skin rash, hepatoxicity, hyperlipidemia, hyperglycemia
Entry Inhibitors					
Enfuvirtide (Fuzeon)	Licensed	In combination with other agents in treatment-experienced patients with evidence of HIV-1 replication despite ongoing antiretroviral therapy	90 mg SC bid	In treatment of experienced patients, superior to placebo when added to new optimized background (37% vs 16% with <400 HIV RNA copies/mL at 24 weeks; + 71 vs + 35 CD4+ T cells at 24 weeks)	Local injection reactions, hypersensitivity reactions, increased rate of bacterial pneumonia

(*continued*)

TABLE 93-20

ANTIRETROVIRAL DRUGS USED IN THE TREATMENT OF HIV INFECTION (*CONTINUED*)

DRUG	STATUS	INDICATION	DOSE IN COMBINATION	SUPPORTING DATA	TOXICITY
Entry Inhibitors (*continued*)					
Maraviroc (Selzentry)	Licensed	In combination with other antiretroviral agents in adults infected with only CCR5-tropic HIV-1	150–600 mg bid depending on concomitant medications (see text)	At 24 weeks, among 635 patients with CCR5-tropic virus and HIV-1 RNA >5000 copies/mL despite at least 6 months of prior therapy with at least 1 agent from 3 of the 4 antiretroviral drug classes, 61% of patients randomized to maraviroc achieved HIV RNA levels <400 copies/mL compared with 28% of patients randomized to placebo	Hepatotoxicity, nasopharyngitis, fever, cough, rash, abdominal pain, dizziness, musculoskeletal symptoms
Integrase Inhibitors					
Raltegravir (Isentress)	Licensed	In combination with other antiretroviral agents	400 mg bid	At 24 weeks, among 436 patients with 3-class drug resistance, 76% of patients randomized to receive raltegravir achieved HIV RNA levels <400 copies/mL compared with 41% of patients randomized to receive placebo	Nausea, headache, diarrhea, CPK elevation, muscle weakness and rhabdomyolysis
Elvitegravir	Investigational	In combination	150 mg qdt pharmacoenhancing agent cobicistat	Non-inferior to raltegravir in treatment-experienced patients	

Abbreviations: ARC, AIDS-related complex; NRTIs, nonnucleoside reverse transcriptase inhibitors.

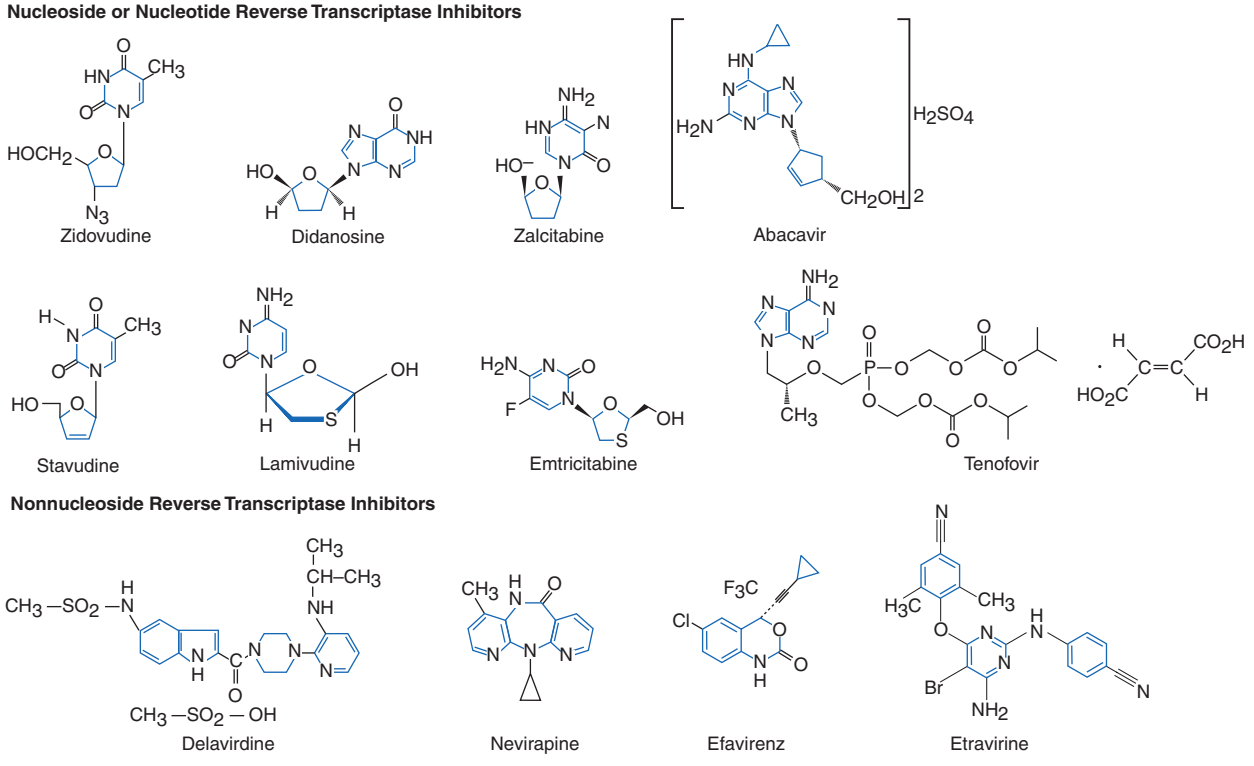
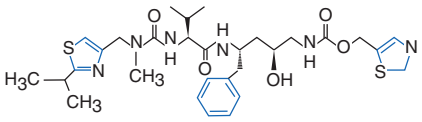
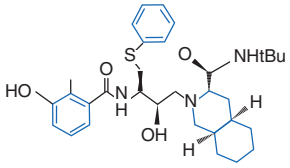


FIGURE 93-46
Molecular structures of antiretroviral agents.

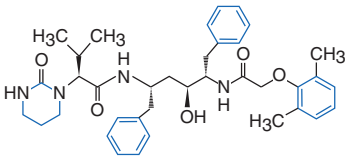
Protease Inhibitors



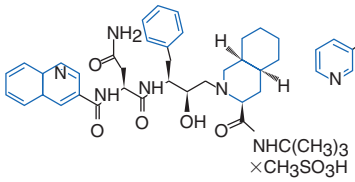
Ritonavir



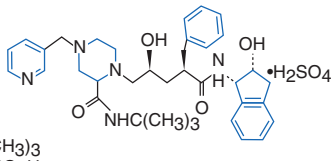
Nelfinavir mesylate



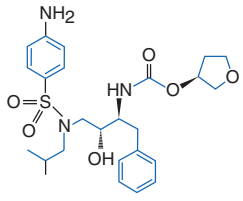
Lopinavir



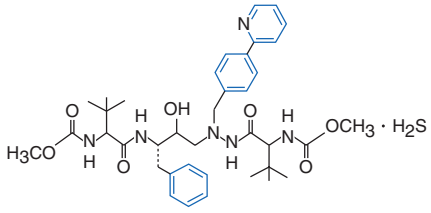
Saquinavir mesylate



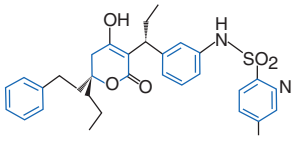
Indinavir sulfate



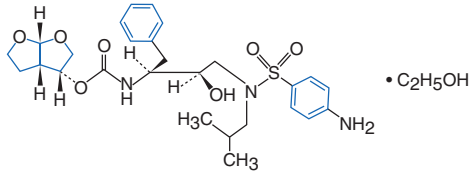
Amprenavir



Atazanavir

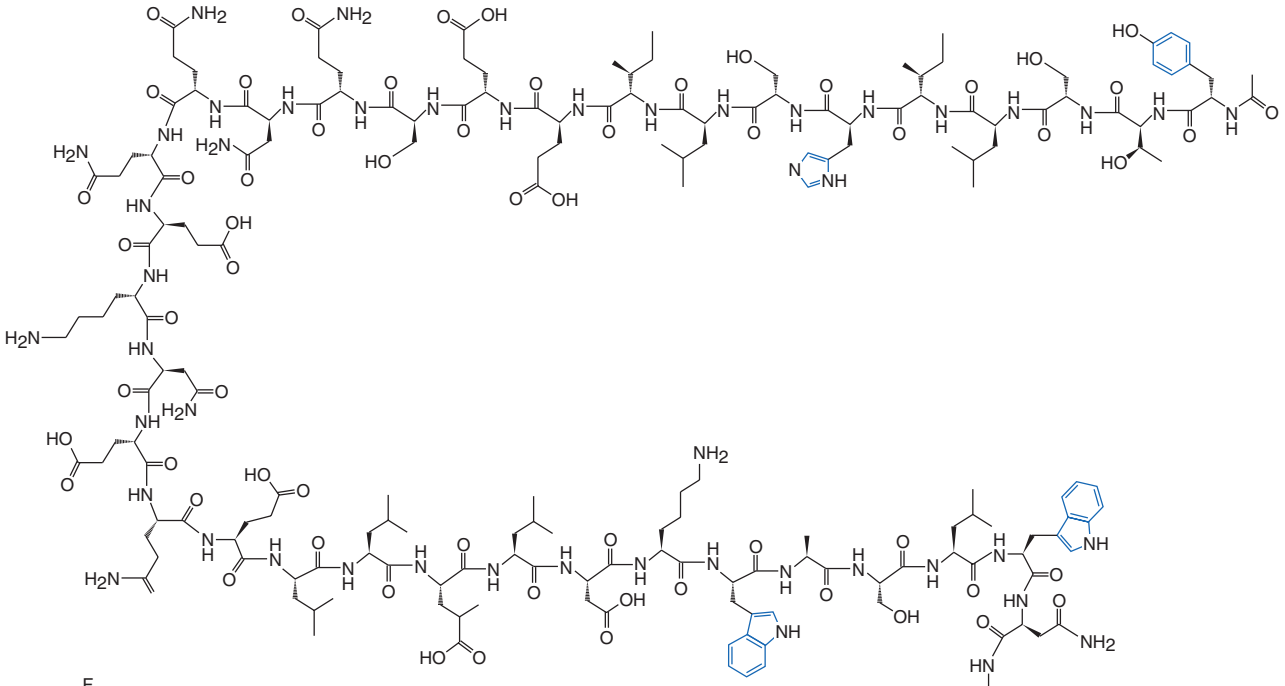


Tipranavir

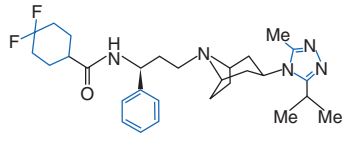


Darunavir

Entry Inhibitors

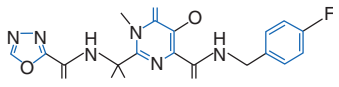


Enfuvirtide



Maraviroc

Integrase Inhibitor



Raltegravir

FIGURE 93-46
(***Continued***)

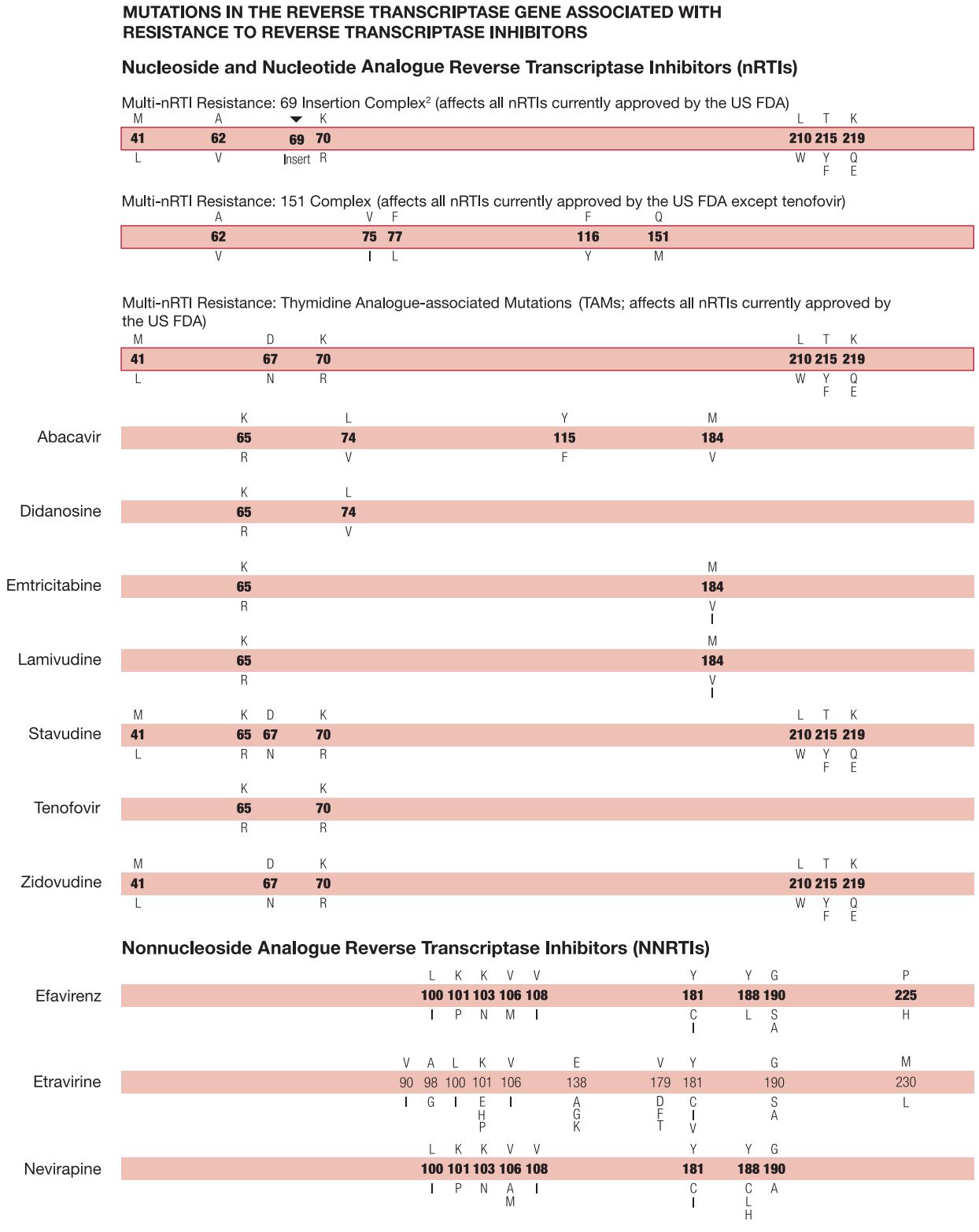
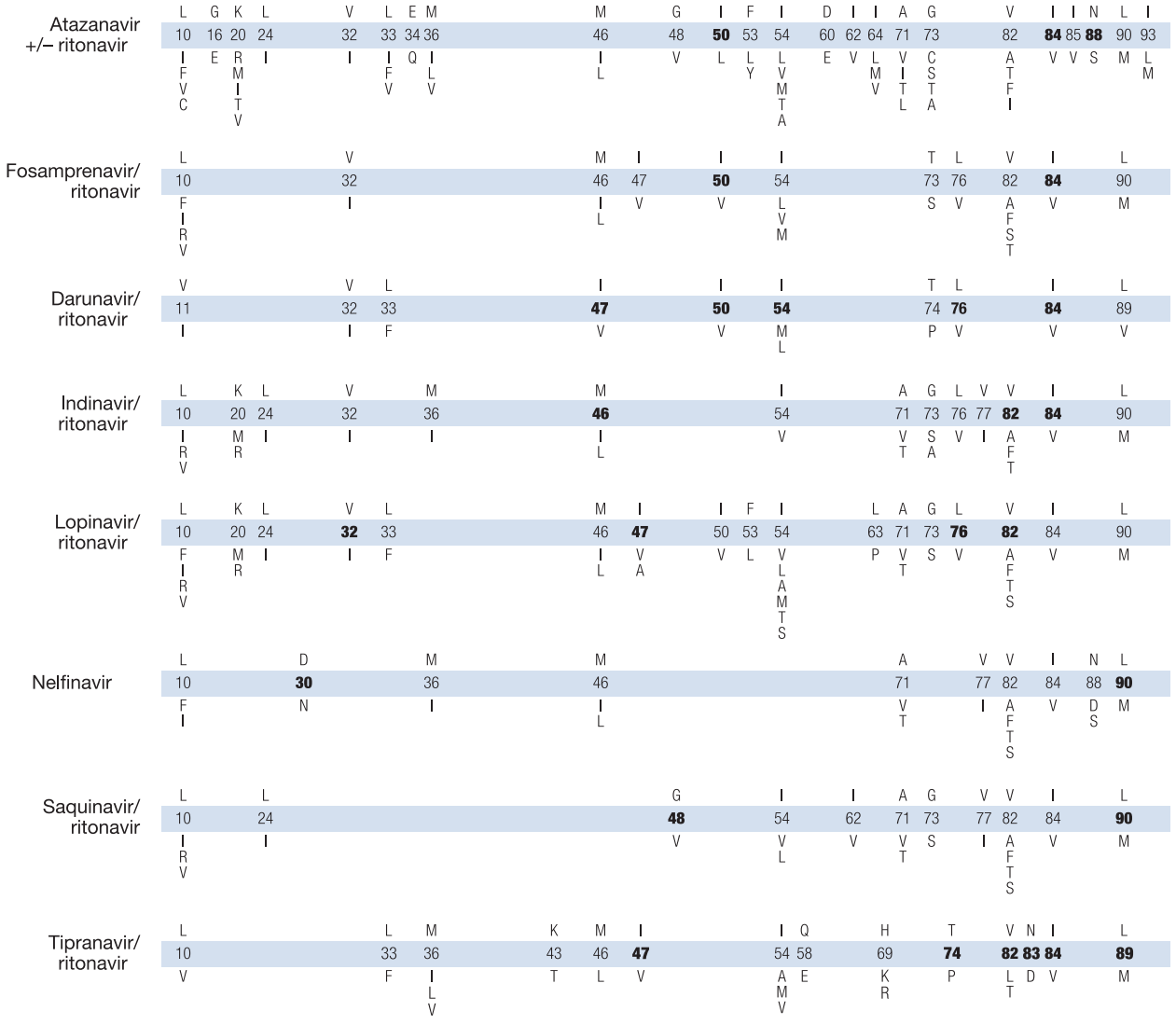


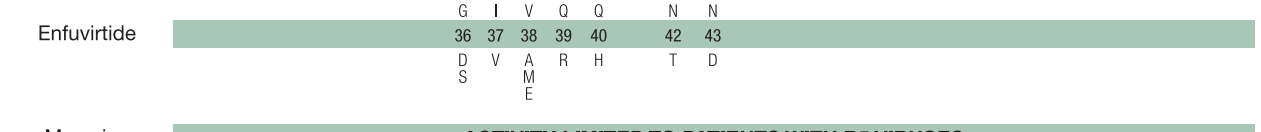
FIGURE 93-47

Amino acid substitutions conferring resistance to antiretroviral drugs. For each amino acid residue, the letter above the bar indicates the amino acid associated with wild-type virus and the letter(s) below indicate the substitution(s) that confer viral resistance. The number shows the position of the mutation in the protein. Mutations selected by protease inhibitors in Gag cleavage sites are not listed. HR1 indicates first heptad repeat; TAMs indicates nRTI-associated mutations; nRTI indicates nucleoside reverse transcriptase inhibitor; NNRTI indicates nonnucleoside reverse transcriptase inhibitor; PI indicates protease inhibitor. Amino acid abbreviations: A, alanine; C, cysteine; D, aspartate; E, glutamic acid; F, phenylalanine; G, glycine; H, histidine; I, isoleucine; K, lysine; L, leucine; M, methionine; N, asparagine; P, proline; Q, glutamine; R, arginine; S, serine; T, threonine; V, valine; W, tryptophan; Y, tyrosine. (*Reprinted with permission from the International AIDS Society—USA. VA Johnson et al: Update of the Drug Resistance Mutations in HIV-1: December 2010. Topics in HIV Medicine 18:156–163, 2010. Updated information [with thorough explanatory notes] is available at www.iasusa.org.*)

MUTATIONS IN THE PROTEASE GENE ASSOCIATED WITH RESISTANCE TO PROTEASE INHIBITORS



MUTATIONS IN THE ENVELOPE GENE ASSOCIATED WITH RESISTANCE TO ENTRY INHIBITORS



MUTATIONS IN THE INTEGRASE GENE ASSOCIATED WITH RESISTANCE TO INTEGRASE INHIBITORS

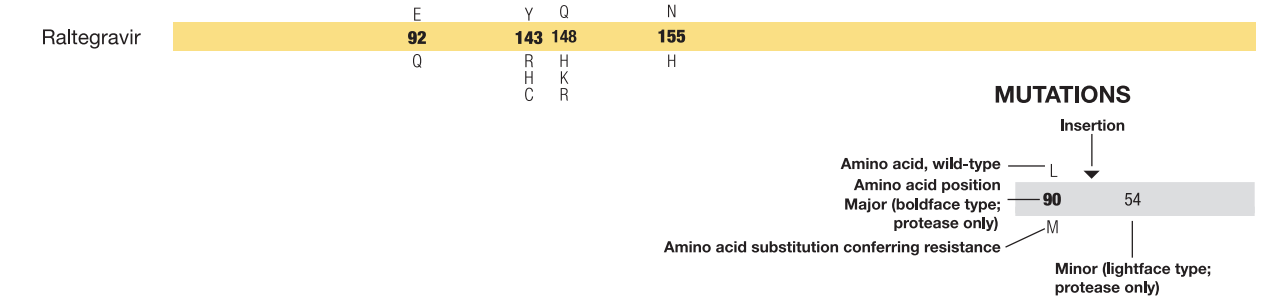


FIGURE 93-47
(*Continued*)

patients receiving >400 mg/d. It generally resolves with discontinuation of the drug and may not recur if the drug is resumed at a reduced dose. At higher doses than are currently used, one may see pancreatitis in ~10% of patients. Pancreatitis associated with didanosine therapy can be fatal. Didanosine should be discontinued if a patient experiences abdominal pain consistent with pancreatitis or if an elevated serum amylase or lipase level is found in association with an edematous pancreas on ultrasound. Didanosine is contraindicated in patients with a prior history of pancreatitis, regardless of etiology. A higher incidence of didanosine-associated toxicities has been seen when it is used in combination with stavudine, hydroxyurea, ribavirin, or tenofovir.

Zalcitabine (ddC; 2′,3′-dideoxycytidine) is rarely used today in the management of patients with HIV infection and was discontinued from the U.S. market in 2006. Among the nucleoside analogues licensed for the treatment of HIV infection, it is probably the weakest. The main toxicities of ddC are peripheral neuropathy and pancreatitis.

Stavudine (d4T; 2′,3′-didehydro-3′-deoxythymidine) was the fourth drug licensed for the treatment of HIV infection. Like zidovudine, stavudine is a thymidine analogue. These two drugs are antagonistic in vitro and in vivo and should not be given together. Stavudine has been associated with a higher incidence of mitochondrial toxicity than the other licensed nucleoside analogues. Peripheral neuropathy, lipoatrophy, lactic acidosis, and hepatic steatosis are the main toxicities of stavudine.

Lamivudine (3TC; 2′,3′-dideoxy-3′-thiacytidine) is the fifth of the nucleoside analogues to be licensed in the United States. It is the negative enantiomer of a dideoxy analogue of cytidine. In actual practice, lamivudine or the closely related drug emtricitabine (see later) is a frequent element of many different combination regimens currently in use. These two drugs and the nucleotide reverse transcriptase inhibitor tenofovir (see later) also have activity against hepatitis B virus. For this reason flares of hepatitis may be seen in co-infected patients starting and/or or stopping any of these three agents due to the confounding issues of direct effects on hepatitis B, direct effects on HIV, and immune reconstitution (see earlier). To prevent the development of resistant strains of HIV, these drugs should never be used on their own for the treatment of hepatitis B in the patient with HIV infection. Lamivudine is available either alone or in coformulations including zidovudine and/or abacavir (Table 93-21). One reason behind the excellent synergy seen between lamivudine and the other nucleoside analogues may be that strains of HIV resistant to lamivudine (M184V substitution) appear to have enhanced sensitivity to other nucleosides, and thus development of dual resistance is more difficult. In addition, there is a suggestion that 3TC-resistant strains of HIV may be less virulent and are less able to generate new mutants than are strains of HIV that are 3TC-sensitive. Lamivudine is among the best tolerated and least toxic of the nucleoside analogues.

TABLE 93-21

COMBINATION FORMULATIONS OF ANTIRETROVIRAL DRUGS

NAME	COMBINATION
Combivir	Zidovudine + lamivudine
Epzicom	Zidovudine + abacavir
Trizivir	Zidovudine + lamivudine + abacavir
Truvada	Tenofovir + emtricitabine
Atripla	Tenofovir + emtricitabine + efavirenz
Triomune[a]	Stavudine + lamivudine + nevirapine

[a]Not licensed in the United States.

Emtricitabine (FTC; 5-fluoro-1-(2R,5S)-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine) is the negative enantiomer of a thio analogue of cytidine with a fluorine in the 5 position. It is licensed for use in combination with other antiretroviral agents for treatment of HIV-1 infection in adults. Compared with lamivudine, it is similar in activity and has a longer half-life. It is available either alone or coformulated with tenofovir or tenofovir and efavirenz (Table 93-21). As with lamivudine, resistance to emtricitabine is associated with the M184V mutation in reverse transcriptase. Viruses showing the K65R mutation in reverse transcriptase may have reduced susceptibility to emtricitabine.

Abacavir {(1*S*,*cis*)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol sulfate (salt) (2:1)} is a synthetic carbocyclic analogue of the nucleoside guanosine. It is licensed to be used in combination with other antiretroviral agents for the treatment of HIV-1 infection. Hypersensitivity reactions that may occur with initial therapy or rechallenge have been reported in ~4% of patients treated with this drug, and patients developing signs or symptoms of hypersensitivity such as fever, skin rash, fatigue, and GI symptoms should discontinue the drug and not restart it. Fatal hypersensitivity reactions have been reported with rechallenge. Abacavir hypersensitivity occurs with a higher frequency in patients who are HLA-B5701-positive. It is recommended that patients be screened for HLA-B5701 prior to initiation of abacavir and that abacavir only be used as a last resort and with close monitoring in patients who are HLA-B5701-positive. Abacavir-resistant strains of HIV are typically also resistant to lamivudine, emtricitabine, didanosine, and zalcitabine. Abacavir is formulated alone as well as in combination with lamivudine or zidovudine and lamivudine.

Tenofovir disoproxil fumarate (9-[(*R*)-2-[[bis[[(isopropoxycarbonyl)oxy]methoxy]phosphinyl]methoxy]propyl] adenine fumarate (1:1)) is an acyclic nucleoside phosphonate diester analogue of adenosine monophosphate. It undergoes diester hydrolysis to form the nucleoside monophosphate tenofovir and is the first nucleotide analogue to be licensed for treatment of HIV infection. It is indicated in combination with other

antiretroviral agents for the treatment of HIV-1 infection. HIV isolates with increased resistance typically express a K65R mutation in reverse transcriptase and a three- to fourfold reduction in sensitivity to tenofovir. Tenofovir is primarily eliminated by the kidneys, and renal impairment including a Fanconi-like syndrome with hypophosphatemia may occur. Tenofovir is contraindicated in patients with renal impairment. Coadministration with didanosine leads to a 60% increase in didanosine levels, and thus doses of didanosine need to be adjusted and patients monitored carefully if these two drugs are used in combination. In addition, CD4+ T cell increases may be blunted in patients on this combination. Coadministration of tenofovir with atazanavir leads to a decrease in atazanavir levels and, thus, low-dose ritonavir (see later) needs to be added when these drugs are used in combination. Tenofovir is available alone and coformulated with emtricitabine or emtricitabine and efavirenz.

Nevirapine, *delavirdine*, *efavirenz, etravirine*, and *rilpivirine* are nonnucleoside inhibitors of the HIV-1 reverse transcriptase and are licensed for use in combination with nucleoside analogues for the treatment of HIV-infected adults. Coformulations that include efavirenz or nevirapine are available (Table 93-21). These agents inhibit reverse transcriptase by binding to regions of the enzyme outside the active site and causing conformational changes in the enzyme that render it inactive. Although these agents are active in the nanomolar range, they are also very selective for the reverse transcriptase of HIV-1, have no activity against HIV-2, and, when used as monotherapy, are associated with the rapid emergence of drug-resistant mutants (Table 93-20; Fig. 93-47). Efavirenz and rilpivirine are administered once a day, nevirapine and etravirine twice a day, and delavirdine three times a day. All are associated with the development of a maculopapular rash, generally seen within the first few weeks of therapy. While it is possible to treat through this rash, it is important to be sure that one is not dealing with a more severe eruption such as Stevens-Johnson syndrome by looking carefully for signs of mucosal involvement, significant fever, or painful lesions with desquamation. Severe, life-threatening, and in some cases fatal hepatotoxicity, including fulminant and cholestatic hepatitis, hepatic necrosis, and hepatic failure, have been reported in patients treated with nevirapine. There is a suggestion that this is more common in women with higher CD4+ T cell counts. Many patients treated with efavirenz note feeling light-headed, dizzy, or out of sorts following the initiation of therapy. Some complain of vivid dreams. These symptoms tend to disappear after several weeks of therapy. Aside from difficulties with dreams, taking efavirenz at bedtime may minimize the side effects. Efavirenz may cause fetal harm when administered during the first trimester to a pregnant woman. Women of childbearing potential should undergo pregnancy testing prior to initiation of efavirenz. Efavirenz is commonly used in combination with two nucleoside analogues as part of initial treatment regimens. Etravirine is a diarylpyrimidine derivative currently licensed for treatment of HIV infection in combination with other agents. In contrast to the other nonnucleoside reverse transcriptase inhibitors, which all exhibit cross-resistance, etravirine may be active against strains of HIV that are resistant to other nonnucleoside reverse transcriptase inhibitors. Among its side effects are rash, headache, nausea, and diarrhea. Rilpivirine is effective across a broad range of NNRTI-resistant viruses and shares cross-resistance with etravirine. It is better tolerated and has a higher rate of virologic failure than efavirenz, particularly in those with HIV RNA >100,000.

The HIV-1 protease inhibitors (saquinavir, indinavir, ritonavir, nelfinavir, amprenavir, fosamprenavir, lopinavir/ritonavir, atazanavir, tipranavir, and darunavir) are a major part of the therapeutic armamentarium of antiretrovirals. When used as part of initial regimens in combination with reverse transcriptase inhibitors, these agents have been shown to be capable of suppressing levels of HIV replication to under 50 copies per milliliter in the majority of patients for a minimum of 5 years. As in the case of reverse transcriptase inhibitors, resistance to protease inhibitors can develop rapidly in the setting of monotherapy, and thus these agents should be used only as part of combination therapeutic regimens. A summary of known resistance mutations for protease inhibitors is shown in Fig. 93-47.

Saquinavir was the first of the HIV-1 protease inhibitors to be licensed. It is typically given with low doses of ritonavir to obtain therapeutic levels. Saquinavir is metabolized by the cytochrome P450 system in both the GI tract and the liver. Low-dose ritonavir results in inhibition of cytochrome P450. Thus, when both drugs are administered together there is an increase in saquinavir levels. This use of low doses of ritonavir to provide pharmacodynamic boosting of other agents is a common strategy in HIV therapy. Saquinavir is among the best-tolerated protease inhibitors.

Ritonavir was the first protease inhibitor for which clinical efficacy was demonstrated. In a study of 1090 patients with CD4+ T cell counts <100/μL who were randomized to receive either placebo or ritonavir in addition to any other licensed medications, patients receiving ritonavir had a reduction in the cumulative incidence of clinical progression or death from 34% to 17%. Mortality decreased from 10.1 to 5.8%. At full doses, ritonavir is poorly tolerated. Among the main side effects are nausea, diarrhea, abdominal pain, hyperlipidemia, and circumoral paresthesia. Ritonavir has a high affinity for several isoforms of cytochrome P450 (3A4, 2D6), and its use can result in large increases in the plasma concentrations of drugs metabolized by these pathways. Among the agents affected in this manner are most other protease inhibitors, macrolide antibiotics, *R*-warfarin, ondansetron, rifabutin, most calcium channel blockers, glucocorticoids, and some of the chemotherapeutic agents used to treat KS and/or lymphomas. In addition, ritonavir may increase the activity

of glucuronyltransferases, thus decreasing the levels of drugs metabolized by this pathway. Overall, great care must be taken when prescribing additional drugs to patients taking protease inhibitors in general and ritonavir in particular. As mentioned earlier, the pharmacodynamic boosting property of ritonavir, seen with doses as low as 100–200 mg once or twice a day, is often used in the setting of cART for HIV infection to derive more convenient regimens. For example, when given with low-dose ritonavir, saquinavir and indinavir can be given on twice-a-day schedules and taken with food.

Indinavir was the first protease inhibitor used in combination with dual nucleoside therapy. The combination of zidovudine, lamivudine, and indinavir was the first "triple combination" shown to have a profound effect on HIV replication. The main side effects of indinavir are nephrolithiasis (seen in 4% of patients) and asymptomatic indirect hyperbilirubinemia (seen in 10%). Indinavir is predominantly metabolized by the liver. The dose should be lowered in patients with cirrhosis. Levels of indinavir are decreased during concurrent therapy with rifabutin, efavirenz, or nevirapine and increased during concurrent therapy with ketoconazole, delavirdine, or ritonavir. Dosages should be modified appropriately in these circumstances. (Table 93-20).

Nelfinavir was approved in 1997 and *amprenavir* was approved in 1999 for the treatment of adult or pediatric HIV infection when cART is warranted. As with most of the antiretroviral agents licensed since 1999, these approvals were based on randomized, controlled trials that demonstrated decreases in plasma HIV RNA levels and increases in CD4+ T cell counts rather than clinical endpoints. Both nelfinavir and amprenavir have unique resistance profiles. Nelfinavir resistance is associated with a D30N substitution in the protease gene. Viruses harboring this single mutation retain sensitivity to other protease inhibitors. While it has been suggested that for this reason nelfinavir is a good initial protease inhibitor, enthusiasm for its use waned following 48-week clinical trials data demonstrating the virologic inferiority of nelfinavir to lopinavir/ritonavir, fosamprenavir, and efavirenz. Protease inhibitor resistance typically involves multiple amino acid substitutions and reduced susceptibility across the class. Amprenavir resistance is associated with a unique substitution at amino acid 50 (I50V). Nelfinavir and amprenavir are both associated with GI side effects. About 1% of patients receiving amprenavir have experienced severe and life-threatening skin reactions. An additional disadvantage of amprenavir is that the original formulation requires the patient to take 8 large capsules twice a day. Amprenavir has largely been replaced by fosamprenavir (see next).

Fosamprenavir was licensed in 2003 for the treatment of HIV infection in combination with other antiretroviral agents in adults. It is a prodrug of amprenavir that is rapidly converted to amprenavir by cellular phosphatases. It is supplied as a 700-mg tablet. The recommended dosage regimens are as follows: 1400 mg twice a day; 700 mg twice a day with ritonavir, 100 mg twice a day; or 1400 mg once a day with ritonavir, 200 mg once a day. As noted earlier, ritonavir-boosted fosamprenavir has been shown to have efficacy comparable to lopinavir/ritonavir and to efavirenz in combination regimens.

Lopinavir/ritonavir (Kaletra) is a fixed-dose combination of the protease inhibitors lopinavir (200 mg) and ritonavir (50 mg). It was licensed in 2000 for treatment of HIV-1 infection in adults and children in combination with other agents. A main advantage of this pill is that it combines the pharmacologic enhancement of low-dose ritonavir with a second protease inhibitor in a single capsule. In a randomized, controlled trial, this combination capsule was found to be superior to nelfinavir. Its main complications are GI upset and hyperlipidemia.

Atazanavir is an azapeptide inhibitor of the HIV-1 protease that was licensed in 2003. An advantage of atazanavir is that total cholesterol and triglyceride levels do not increase as much with atazanavir as with other protease inhibitors. This coupled with the fact that it can be given on a once-daily schedule has made atazanavir a popular component of initial treatment regimens. Atazanavir is associated with increases in serum bilirubin and prolongations of the ECG PR interval. Atazanavir-resistant isolates emerging in previously treatment-naïve individuals frequently harbor an I50L substitution. This mutation in some instances is associated with increased sensitivity to other protease inhibitors. Atazanavir requires an acidic gastric pH for absorption, and its use in combination with a proton pump inhibitor is contraindicated due to concerns about absorption. Atazanavir is an inhibitor of cytochrome P3A, and its use may be associated with increased levels of calcium channel blockers, macrolide antibiotics, HMG-CoA reductase inhibitors, and sildenafil. Levels of atazanavir are lower in the presence of tenofovir or efavirenz. In these settings, levels of atazanavir should be boosted with the use of low-dose ritonavir.

Tipranavir is a nonpeptidic HIV protease inhibitor licensed in 2005. It is licensed for use in combination with 200 mg ritonavir and is indicated for cART of HIV-1 infection in treatment-experienced adults or in adults with evidence of HIV-1 strains resistant to multiple protease inhibitors. Tipranavir was found to be inferior to lopinavir/ritonavir in a randomized controlled trial in naïve patients. In that study, at lower doses it was virologically inferior, while at higher doses it exhibited a greater degree of hepatotoxicity. The main side effects of tipranavir are GI intolerance and skin rash; the latter is seen in ~10% of patients and may be related to the sulfonamide moiety in the molecule. Tipranavir coadministered with ritonavir has also been associated with reports of intracranial hemorrhage as well as reports of clinical hepatitis and hepatic decompensation, including some fatalities in both settings. The risk of hepatotoxicity is increased in patients with hepatitis B or C co-infection.

Darunavir is a nonpeptidic HIV protease inhibitor initially licensed in 2006. It is indicated for coadministration with 100 mg of ritonavir and other antiretroviral agents for the treatment of HIV infection. In initial studies

in treatment-experienced subjects, 46% of patients achieved a reduction in HIV RNA viral loads to <50 copies per milliliter. Studies in treatment-naïve patients demonstrated efficacy comparable to lopinavir/ritonavir-containing regimens. Skin rash, which may be severe, is seen in 7% of patients and may be related to the sulfonamide moiety contained in the molecule. GI intolerance and headache are the other most frequent side effects.

Entry inhibitors act by interfering with the binding of HIV to its receptor or co-receptor or by interfering with the process of fusion (see earlier). The first drug in this class to be licensed was the fusion inhibitor *enfuvirtide*, or T-20, followed by the CCR5 antagonist *maraviroc*. A variety of additional small molecules that bind to HIV-1 co-receptors are currently in clinical trials.

Enfuvirtide is a linear 36-amino-acid synthetic peptide with the *N* terminus acetylated and the *C* terminus a carboxamide. It is composed of naturally occurring l-amino acid residues and interferes with the fusion of the viral and cellular membranes by binding to the HR1 region in the gp41 subunit of the HIV-1 envelope. This binding interferes with the coil-coil interaction required to approximate the viral envelope and the host cell membrane during the process of viral fusion. Enfuvirtide was licensed in 2003 for treatment of HIV-1 infection in combination with other antiretroviral agents in treatment-experienced patients with ongoing viral replication despite antiretroviral therapy. Enfuvirtide is not active against HIV-2. Enfuvirtide resistant isolates of HIV exhibit amino acid changes in positions 36–45 of gp41. In two independent studies, patients who had persistent viremia despite prior treatment with agents from all three available classes of drugs were randomized to receive an individualized regimen (based on prior treatment history and resistance profile) with or without enfuvirtide. The change in plasma HIV-1 RNA from baseline was ~1 log greater (–1.53 vs. –0.68) in patients randomized to receive enfuvirtide. Among the drawbacks of this agent are the requirement for twice-a-day injection, the occurrence of injection site reactions in close to 100% of patients, and an increase in bacterial pneumonia in the enfuvirtide-treated patients compared with the control patients (4.68 vs 0.61 events per 100 patient-years) in the phase III studies.

Maraviroc is a CCR5 antagonist that interferes with HIV binding at the stage of co-receptor engagement. It was licensed in 2007 for treatment of HIV infection in combination with other agents in treatment-experienced patients infected with only CCR5-tropic (R5) virus resistant to multiple agents. The license was extended in 2009 to include treatment-naïve patients with R5 virus. A co-receptor tropism assay should be performed if one is considering the use of maraviroc to ensure that the potential patient is harboring R5 virus. In phase III trials of treatment-experienced patients randomized to receive optimal therapy plus maraviroc or placebo, 61% of patients randomized to maraviroc achieved HIV RNA levels <400 copies/mL compared with 28% of patients randomized to placebo. An allergic reaction–associated hepatotoxicity has been reported with maraviroc. Among the most common side effects of maraviroc are dizziness due to postural hypotension, cough, fever, colds, rash, muscle and joint pain, and stomach pain. Maraviroc is a substrate of CYP3A and Pgp, and the recommend dose varies depending on concomitant medications. In combination with nucleoside analogues, tipranavir/ritonavir, enfuvirtide, and/or nevirapine, the dose is 300 mg twice daily. In the presence of CYP3A inhibitors, such as most protease inhibitors, the dose is 150 mg twice daily. In the presence of CYP3A inducers such as efavirenz, the dose is 600 mg twice daily.

The newest class of antiretroviral compounds is the *integrase inhibitors*. *Raltegravir* is an inhibitor of the viral enzyme integrase and the first of this class to be approved. Elvitegravir is currently in clinical trials. Raltegravir was approved in 2007 for treatment of HIV infection in combination with other agents in treatment-experienced patients, and the approval was extended in 2009 to include treatment-naïve patients. Raltegravir exhibits a wide range of activity against HIV-1 and HIV-2, including viruses with multiple resistance mutations to other classes of drugs. As with several other compounds, resistance to raltegravir comes at the expense of replicative fitness. In two phase III studies in which 436 patients with 3-class antiretroviral drug resistance were randomized to an optimized background regimen with raltegravir or placebo, 76% of patients receiving raltegravir achieved HIV RNA levels <400 copies/mL compared with 41% of patients randomized to the placebo arm. In contrast to many other antiretroviral drugs the side-effect profile of raltegravir is minimal, with similar side-effect profiles noted for the raltegravir and placebo groups.

PRINCIPLES OF THERAPY The principles of therapy for HIV infection have been articulated by a panel sponsored by the U.S. Department of Health and Human Services as a working group of the NIH Office of AIDS Research Advisory Council. These principles are summarized in Table 93-22. As noted in these guidelines, cART of HIV infection does not lead to eradication or cure of HIV. Treatment decisions must take into account the fact that one is dealing with a chronic infection. While early therapy is generally the rule in infectious diseases, immediate treatment of every HIV-infected individual upon diagnosis may not be prudent, and therapeutic decisions must take into account the balance between risks and benefits. Patients initiating antiretroviral therapy must be willing to commit to life-long treatment and understand the importance of adherence to their prescribed regimen. The importance of adherence is illustrated by the observation that treatment interruption is associated with rapid increases in HIV RNA levels, rapid declines in CD4+ T cell counts, and an increased risk of clinical progression. While it seems reasonable to assume that the complications associated with cART could be minimized by regimens designed to minimize exposure to the drugs in question, all efforts to do so have paradoxically been associated with an increase in serious adverse events in the patients randomized to intermittent therapy, suggesting that some "non-AIDS-associated" serious adverse events such

TABLE 93-22

PRINCIPLES OF THERAPY FOR HIV INFECTION

1. Ongoing HIV replication leads to immune system damage and progression to AIDS.
2. Plasma HIV RNA levels indicate the magnitude of HIV replication and the rate of CD4+ T cell destruction. CD4+ T cell counts indicate the current level of competence of the immune system.
3. Rates of disease progression differ among individuals, and treatment decisions should be individualized based on plasma HIV RNA levels and CD4+ T cell counts.
4. Maximal suppression of viral replication is a goal of therapy; the greater the suppression, the less likely the appearance of drug-resistant quasispecies.
5. The most effective therapeutic strategies involve the simultaneous initiation of combinations of effective anti-HIV drugs with which the patient has not been previously treated and that are not cross-resistant with antiretroviral agents that the patient has already received.
6. The antiretroviral drugs used in combination regimens should be used according to optimum schedules and dosages.
7. The number of available drugs is limited. Any decisions on antiretroviral therapy have a long-term impact on future options for the patient.
8. Women should receive optimal antiretroviral therapy regardless of pregnancy status.
9. The same principles apply to children and adults. The treatment of HIV-infected children involves unique pharmacologic, virologic, and immunologic considerations.
10. Compliance is an important part of ensuring maximal effect from a given regimen. The simpler the regimen, the easier it is for the patient to be compliant.

Source: Modified from *Principles of Therapy of HIV Infection*, USPHS, and the Henry J. Kaiser Family Foundation.

TABLE 93-23

INDICATIONS FOR THE INITIATION OF ANTIRETROVIRAL THERAPY IN PATIENTS WITH HIV INFECTION

I. Acute infection syndrome
II. Chronic infection
  A. Symptomatic disease (including HIV-associated nephropathy)
  B. Asymptomatic disease
    1. CD4+ T cell count <500/μL[a]
    2. Pregnancy
III. Postexposure prophylaxis

[a]This is an area of controversy. Some experts would treat everyone regardless of CD4+ T cell count.

Source: *Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents,* USPHS.

as heart attack and stroke may be linked to HIV replication. Thus, unless contraindicated for reasons of toxicity, patients started on cART should remain on cART.

At present, a reasonable course of action is to initiate cART in anyone with the acute HIV syndrome; all pregnant women; patients with an AIDS-defining illness; patients with HIV-associated nephropathy; patients with hepatitis B infection when treatment for hepatitis B is indicated; and patients with asymptomatic disease with CD4+ T cell counts <500/μL (Table 93-23). Clinical trials are underway to determine the value of even earlier intervention, and some experts would place everyone with HIV infection on antiretroviral therapy. In addition, one may wish to administer a 6-week course of therapy to uninfected individuals immediately following a high-risk exposure to HIV. Studies are underway to define the role of pre-exposure prophylaxis. For patients diagnosed with an opportunistic infection and HIV infection at the same time, one may consider a 2- to 4-week delay in the initiation of antiretroviral therapy during which time treatment is focused on the opportunistic infection. While not proven, it is postulated that this delay may decrease the severity of any subsequent immune reconstitution inflammatory syndrome by lowering the antigenic burden of the opportunistic infection.

Once the decision has been made to initiate therapy, the health care provider must decide which drugs to use as the first regimen. The decision regarding choice of drugs not only will affect the immediate response to therapy but also will have implications regarding options for future therapeutic regimens. The initial regimen is usually the most effective insofar as the virus has yet to develop significant resistance. Given that patients can be infected with viruses that harbor drug resistance mutations, it is recommended that a viral genotype be done prior to the initiation of therapy to optimize the selection of antiretroviral agents. The three options for initial therapy most commonly in use today are three different three-drug regimens. The first regimen utilizes a nucleotide and a nucleoside analogue (tenofovir and emtricitabine) and a nonnucleoside reverse transcriptase inhibitor (efavirenz). The second regimen utilizes a ritonavir-boosted protease inhibitor (atazanavir or darunavir) in place of the nonnucleoside reverse transcriptase inhibitor. The third regimen utilizes an integrase inhibitor (raltegravir) in place of the nonnucleoside reverse transcriptase inhibitor. Unfortunately there are no clear data at present on which to base distinctions among these three approaches. Following the initiation of therapy, one should expect a rapid, at least 1-log (tenfold) reduction in plasma HIV RNA levels within 1–2 months and then a slower decline in plasma HIV RNA levels to <50 copies per milliliter within 6 months. During this same time, there should be a rise in the CD4+ T cell count of 100–150/μL that is particularly brisk during the first month of therapy. Subsequently, one should anticipate a CD4+ T cell count increase of 50–100 cells/year until numbers approach normal. Many clinicians feel that failure to achieve these endpoints is an indication for a change in therapy. Other reasons for a change in therapy include a persistently declining CD4+ T cell count, a consistent increase in HIV RNA levels to >1000 copies/mL, clinical deterioration, or drug toxicity (Table 93-24). As in the case of initiating

TABLE 93-24

INDICATIONS FOR CHANGING ANTIRETROVIRAL THERAPY IN PATIENTS WITH HIV INFECTION[a]

Less than a 1-log drop in plasma HIV RNA by 4 weeks following the initiation of therapy
A reproducible significant increase (defined as threefold or greater) from the nadir of plasma HIV RNA level not attributable to intercurrent infection, vaccination, or test methodology
Persistently declining CD4+ T cell numbers
Clinical deterioration
Side effects

[a]Generally speaking, a change should involve the initiation of at least two drugs felt to be effective in the given patient. The exception to this is when change is being made to manage toxicity, in which case a single substitution is reasonable.

Source: *Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents*, USPHS.

therapy, changing therapy may have a lasting impact on future therapeutic options. When changing therapy because of treatment failure (clinical progression or worsening laboratory parameters), it is important to attempt to provide a regimen with at least two new active drugs. This decision can be guided by resistance testing (see later). In the patient in whom a change is made for reasons of drug toxicity, a simple replacement of one drug is reasonable. It should be stressed that in attempting to sort out a drug toxicity it may be advisable to hold all therapy for a period of time to distinguish between drug toxicity and disease progression. Drug toxicity will usually begin to show signs of reversal within 1–2 weeks. Prior to changing a treatment regimen because of drug failure, it is important to ensure that the patient has been adherent to the prescribed regimen. As in the case of initial therapy, the simpler the new therapeutic regimen, the easier it is for the patient to be compliant. Plasma HIV RNA levels and CD4+ T lymphocyte counts should be monitored every 3–6 months during therapy and more frequently if one is contemplating a change in regimen or immediately following a change in regimen.

In an attempt to determine an optimal therapeutic regimen for initial therapy or for a patient on a failing regimen, one may attempt to measure antiretroviral drug susceptibility through genotyping or phenotyping of HIV quasispecies and to determine adequacy of dosing through measurement of drug levels. Genotyping may be done through dideoxynucleotide sequencing, DNA chip hybridization, or line probe assays. Phenotypic assays typically measure the enzymatic activity of viral enzymes in the presence or absence of different concentrations of different drugs and have also been used to determine co-receptor tropism. These assays will generally detect quasispecies present at a frequency of ≥10%. It is generally recommended that resistance testing be used in selecting initial therapy in settings where the risk of transmission of resistant virus is high (such as the United States and Europe) and in determining new regimens for patients experiencing virologic failure while on therapy. Resistance testing may be of particular value in distinguishing drug-resistant virus from poor patient compliance. Due to the rapid rate at which drug-resistant viruses revert to wild-type, it is recommended that resistance testing performed in the setting of drug failure be carried out while the patient is still on the failing regimen. Measurement of plasma drug levels can also be used to tailor an individual treatment. The inhibitory quotient, defined as the trough blood level/IC_{50} of the patient's virus, is used by some to determine the adequacy of dosing of a given treatment regimen. Despite the best of efforts there will still be patients with ongoing high levels of HIV replication while receiving the best available therapy. These patients will receive benefit from remaining on antiretroviral therapy even though it is not fully suppressive.

In addition to the licensed medications discussed earlier, a large number of experimental agents are being evaluated as possible therapies for HIV infection. Therapeutic strategies are being developed that interfere with virtually every step of the replication cycle of the virus (Fig. 93-3). In addition, as more is discovered about the role of the immune system in controlling viral replication, additional strategies, generically referred to as "immune-based therapies," are being developed as a complement to antiviral therapy. Among the antiviral agents in early clinical trials are additional nucleoside and nucleotide analogues, protease inhibitors, fusion inhibitors, receptor and co-receptor antagonists, and integrase inhibitors as well as new antiviral strategies, including antisense nucleic acids and maturation inhibitors. Among the immune-based therapies being evaluated are IFN-α, bone marrow transplantation, adoptive transfer of lymphocytes genetically modified to resist infection or enhance HIV-specific immunity, active immunotherapy with inactivated HIV or its components, IL-7, and IL-15.

HIV AND THE HEALTH CARE WORKER

Health care workers, especially those who deal with large numbers of HIV-infected patients, have a small but definite risk of becoming infected with HIV as a result of professional activities (see "Occupational Transmission of HIV: Health Care Workers, Laboratory Workers, and the Health Care Setting," earlier in the chapter). The first case of HIV transmission from a patient to a health care worker was reported in 1984. Occupational transmission of HIV has been reported in most countries, but the global surveillance data required to estimate the true frequency of this problem are not available.

In the United States between 1981 and 2006, 57 health care workers for whom case investigations were completed had documented seroconversions to HIV following occupational exposures. The routes of exposure resulting in infection were as follows: 48 percutaneous

(puncture/cut injury); 5 mucocutaneous (mucous membrane and/or skin); 2 both percutaneous and mucocutaneous; and 2 of unknown route. Of the 57 health care personnel, 49 were exposed to HIV-infected blood; 3 to concentrated virus in a laboratory; 1 to visibly bloody fluid; and 4 to an unspecified fluid. The individuals with documented seroconversions included 19 laboratory workers (16 of whom were clinical laboratory workers), 24 nurses, 6 physicians, 2 surgical technicians, 1 dialysis technician, 1 respiratory therapist, 1 health aide, 1 embalmer/morgue technician, and 2 housekeeper/maintenance workers. In addition, at least 140 possible cases of occupationally acquired HIV infection have been reported among health care personnel in the United States. The number of these workers who actually acquired their infection through occupational exposures is not known. Taken together, data from several large studies suggest that the risk of HIV infection following a percutaneous exposure to HIV-contaminated blood is ~0.3%, and after a mucous membrane exposure, ~0.09%. Although episodes of HIV transmission after nonintact skin exposure have been documented, the average risk for transmission by this route has not been precisely quantified but is estimated to be less than the risk for mucous membrane exposures. The risk for transmission after exposure to fluids or tissues other than HIV-infected blood also has not been quantified but is probably considerably lower than for blood exposures. A seroprevalence survey of 3420 orthopedic surgeons, 75% of whom practiced in an area with a relatively high prevalence of HIV infection and 39% of whom reported percutaneous exposure to patient blood (usually through an accident involving a suture needle), failed to reveal any cases of possible occupational infection, suggesting that the risk of infection with a suture needle may be considerably less than that with a blood-drawing (hollow-bore) needle.

Most cases of health care worker seroconversion occur as a result of needle-stick injuries. When one considers the circumstances that result in needle-stick injuries, it is immediately obvious that adhering to the standard guidelines for dealing with sharp objects would result in a significant decrease in this type of accident. In one study, 27% of needle-stick injuries resulted from improper disposal of the needle (over half of these were due to recapping the needle), 23% occurred during attempts to start an IV line, 22% occurred during blood drawing, 16% were associated with an IM or SC injection, and 12% were associated with giving an IV infusion.

Clinicians should consider potential occupational exposures to HIV as urgent medical concerns to ensure timely postexposure management and possible administration of postexposure antiretroviral prophylaxis (PEP). Recommendations regarding PEP must take into account that a variety of circumstances determine the risk of transmission of HIV following occupational exposure. In this regard, several factors have been associated with an increased risk for occupational transmission of HIV infection, including deep injury, the presence of visible blood on the instrument causing the exposure, injury with a device that had been placed in the vein or artery of the source patient, terminal illness in the source patient, and lack of postexposure cART in the exposed health care worker. Other important issues when considering PEP in the health care worker include known or suspected pregnancy or breast-feeding, the possibility of exposure to drug-resistant virus, and toxicities of PEP regimens. Regardless of the decision to use PEP, the wound should be cleansed immediately and antiseptic applied. If a decision is made to offer PEP, U.S. Public Health Service guidelines recommend (1) a combination of two nucleoside analogue reverse transcriptase inhibitors given for 4 weeks for less severe exposures, or (2) a combination of two nucleoside analogue reverse transcriptase inhibitors plus a third drug given for 4 weeks for more severe exposures. Most clinicians administer the latter regimen in all cases in which a decision is made to treat. Detailed guidelines are available from the *Updated U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HIV and Recommendations for Postexposure Prophylaxis* (CDC, 2005). The report emphasizes the importance of adherence to PEP when it is indicated, follow-up of exposed workers to improve PEP adherence, monitoring for adverse events (including seroconversion), and expert consultation in the management of exposures.

For consultation on the treatment of occupational exposures to HIV and other bloodborne pathogens, the clinician managing the exposed patient can call the National Clinicians' Post-Exposure Prophylaxis Hotline (PEPline) at 888-448-4911. This service is available 24 hours a day at no charge. (Additional information on the Internet is available at *www.nccc.ucsf.edu*.) PEPline support may be especially useful in challenging situations, such as when drug-resistant HIV strains are suspected or the health care worker is pregnant.

Health care workers can minimize their risk of occupational HIV infection by following the CDC guidelines of July 1991, which include adherence to universal precautions, refraining from direct patient care if one has exudative lesions or weeping dermatitis, and disinfecting and sterilizing reusable devices employed in invasive procedures. The premise of universal precautions is that every specimen should be handled as if it came from someone infected with a bloodborne pathogen. All samples should be double-bagged, gloves should be worn when drawing blood, and spills should be immediately disinfected with bleach.

In attempting to put this small but definite risk to the health care worker in perspective, it is important to point out that ~200 health care workers die each year as a result of occupationally acquired hepatitis B infection. The tragedy in this instance is that these infections and deaths due to HBV could be greatly decreased by more extended use of the HBV vaccine. The risk of HBV infection following a needle-stick injury from a hepatitis antigen–positive patient is much higher than the risk of HIV infection (see "Transmission," mentioned earlier). There are multiple examples of needle-stick injuries where the patient was positive for both HBV and HIV and the health care worker became infected only with HBV.

For these reasons, it is advisable, given the high prevalence of HBV infection in HIV-infected individuals, that all health care workers dealing with HIV-infected patients be immunized with the HBV vaccine.

TB is another infection common to HIV-infected patients that can be transmitted to the health care worker. For this reason, all health care workers should know their PPD status, have it checked yearly, and receive 6 months of isoniazid treatment if their skin test converts to positive. In addition, all patients in whom a diagnosis of TB is being entertained should be placed immediately in respiratory isolation, pending results of the diagnostic evaluation. The emergence of drug-resistant organisms, including the extensively drug-resistant TB strains that have been identified in Africa, has made TB an increasing problem for health care workers. This is particularly true for the health care worker with preexisting HIV infection.

One of the most charged issues ever to come between health care workers and patients is that of transmission of infection from HIV-infected health care workers to their patients. This is discussed under "Occupational Transmission of HIV: Health Care Workers, Laboratory Workers, and the Health Care Setting.") Theoretically, the same universal precautions that are used to protect the health care worker from the HIV-infected patient will also protect the patient from the HIV-infected health care worker.

A PREVENTIVE VACCINE AGAINST HIV INFECTION

Given that human behavior, especially human sexual behavior, is extremely difficult to change, a critical modality for preventing the spread of HIV infection is the development of a safe and effective vaccine. Historically, vaccines have provided a safe, cost-effective, and efficient means of preventing illness, disability, and death from infectious diseases. Successful vaccines for the most part are predicated on the assumptions that the body can mount an adequate immune response to the microbe or virus in question during natural infection and that the vaccine will mimic the natural response to infection. Even with serious diseases, such as smallpox, poliomyelitis, measles, and influenza, the body in the vast majority of cases clears the infectious agent and provides protection, which is usually life-long, against future exposure. Unfortunately, this is not the case with HIV infection since the natural immune response to HIV infection is unable to clear the virus from the body and cases of superinfection have been reported. Some of the factors that contribute to the problematic nature of development of a preventive HIV vaccine are the high mutability of the virus, the fact that the infection can be transmitted by cell-free or cell-associated virus, the fact that the HIV provirus integrates itself into the genome of the target cell and may remain in a latent form unexposed to the immune system, the likely need for the development of effective mucosal immunity, and the fact that it has been difficult to establish the precise correlates of protective immunity to HIV infection. Some HIV-infected individuals are long-term nonprogressors, and a number of individuals have been exposed to HIV multiple times but remain uninfected; these facts suggest that there are elements of host defense or an HIV-specific immune response that have the potential to be protective. Early attempts to develop a vaccine with the envelope protein gp120, aimed at inducing neutralizing antibodies in humans, were performed based on the induction of neutralizing antibodies in nonhuman primates. The significance of the laboratory assays were unknown at the time, and the elicited antisera failed to neutralize primary isolates of HIV cultured and tested in fresh peripheral blood mononuclear cells. In this regard, two phase 3 trials were undertaken in the United States and Thailand using soluble gp120, and the vaccines failed to protect volunteers from HIV infection. A number of studies in monkeys using vaccines that induce predominantly cellular (T cell) immune responses have not protected the animals against infection but have lowered the initial burst of viremia following acute infection as well as decreased temporarily the viral set point. Since most sexually transmitted HIV infections occur when the transmitting partner is experiencing high levels of viremia (e.g., during the acute phase of HIV infection or during the advanced stage of disease when the viral load is high), such a vaccine, which might limit the initial burst of viremia in primary infection and decrease the established viral set point, could have benefits for individuals as well as for their sexual partners. However, such a "T cell vaccine" failed in human clinical trials to lower either the initial burst of viremia or the viral set point after acquisition of infection. Recently, a vaccine using a poxvirus vector prime expressing various viral proteins followed by an envelope protein boost was tested in a 16,000-person clinical trial conducted in Thailand among predominantly low-prevalence heterosexuals. The vaccine provided the first positive, albeit very modest, signal ever reported in an HIV vaccine trial, showing 31% protection against acquisition of infection. Such a result is certainly not sufficient justification for clinical use of the vaccine, but it serves as an important first step in the direction of the development of a safe and effective vaccine against HIV infection. The next important step is to determine the correlate or correlates of immunity that provided the modest protection against infection.

PREVENTION

Education, counseling, and behavior modification are the cornerstones of an HIV prevention strategy. A major problem in the United States and elsewhere is that many infections are passed on by those who do not know that they are infected. Of the ~1.1 million persons in the United States who are HIV-infected, it is estimated that ~21% do not know their HIV status and thus may be putting others at risk by their own behavior. In this regard, the CDC has recently recommended

that HIV testing become part of routine medical care and that all individuals between the ages of 13 and 64 years be informed of the testing and be tested without the need for written informed consent. The individual could "opt out" of testing, but if not, testing would be routinely administered. In addition to identifying individuals who might benefit from cART, information gathered from such an approach should serve as the basis for behavior-modification programs, both for infected individuals who may be unaware of their HIV status and who could infect others and for uninfected individuals practicing high-risk behavior. The practice of "safer sex" is the most effective way for sexually active uninfected individuals to avoid contracting HIV infection and for infected individuals to avoid spreading infection. Abstinence from sexual relations is the only absolute way to prevent sexual transmission of HIV infection. However, for many individuals this may not be feasible, and there are a number of relatively safe practices that can markedly decrease the chances of transmission of HIV infection. Partners engaged in monogamous sexual relationships who wish to be assured of safety should both be tested for HIV antibody. If both are negative, it must be understood that any divergence from monogamy puts both partners at risk; open discussion of the importance of honesty in such relationships should be encouraged. When the HIV status of either partner is not known, or when one partner is positive, there are a number of options. Use of condoms can markedly decrease the chance of HIV transmission. It should be remembered that condoms are not 100% effective in preventing transmission of HIV infection, and there is a ~10% failure rate of condoms used for contraceptive purposes. Most condom failures result from breakage or improper usage, such as not wearing the condom for the entire period of intercourse. Latex condoms are preferable, since virus has been shown to leak through natural skin condoms. Petroleum-based gels should never be used for lubrication of the condom, since they increase the likelihood of condom rupture. Some men who have sex with men practice fellatio as a "minimal risk" activity compared to anal intercourse. It should be emphasized that receptive fellatio is definitely not safe sex, and although the incidence of transmission via fellatio is considerably less than that of rectal or vaginal intercourse, there has been documentation of transmission of HIV where receptive fellatio was the only sexual act performed (see "Transmission," mentioned earlier). Topical microbicides for vaginal and anal use are being pursued actively as a means by which individuals could avoid infection when the insertive partner cannot be relied on to use a condom. In 2010, a topical microbicide composed of 1% tenofovir in a gel was demonstrated in a clinical trial in South Africa to be 39% effective in preventing acquisition of HIV infection in women engaging in vaginal intercourse. Three clinical trials of heterosexual men in South Africa, Uganda, and Kenya have shown that adult male circumcision results in a 50% to 65% reduction in HIV acquisition in the circumcised subject. Clearly, this approach has considerable potential as a preventive strategy for HIV infection and is currently being pursued, particularly in developing nations, as a component of HIV prevention. In 2010, a study of pre-exposure prophylaxis using two drugs (tenofovir plus emtricitabine; see "Treatment", mentioned earlier) on a daily basis in uninfected men who have sex with men and transgender women demonstrated a 44% efficacy. When participants had a high level of adherence to the regimen, the level of protection rose to 73%. Also in 2010, a study demonstrated that antiretroviral treatment of the infected partner in an HIV-discordant relationship provided 92% protection to the uninfected partner.

The most effective way to prevent transmission of HIV infection among IDUs is to stop the use of injectable drugs. Unfortunately, that is extremely difficult to accomplish unless the individual enters a treatment program. For those who will not or cannot participate in a drug treatment program and who will continue to inject drugs, the avoidance of sharing of needles and other paraphernalia ("works") is the next best way to avoid transmission of infection. However, the cultural and social factors that contribute to the sharing of paraphernalia are complex and difficult to overcome. In addition, needles and syringes may be in short supply. Under these circumstances, paraphernalia should be cleaned after each usage with a virucidal solution, such as undiluted sodium hypochlorite (household bleach). Data from a number of studies have indicated that programs that provide sterile needles to addicts in exchange for used needles have resulted in a decrease in HIV transmission without increasing the use of injection drugs. It is important for IDUs to be tested for HIV infection and counseled to avoid transmission to their sexual partners. Secondary and tertiary spread of HIV infection by the heterosexual route within settings of a high level of injection drug use has increased greatly in the United States, particularly among African Americans. Studies are underway to determine the safety and efficacy of preexposure administration of antiretroviral drugs for the prevention of HIV infection.

Transmission of HIV via transfused blood or blood products has been decreased dramatically by a combination of screening of all blood donors for HIV infection by assays for both HIV antibody and nucleic acid and self-deferral of individuals at risk for HIV infection. In addition, clotting factor concentrates are heat-treated, essentially eliminating the risk to hemophiliacs who require these products. Autologous transfusions are preferable to transfusions from another individual. However, logistic constraints as well as the unpredictability of the need for most transfusions limit the feasibility of this approach. At present the risk of becoming HIV-infected from a contaminated blood transfusion is approximately 1 in 1.5 million donations in the United States.

Treatment of an HIV-infected mother with antiretroviral therapy during pregnancy and the infant during the first weeks following birth has proved very effective in dramatically decreasing mother-to-child transmission of HIV. In situations such as that seen in certain developing countries where pregnant women frequently present to a health care system during labor, administration of a short course (as little as a single dose of

one drug) of antiretroviral therapy to the mother during labor and to the infant within 48 h of birth has also been successful in decreasing the incidence of mother-to-child transmission of HIV.

HIV can be transmitted via breast milk and colostrum. The avoidance of breast-feeding may not be practical in developing countries, where nutritional concerns override the risk of HIV transmission. However, it is becoming appreciated that 5–15% of infants who were born of HIV-infected mothers and who were fortunate enough not to have been infected intrapartum or peripartum are infected via breast-feeding. Therefore, in developing countries, breast-feeding from an infected mother should be avoided if at all possible. Unfortunately, this is rarely the case, and given the disadvantages of withholding breast-feeding in developing countries, health authorities in most developing countries continue to recommend breast-feeding despite the potential for HIV transmission. In this regard, the most effective way to avoid mother-to-child transmission of HIV is to treat the infected mother throughout the entire pregnancy and to continue therapy during breast-feeding and beyond if the mother's clinical status warrants such treatment. Such an approach has become more feasible over the past few years as the availability of antiretroviral therapy in the developing world has increased as a result of programs such as the President's Emergency Plan for AIDS Relief (PEPFAR) and the Global Fund to Fight AIDS, Tuberculosis and Malaria. In developed countries such as the United States, where bottled formula and milk are readily accessible, breast-feeding is contraindicated when a mother is HIV-positive, even if she is receiving antiretroviral therapy.

It is clear that in order to control and ultimately end the AIDS pandemic, effective prevention is essential. There are a number of HIV preventive modalities that have been demonstrated to be effective in various target populations if properly implemented and adhered to, and several others that are showing promise in clinical trials. It is unlikely that major successes in HIV prevention will be achieved with a uni-dimensional approach. What will almost certainly be required are various versions of combination prevention strategies, depending on the target population.

CHAPTER 94

VIRAL GASTROENTERITIS

Umesh D. Parashar ■ Roger I. Glass

Acute infectious gastroenteritis is a common illness that affects persons of all ages worldwide. It is a leading cause of mortality among children in developing countries, accounting for an estimated 1.8 million deaths each year, and is responsible for up to 10–12% of all hospitalizations among children in industrialized countries, including the United States. Elderly persons, especially those with debilitating health conditions, are also at risk of severe complications and death from acute gastroenteritis. Among healthy young adults, acute gastroenteritis is rarely fatal but incurs substantial medical and social costs, including those of time lost from work.

Several enteric viruses have been recognized as important etiologic agents of acute infectious gastroenteritis **(Table 94-1, Fig. 94-1)**. Although most viral gastroenteritis is caused by RNA viruses, the DNA viruses that are occasionally involved (e.g., adenovirus types 40 and 41) are included in this chapter. Illness caused by these viruses is characterized by the acute onset of vomiting and/or diarrhea, which may be accompanied by fever, nausea, abdominal cramps, anorexia, and malaise. As shown in **Table 94-2**, several features can help distinguish gastroenteritis caused by viruses from that caused by bacterial agents. However, the distinction based on clinical and epidemiologic parameters alone is often difficult, and laboratory tests may be required to confirm the diagnosis.

HUMAN CALICIVIRUSES

Etiologic agent

The Norwalk virus is the prototype strain of a group of nonenveloped, small (27–40 nm), round, icosahedral viruses with relatively amorphous surface features on

TABLE 94-1

VIRAL CAUSES OF GASTROENTERITIS AMONG HUMANS

VIRUS	FAMILY	GENOME	PRIMARY AGE GROUP AT RISK	CLINICAL SEVERITY	DETECTION ASSAYS
Group A rotavirus	Reoviridae	Double-strand segmented RNA	Children <5 years	+++	EM, EIA (commercial), PAGE, RT-PCR
Norovirus	Caliciviridae	Positive-sense single-strand RNA	All ages	++	EM, EIA, RT-PCR
Sapovirus	Caliciviridae	Positive-sense single-strand RNA	Children <5 years	+	EM, EIA, RT-PCR
Astrovirus	Astroviridae	Positive-sense single-strand RNA	Children <5 years	+	EM, EIA, RT-PCR
Adenovirus (types 40 and 41)	Adenoviridae	Double-strand DNA	Children <5 years	+/++	EM, EIA (commercial), PCR

Abbreviations: EIA, enzyme immunoassay; EM, electron microscopy; PAGE, polyacrylamide gel electrophoresis; PCR, polymerase chain reaction; RT-PCR, reverse-transcription PCR.

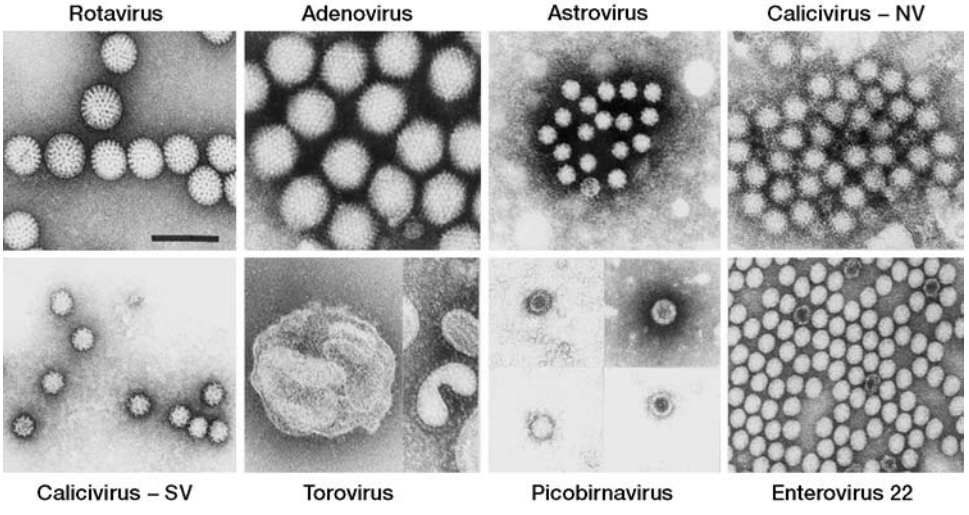


FIGURE 94-1
Viral agents of gastroenteritis. NV, norovirus; SV, sapovirus.

visualization by electron microscopy. These viruses have been difficult to classify because they have not been adapted to cell culture, they often are shed in low titers for only a few days, and no animal models are available. Molecular cloning and characterization have demonstrated that the viruses have a single, positive-strand RNA genome ~7.5 kb in length and that they possess a single virion-associated protein—similar to that of typical caliciviruses—with a molecular mass of 60 kDa. On the basis of these molecular characteristics, these viruses are presently classified in two genera belonging to the family Caliciviridae: the *noroviruses* and the *sapoviruses* (previously called Norwalk-like viruses and Sapporo-like viruses, respectively).

Epidemiology

Infections with the Norwalk and related human caliciviruses are common worldwide, and most adults have antibodies to these viruses. Antibody is acquired at an earlier age in developing countries—a pattern consistent with the presumed fecal-oral mode of transmission. Infections occur year-round, although, in temperate climates, a distinct increase has been noted in cold-weather months. Noroviruses may be the most common infectious agents of mild gastroenteritis in the community and affect all age groups, whereas sapoviruses primarily cause gastroenteritis in children. Noroviruses also cause traveler's diarrhea, and outbreaks have occurred

TABLE 94-2

CHARACTERISTICS OF GASTROENTERITIS CAUSED BY VIRAL AND BACTERIAL AGENTS

FEATURE	VIRAL GASTROENTERITIS	BACTERIAL GASTROENTERITIS
Setting	Incidence similar in developing and developed countries	More common in settings with poor hygiene and sanitation
Infectious dose	Low (10–100 viral particles) for most agents	High (>10^5 bacteria) for *Escherichia coli, Salmonella, Vibrio;* medium (10^2–10^5 bacteria) for *Campylobacter jejuni;* low (10–100 bacteria) for *Shigella*
Seasonality	In temperate climates, winter seasonality for most agents; year-round occurrence in tropical areas	More common in summer or rainy months, particularly in developing countries with a high disease burden
Incubation period	1–3 days for most agents; can be shorter for norovirus	1–7 days for common agents (e.g., *Campylobacter, E. coli, Shigella, Salmonella);* a few hours for bacteria producing preformed toxins (e.g., *Staphylococcus aureus, Bacillus cereus*)
Reservoir	Primarily humans	Depending on species, human (e.g., *Shigella, Salmonella*), animal (e.g., *Campylobacter, Salmonella, E. coli*), and water (e.g., *Vibrio*) reservoirs exist.
Fever	Common with rotavirus and norovirus; uncommon with other agents	Common with agents causing inflammatory diarrhea (e.g., *Salmonella, Shigella*)
Vomiting	Prominent and can be the only presenting feature, especially in children	Common with bacteria producing preformed toxins; less prominent in diarrhea due to other agents
Diarrhea	Common; nonbloody in almost all cases	Prominent and frequently bloody with agents causing inflammatory diarrhea
Duration	1–3 days for norovirus and sapovirus; 2–8 days for other viruses	1–2 days for bacteria producing preformed toxins; 2–8 days for most other bacteria
Diagnosis	This is often a diagnosis of exclusion in clinical practice. Commercial enzyme immunoassays are available for detection of rotavirus and adenovirus, but identification of other agents is limited to research and public health laboratories.	Fecal examination for leukocytes and blood is helpful in differential diagnosis. Culture of stool specimens, sometimes on special media, can identify several pathogens. Molecular techniques are useful epidemiologic tools but are not routinely used in most laboratories.
Treatment	Supportive therapy to maintain adequate hydration and nutrition should be given. Antibiotics and antimotility agents are contraindicated.	Supportive hydration therapy is adequate for most patients. Antibiotics are recommended for patients with dysentery caused by *Shigella* or *Vibrio cholerae* and for some patients with *Clostridium difficile* colitis.

among military personnel deployed to various parts of the world. The limited data available indicate that norovirus may be the second most common viral agent (after rotavirus) among young children and the most common agent among older children and adults. For example, in a comprehensive evaluation of eight enteric pathogens in patients with gastroenteritis in England, three-fourths of patients had at least one pathogen detected in fecal specimens, and noroviruses were the most prevalent, detected in 36% of patients and 18% of healthy controls. Noroviruses are also recognized as the major cause of epidemics of gastroenteritis worldwide. In the United States, >90% of outbreaks of nonbacterial gastroenteritis are caused by noroviruses.

Virus is transmitted predominantly by the fecal-oral route, but is also present in vomitus. Because an inoculum with very few viruses can be infectious, transmission can occur by aerosolization, by contact with contaminated fomites, and by person-to-person contact. Viral shedding and infectivity are greatest during the acute illness, but challenge studies with Norwalk virus in volunteers indicate that viral antigen may be shed by asymptomatically infected persons and also by symptomatic persons before the onset of symptoms and for several weeks after the resolution of illness.

Pathogenesis

The exact sites and cellular receptors for attachment of viral particles have not been determined. Data suggest that carbohydrates that are similar to human histo-blood group antigens and are present on the gastroduodenal epithelium of individuals with the secretor phenotype may serve as ligands for the attachment of Norwalk virus. Additional studies must more fully elucidate norovirus-carbohydrate interactions, including potential strain-specific variations. After the infection of volunteers, reversible lesions are noted in the upper jejunum, with broadening and blunting of the villi, shortening of the microvilli, vacuolization of the lining epithelium, crypt hyperplasia, and infiltration of the lamina propria by polymorphonuclear neutrophils and lymphocytes.

The lesions persist for at least 4 days after the resolution of symptoms and are associated with malabsorption of carbohydrates and fats and a decreased level of brush-border enzymes. Adenylate cyclase activity is not altered. No histopathologic changes are seen in the stomach or colon, but gastric motor function is delayed, and this alteration is believed to contribute to the nausea and vomiting that are typical of this illness.

Clinical manifestations

Gastroenteritis caused by Norwalk and related human caliciviruses has a sudden onset, following an average incubation period of 24 h (range, 12–72 h). The illness generally lasts 12–60 h and is characterized by one or more of the following symptoms: nausea, vomiting, abdominal cramps, and diarrhea. Vomiting is more prevalent among children, whereas a greater proportion of adults develop diarrhea. Constitutional symptoms are common, including headache, fever, chills, and myalgias. The stools are characteristically loose and watery, without blood, mucus, or leukocytes. White cell counts are generally normal; rarely, leukocytosis with relative lymphopenia may be observed. Death is a rare outcome and usually results from severe dehydration in vulnerable persons (e.g., elderly patients with debilitating health conditions).

Immunity

Approximately 50% of persons challenged with Norwalk virus become ill and acquire short-term immunity against the infecting strain. Immunity to Norwalk virus appears to correlate inversely with level of antibody; i.e., persons with higher levels of preexisting antibody to Norwalk virus are more susceptible to illness. This observation suggests that some individuals have a genetic predisposition to illness. Specific ABO, Lewis, and secretor blood group phenotypes may influence susceptibility to norovirus infection.

Diagnosis

Cloning and sequencing of the genomes of Norwalk and several other human caliciviruses have allowed the development of assays based on polymerase chain reaction (PCR) for detection of virus in stool and vomitus. Virus-like particles produced by expression of capsid proteins in a recombinant baculovirus vector have been used to develop enzyme immunoassays (EIAs) for detection of virus in stool or a serologic response to a specific viral antigen. These newer diagnostic techniques are considerably more sensitive than previous detection methods, such as electron microscopy, immune electron microscopy, and EIAs based on reagents derived from humans. However, no currently available single assay can detect all human caliciviruses because of their great genetic and antigenic diversity. In addition, the assays are still cumbersome and are available primarily in research laboratories, although they are increasingly being adopted by public health laboratories for routine screening of fecal specimens from patients affected by outbreaks of gastroenteritis. Commercial EIA kits, which are available in some European countries and in Japan but not yet in the United States, have limited sensitivity and usefulness in clinical practice and are of greatest utility in outbreaks, in which many specimens are tested and only a few need be positive to identify norovirus as the cause.

TREATMENT **Infections with Norwalk and Related Human Caliciviruses**

The disease is self-limited, and oral rehydration therapy is generally adequate. If severe dehydration develops, IV fluid therapy is indicated. No specific antiviral therapy is available.

Prevention

Epidemic prevention relies on situation-specific measures, such as control of contamination of food and water, exclusion of ill food handlers, and reduction of person-to-person spread through good personal hygiene and disinfection of contaminated fomites. The role of immunoprophylaxis is not clear, given the lack of long-term immunity from natural disease, but efforts to develop norovirus vaccines are ongoing.

ROTAVIRUS

Etiologic agent

Rotaviruses are members of the family Reoviridae. The viral genome consists of 11 segments of double-strand RNA that are enclosed in a triple-layered, nonenveloped, icosahedral capsid 75 nm in diameter. Viral protein 6 (VP6), the major structural protein, is the target of commercial immunoassays and determines the group specificity of rotaviruses. There are seven major groups of rotavirus (A through G); human illness is caused primarily by group A and, to a much lesser extent, by groups B and C. Two outer-capsid proteins, VP7 (G-protein) and VP4 (P-protein), determine serotype specificity, induce neutralizing antibodies, and form the basis for binary classification of rotaviruses (G and P types). The segmented genome of rotavirus allows genetic reassortment (i.e., exchange of genome segments between viruses) during co-infection—a property that may play a role in viral evolution and has been utilized in the development of reassortant animal-human rotavirus–based vaccines.

Epidemiology

Worldwide, nearly all children are infected with rotavirus by 3–5 years of age. Neonatal infections are common but are often asymptomatic or mild, presumably because of protection from maternal antibody

or breast-feeding. First infections after 3 months of age are likely to be symptomatic, and the incidence of disease peaks among children 4–23 months of age. Reinfections are common, but the severity of disease decreases with each repeat infection. Therefore, severe rotavirus infections are relatively uncommon among older children and adults. Nevertheless, rotavirus can cause illness in parents and caretakers of children with rotavirus diarrhea, immunocompromised persons, travelers, and elderly individuals and should be considered in the differential diagnosis of gastroenteritis among adults.

In tropical settings, rotavirus disease occurs year-round, with less pronounced seasonal peaks than in temperate settings, where rotavirus disease occurs predominantly during the cooler fall and winter months. Before the introduction of rotavirus vaccine in the United States, the rotavirus season each year began in the Southwest during the autumn and early winter (October through December) and migrated across the continent, peaking in the Northeast during late winter and spring (March through May). The reasons for this characteristic pattern are not clear, but a recent study suggested a correlation with state-specific differences in birth rates, which could influence the rate of accumulation of susceptible infants after each rotavirus season. After the implementation of routine vaccination of U.S. infants against rotavirus in 2006, the onset of the 2007–2008 and 2008–2009 rotavirus seasons was delayed by 11 weeks and 6 weeks, respectively, and the seasons were shorter, lasting 14 and 17 weeks, respectively, in comparison with a median of 26 weeks in 2000–2006 **(Fig. 94-2)**. These changes in seasonal patterns of rotavirus activity were accompanied by declines in the number of detections of rotavirus by 64% and 60% in 2007–2008 and 2008–2009, respectively, from the figures for 2000–2006, as collected by a national network of sentinel laboratories.

During episodes of rotavirus-associated diarrhea, virus is shed in large quantities in stool (10^7–10^{12}/g). Viral shedding detectable by EIA usually subsides within 1 week but may persist for >30 days in immunocompromised individuals. Viral shedding may be detected for longer periods by sensitive molecular assays, such as PCR. The virus is transmitted predominantly through the fecal-oral route. Spread through respiratory secretions, person-to-person contact, or contaminated environmental surfaces has also been postulated to explain the rapid acquisition of antibody in the first 3 years of life, regardless of sanitary conditions.

At least 10 different G serotypes of group A rotavirus have been identified in humans, but only five types (G1 through G4 and G9) are common. While human rotavirus strains that possess a high degree of genetic homology with animal strains have been identified, animal-to-human transmission appears to be uncommon.

Group B rotaviruses have been associated with several large epidemics of severe gastroenteritis among adults in China since 1982 and have also been identified in India. Group C rotaviruses have been associated with a small proportion of pediatric gastroenteritis cases in several countries worldwide.

Pathogenesis

Rotaviruses infect and ultimately destroy mature enterocytes in the villous epithelium of the proximal small intestine. The loss of absorptive villous epithelium, coupled

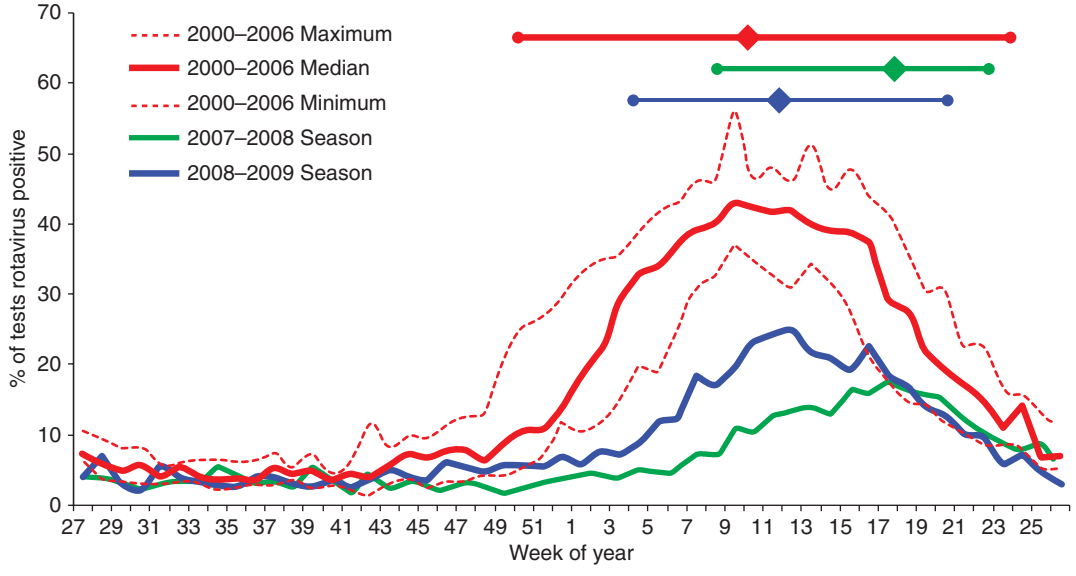


FIGURE 94-2
The maximal or minimal percentage of rotavirus-positive tests for 2000–2006 may have occurred during any of the six baseline seasons. The onset of rotavirus season was defined as the first of two consecutive weeks during which the percentage of stool specimens testing positive for rotavirus was ≥10%, and the end of the season was defined as the latter of two consecutive weeks during which the percentage of stool specimens testing positive for rotavirus was ≥10%. At the top right, the dots bracket the rotavirus season from onset to end, and the diamond indicates the peak week during each period. (*Adapted from Centers for Disease Control and Prevention: MMWR Morb Mortal Wkly Rep 58:1146, 2009.*)

with the proliferation of secretory crypt cells, results in secretory diarrhea. Brush-border enzymes characteristic of differentiated cells are reduced, and this change leads to the accumulation of unmetabolized disaccharides and consequent osmotic diarrhea. Studies in mice indicate that a nonstructural rotavirus protein, NSP4, functions as an enterotoxin and contributes to secretory diarrhea by altering epithelial cell function and permeability. In addition, rotavirus may evoke fluid secretion through activation of the enteric nervous system in the intestinal wall. Recent data indicate that rotavirus antigenemia and viremia are common among children with acute rotavirus infection, although the antigen and RNA levels in serum are substantially lower than those in stool.

Clinical manifestations

The clinical spectrum of rotavirus infection ranges from subclinical infection to severe gastroenteritis leading to life-threatening dehydration. After an incubation period of 1–3 days, the illness has an abrupt onset, with vomiting frequently preceding the onset of diarrhea. Up to one-third of patients may have a temperature of >39°C. The stools are characteristically loose and watery and only infrequently contain red or white cells. Gastrointestinal symptoms generally resolve in 3–7 days.

Respiratory and neurologic features in children with rotavirus infection have been reported, but causal associations have not been proven. Moreover, rotavirus infection has been associated with a variety of other clinical conditions (e.g., sudden infant death syndrome, necrotizing enterocolitis, intussusception, Kawasaki's disease, and type 1 diabetes), but no causal relationship has been confirmed with any of these syndromes.

Rotavirus does not appear to be a major opportunistic pathogen in children with HIV infection. In severely immunodeficient children, rotavirus can cause protracted diarrhea with prolonged viral excretion and, in rare instances, can disseminate systemically. Persons who are immunosuppressed for bone marrow transplantation are also at risk for severe or even fatal rotavirus disease.

Immunity

Protection against rotavirus disease is correlated with the presence of virus-specific secretory IgA antibodies in the intestine and, to some extent, the serum. Because virus-specific IgA production at the intestinal surface is short lived, complete protection against disease is only temporary. However, each infection and subsequent reinfection confers progressively greater immunity; thus, severe disease is most common among young children with first or second infections. Immunologic memory is believed to be important in the attenuation of disease severity upon reinfection.

Diagnosis

Illness caused by rotavirus is difficult to distinguish clinically from that caused by other enteric viruses. Because large quantities of virus are shed in feces, the diagnosis can usually be confirmed by a wide variety of commercially available EIAs or by techniques for detecting viral RNA, such as gel electrophoresis, probe hybridization, or PCR.

TREATMENT **Rotavirus Infections**

Rotavirus gastroenteritis can lead to severe dehydration. Thus appropriate treatment should be instituted early. Standard oral rehydration therapy is successful in most children who can take oral fluids, but IV fluid replacement may be required for patients who are severely dehydrated or are unable to tolerate oral therapy because of frequent vomiting. The therapeutic role of probiotics, bismuth subsalicylate, enkephalinase inhibitors, and nitazoxanide has been evaluated in clinical studies but is not clearly defined. Antibiotics and antimotility agents should be avoided. In immunocompromised children with chronic symptomatic rotavirus disease, orally administered immunoglobulins or colostrum may result in the resolution of symptoms, but the best choices regarding agents and their doses have not been well studied, and treatment decisions are often empirical.

Prevention

Efforts to develop rotavirus vaccines were pursued because it was apparent—given the similar rates in less-developed and industrialized nations—that improvements in hygiene and sanitation were unlikely to reduce disease incidence. The first rotavirus vaccine licensed in the United States in 1998 was withdrawn from the market within 1 year because it was linked with intussusception, a severe bowel obstruction.

In 2006, promising safety and efficacy results for two new rotavirus vaccines were reported from large clinical trials conducted in North America, Europe, and Latin America. Both vaccines are now recommended for routine immunization of all U.S. infants, and their use has rapidly led to a decline in rotavirus hospitalizations and emergency department visits at hospitals across the United States. In Mexico, a decline in deaths from childhood diarrhea following introduction of rotavirus vaccines has been documented. Furthermore, postmarketing surveillance information has not revealed an association of these vaccines with any serious adverse events (including intussusception), although a risk of low magnitude cannot be excluded on the basis of available data.

Rotavirus is ubiquitous and infects nearly all children worldwide by 5 years of age. However, compared with rotavirus disease in industrialized countries, disease in developing countries occurs at a younger age, is less seasonal, and is more frequently caused by uncommon rotavirus strains. Moreover, because of suboptimal access to hydration therapy, rotavirus is a leading cause of diarrheal death among children in the developing world, with the highest mortality rates among children in sub-Saharan Africa and southern Asia **(Fig. 94-3)**.

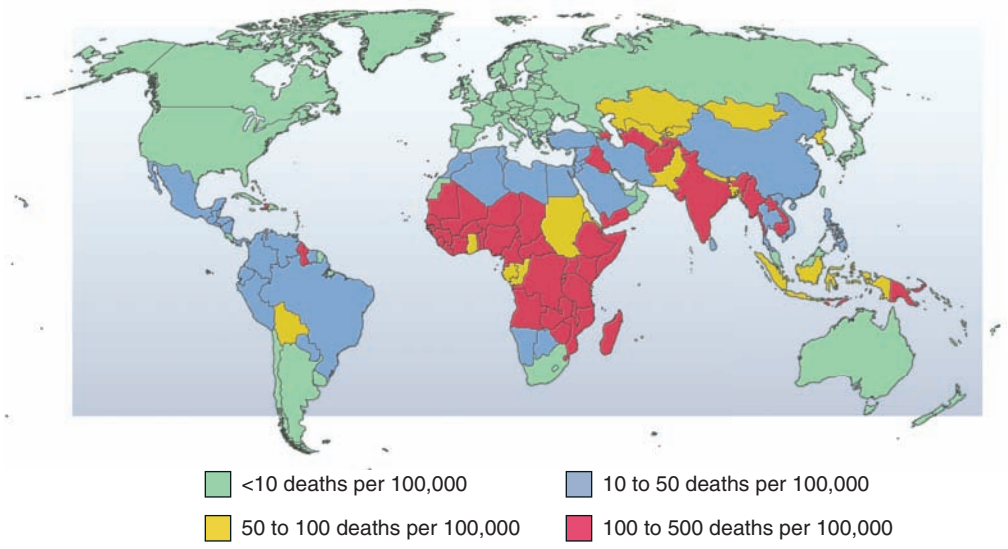


FIGURE 94-3
Rotavirus mortality rates by country, per 100,000 children <5 years of age. (*Reproduced with permission from UD Parashar et al: J Infect Dis 200:S9, 2009.*)

The different epidemiology of rotavirus disease and the greater prevalence of co-infection with other enteric pathogens, of comorbidities, and of malnutrition in developing countries may adversely affect the performance of oral rotavirus vaccines, as is the case with oral vaccines against poliomyelitis, cholera, and typhoid in these regions. Therefore, evaluation of the efficacy of rotavirus vaccines in resource-poor settings of Africa and Asia was specifically recommended, and these trials have now been completed. As anticipated, the efficacy of rotavirus vaccines was moderate (50–75%) in these settings when compared with that in industrialized countries. Nevertheless, even a moderately efficacious rotavirus vaccine would be likely to have substantial public health benefits in these areas with a high disease burden. Given these considerations, in April 2009 the World Health Organization recommended the use of rotavirus vaccines in all countries worldwide.

OTHER VIRAL AGENTS OF GASTROENTERITIS

Enteric *adenoviruses* of serotypes 40 and 41 belonging to subgroup F are 70- to 80-nm viruses with double-strand DNA that cause ~2–12% of all diarrhea episodes in young children. Unlike adenoviruses that cause respiratory illness, enteric adenoviruses are difficult to cultivate in cell lines, but they can be detected with commercially available EIAs.

Astroviruses, 28- to 30-nm viruses with a characteristic icosahedral structure, contain a positive-sense, single-strand RNA. At least seven serotypes have been identified, of which serotype 1 is most common. Astroviruses are primarily pediatric pathogens, causing ~2–10% of cases of mild to moderate gastroenteritis in children. The availability of simple immunoassays to detect virus in fecal specimens and of molecular methods to confirm and characterize strains will permit more comprehensive assessment of the etiologic role of these agents.

Toroviruses are 100- to 140-nm, enveloped, positive-strand RNA viruses that are recognized as causes of gastroenteritis in horses (Berne virus) and cattle (Breda virus). Their role as a cause of diarrhea in humans is still unclear, but studies from Canada have demonstrated associations between torovirus excretion and both nosocomial gastroenteritis and necrotizing enterocolitis in neonates. These associations require further evaluation.

Picobirnaviruses are small, bisegmented, double-strand RNA viruses that cause gastroenteritis in a variety of animals. Their role as primary causes of gastroenteritis in humans remains unclear, but several studies have found an association between picobirnaviruses and gastroenteritis in HIV-infected adults.

Several other viruses (e.g., enteroviruses, reoviruses, pestiviruses, and parvovirus B) have been identified in the feces of patients with diarrhea, but their etiologic role in gastroenteritis has not been proven. Diarrhea has also been noted as a manifestation of infection with recently recognized viruses that primarily cause severe respiratory illness: the severe acute respiratory syndrome–associated coronavirus (SARS-CoV), influenza A/H5N1 virus, and the current pandemic strain of influenza A/H1N1 virus.

CHAPTER 95

ACUTE VIRAL HEPATITIS

Jules L. Dienstag

Acute viral hepatitis is a systemic infection affecting the liver predominantly. Almost all cases of acute viral hepatitis are caused by one of five viral agents: hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), the HBV-associated delta agent or hepatitis D virus (HDV), and hepatitis E virus (HEV). Other transfusion-transmitted agents (e.g., "hepatitis G" virus and "TT" virus) have been identified but do not cause hepatitis. All these human hepatitis viruses are RNA viruses, except for hepatitis B, which is a DNA virus. Although these agents can be distinguished by their molecular and antigenic properties, all types of viral hepatitis produce clinically similar illnesses. These range from asymptomatic and inapparent to fulminant and fatal acute infections common to all types, on the one hand, and from subclinical persistent infections to rapidly progressive chronic liver disease with cirrhosis and even hepatocellular carcinoma, common to the bloodborne types (HBV, HCV, and HDV), on the other.

VIROLOGY AND ETIOLOGY

Hepatitis A

Hepatitis A virus is a nonenveloped 27-nm, heat-, acid-, and ether-resistant RNA virus in the *Hepatovirus* genus of the picornavirus family **(Fig. 95-1)**. Its virion contains four capsid polypeptides, designated VP1 to VP4, which are cleaved posttranslationally from the polyprotein product of a 7500-nucleotide genome. Inactivation of viral activity can be achieved by boiling for 1 minute, by contact with formaldehyde and chlorine, or by ultraviolet irradiation. Despite nucleotide sequence variation of up to 20% among isolates of HAV, and despite the recognition of four genotypes affecting humans, all strains of this virus are immunologically indistinguishable and belong to one serotype. Hepatitis A has an incubation period of ~4 weeks. Its replication is limited to the liver, but the virus is present in the liver, bile, stools, and blood during the late

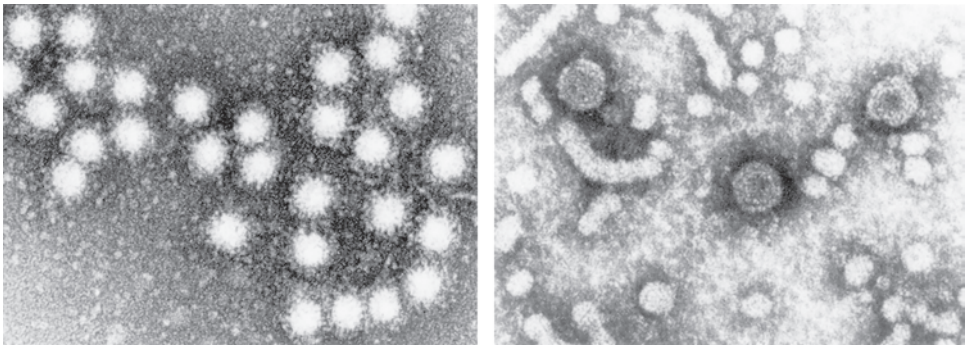


FIGURE 95-1
Electron micrographs of hepatitis A virus particles and serum from a patient with hepatitis B. ***Left:*** 27-nm hepatitis A virus particles purified from stool of a patient with acute hepatitis A and aggregated by antibody to hepatitis A virus. ***Right:*** Concentrated serum from a patient with hepatitis B, demonstrating the 42-nm virions, tubular forms, and spherical 22-nm particles of hepatitis B surface antigen. 132,000×. (Hepatitis D resembles 42-nm virions of hepatitis B but is smaller, 35–37 nm; hepatitis E resembles hepatitis A virus but is slightly larger, 32–34 nm; hepatitis C has been visualized as a 55-nm particle.)

incubation period and acute preicteric phase of illness. Despite persistence of virus in the liver, viral shedding in feces, viremia, and infectivity diminish rapidly once jaundice becomes apparent. HAV can be cultivated reproducibly in vitro.

Antibodies to HAV (anti-HAV) can be detected during acute illness when serum aminotransferase activity is elevated and fecal HAV shedding is still occurring. This early antibody response is predominantly of the IgM class and persists for several months, rarely for 6–12 months. During convalescence, however, anti-HAV of the IgG class becomes the predominant antibody **(Fig. 95-2)**. Therefore, the diagnosis of hepatitis A is made during acute illness by demonstrating anti-HAV of the IgM class. After acute illness, anti-HAV of the IgG class remains detectable indefinitely, and patients with serum anti-HAV are immune to reinfection. Neutralizing antibody activity parallels the appearance of anti-HAV, and the IgG anti-HAV present in immune globulin accounts for the protection it affords against HAV infection.

Hepatitis B

Hepatitis B virus is a DNA virus with a remarkably compact genomic structure; despite its small, circular, 3200-bp size, HBV DNA codes for four sets of viral products with a complex, multiparticle structure. HBV achieves its genomic economy by relying on an efficient strategy of encoding proteins from four overlapping genes: S, C, P, and X **(Fig. 95-3)**, as detailed next. Once thought to be unique among viruses, HBV is now recognized as one of a family of animal viruses, hepadnaviruses (hepatotropic DNA viruses), and is classified as hepadnavirus type 1. Similar viruses infect certain species of woodchucks, ground and tree squirrels, and Pekin ducks, to mention the most carefully characterized. Like HBV, all have the same distinctive three morphologic forms, have counterparts to the envelope and nucleocapsid virus antigens of HBV, replicate in the liver but exist in extrahepatic sites, contain their own endogenous DNA polymerase, have partially double-strand and partially single-strand genomes, are associated with acute and chronic hepatitis and hepatocellular carcinoma,

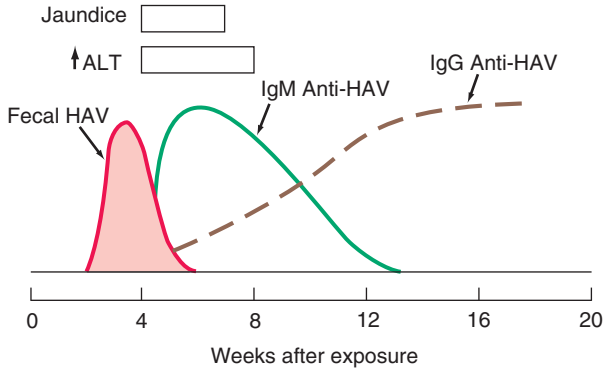


FIGURE 95-2
Scheme of typical clinical and laboratory features of hepatitis A.

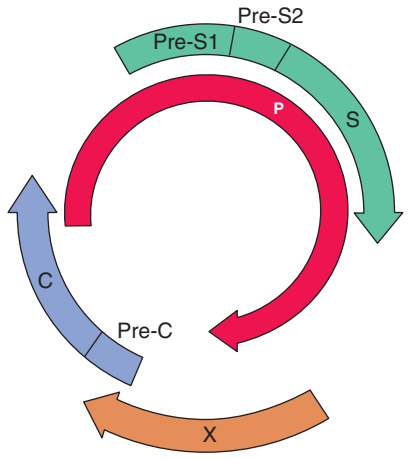


FIGURE 95-3
Compact genomic structure of HBV. This structure, with overlapping genes, permits HBV to code for multiple proteins. The S gene codes for the "major" envelope protein, HBsAg. Pre-S1 and pre-S2, upstream of S, combine with S to code for two larger proteins, "middle" protein, the product of pre-S2 + S, and "large" protein, the product of pre-S1 + pre-S2 + S. The largest gene, P, codes for DNA polymerase. The C gene codes for two nucleocapsid proteins, HBeAg, a soluble, secreted protein (initiation from the pre-C region of the gene) and HBcAg, the intracellular core protein (initiation after pre-C). The X gene codes for HBxAg, which can transactivate the transcription of cellular and viral genes; its clinical relevance is not known, but it may contribute to carcinogenesis by binding to p53.

and rely on a replicative strategy unique among DNA viruses but typical of retroviruses. Instead of DNA replication directly from a DNA template, hepadnaviruses rely on reverse transcription (effected by the DNA polymerase) of minus-strand DNA from a "pregenomic" RNA intermediate. Then plus-strand DNA is transcribed from the minus-strand DNA template by the DNA-dependent DNA polymerase and converted in the hepatocyte nucleus to a covalently closed circular DNA, which serves as a template for messenger RNA and pregenomic RNA. Viral proteins are translated by the messenger RNA, and the proteins and genome are packaged into virions and secreted from the hepatocyte. Although HBV is difficult to cultivate in vitro in the conventional sense from clinical material, several cell lines have been transfected with HBV DNA. Such transfected cells support in vitro replication of the intact virus and its component proteins.

Viral proteins and particles

Of the three particulate forms of HBV **(Table 95-1)**, the most numerous are the 22-nm particles, which appear as spherical or long filamentous forms; these are antigenically indistinguishable from the outer surface or envelope protein of HBV and are thought to represent excess viral envelope protein. Outnumbered in serum by a factor of 100 or 1000 to 1 compared with the spheres and tubules are large, 42-nm, double-shelled

TABLE 95-1

NOMENCLATURE AND FEATURES OF HEPATITIS VIRUSES

HEPATITIS TYPE	VIRUS PARTICLE, nm	MORPHOLOGY	GENOME[a]	CLASSIFICATION	ANTIGEN(S)	ANTIBODIES	REMARKS
HAV	27	Icosahedral nonenveloped	7.5-kb RNA, linear, ss, +	Hepatovirus	HAV	Anti-HAV	Early fecal shedding Diagnosis: IgM anti-HAV Previous infection: IgG anti-HAV
HBV	42	Double-shelled virion (surface and core), spherical	3.2-kb DNA, circular, ss/ds	Hepadnavirus	HBsAg HBcAg HBeAg	Anti-HBs Anti-HBc Anti-HBe	Bloodborne virus; carrier state Acute diagnosis: HBsAg, IgM anti-HBc Chronic diagnosis: IgG anti-HBc, HBsAg Markers of replication: HBeAg, HBV DNA Liver, lymphocytes, other organs
	27	Nucleocapsid core			HBcAg HBeAg	Anti-HBc Anti-HBe	Nucleocapsid contains DNA and DNA polymerase; present in hepatocyte nucleus; HBcAg does not circulate; HBeAg (soluble, nonparticulate) and HBV DNA circulate—correlate with infectivity and complete virions
	22	Spherical and filamentous; represents excess virus coat material			HBsAg	Anti-HBs	HBsAg detectable in >95% of patients with acute hepatitis B; found in serum, body fluids, hepatocyte cytoplasm; anti-HBs appears following infection—protective antibody
HCV	Approx. 40–60	Enveloped	9.4-kb RNA, linear, ss, +	Hepacivirus	HCV C100-3 C33c C22-3 NS5	Anti-HCV	Bloodborne agent, formerly labeled non-A, non-B hepatitis Acute diagnosis: anti-HCV (C33c, C22-3, NS5), HCV RNA Chronic diagnosis: anti-HCV (C100-3, C33c, C22-3, NS5) and HCV RNA; cytoplasmic location in hepatocytes
HDV	35–37	Enveloped hybrid particle with HBsAg coat and HDV core	1.7-kb RNA, circular, ss, –	Resembles viroids and plant satellite viruses	HBsAg HDV antigen	Anti-HBs Anti-HDV	Defective RNA virus, requires helper function of HBV (hepadnaviruses); HDV antigen present in hepatocyte nucleus Diagnosis: anti-HDV, HDV RNA; HBV/HDV co-infection—IgM anti-HBc and anti-HDV; HDV superinfection—IgG anti-HBc and anti-HDV
HEV	32–34	Nonenveloped icosahedral	7.6-kb RNA, linear, ss, +	Hepevirus	HEV antigen	Anti-HEV	Agent of enterically transmitted hepatitis; rare in USA; occurs in Asia, Mediterranean countries, Central America Diagnosis: IgM/IgG anti-HEV (assays not routinely available); virus in stool, bile, hepatocyte cytoplasm

[a]*Abbreviations:* ss, single-strand; ss/ds, partially single-strand, partially double-strand; –, minus-strand; +, plus-strand.

spherical particles, which represent the intact hepatitis B virion (Fig. 95-1). The envelope protein expressed on the outer surface of the virion and on the smaller spherical and tubular structures is referred to as *hepatitis B surface antigen* (HBsAg). The concentration of HBsAg and virus particles in the blood may reach 500 μg/mL and 10 trillion particles per milliliter, respectively. The envelope protein, HBsAg, is the product of the S gene of HBV.

A number of different HBsAg subdeterminants have been identified. There is a common group-reactive antigen, *a*, shared by all HBsAg isolates. In addition, HBsAg may contain one of several subtype-specific antigens—namely, *d* or *y*, *w* or *r*—as well as other more recently characterized specificities. Hepatitis B isolates fall into one of at least eight subtypes and eight genotypes (A–H). Geographic distribution of genotypes and subtypes varies; genotypes A (corresponding to subtype *adw*) and D (*ayw*) predominate in the United States and Europe, while genotypes B (*adw*) and C (*adr*) predominate in Asia. Clinical course and outcome are independent of subtype, but preliminary reports suggest that genotype B is associated with less rapidly progressive liver disease and a lower likelihood, or delayed appearance, of hepatocellular carcinoma than genotype C. Patients with genotype A appear to be more likely to clear circulating viremia and to achieve HBsAg seroconversion, both spontaneously and in response to antiviral therapy. In addition, "precore" mutations are favored by certain genotypes (see later in the chapter).

Upstream of the S gene are the pre-S genes (Fig. 95-3), which code for pre-S gene products, including receptors on the HBV surface for polymerized human serum albumin and for hepatocyte membrane proteins. The pre-S region actually consists of both pre-S1 and pre-S2. Depending on where translation is initiated, three potential HBsAg gene products are synthesized. The protein product of the S gene is HBsAg (*major protein*), the product of the S region plus the adjacent pre-S2 region is the *middle protein*, and the product of the pre-S1 plus pre-S2 plus S regions is the *large protein*. Compared with the smaller spherical and tubular particles of HBV, complete 42-nm virions are enriched in the large protein. Both pre-S proteins and their respective antibodies can be detected during HBV infection, and the period of pre-S antigenemia appears to coincide with other markers of virus replication, as detailed next.

The intact 42-nm virion contains a 27-nm nucleocapsid core particle. Nucleocapsid proteins are coded for by the C gene. The antigen expressed on the surface of the nucleocapsid core is referred to as *hepatitis B core antigen* (HBcAg), and its corresponding antibody is anti-HBc. A third HBV antigen is *hepatitis B e antigen* (HBeAg), a soluble, nonparticulate, nucleocapsid protein that is immunologically distinct from intact HBcAg, but is a product of the same C gene. The C gene has two initiation codons, a precore and a core region (Fig. 95-3). If translation is initiated at the precore region, the protein product is HBeAg, which has a signal peptide that binds it to the smooth endoplasmic reticulum and leads to its secretion into the circulation. If translation begins with the core region, HBcAg is the protein product; it has no signal peptide, it is not secreted, but it assembles into nucleocapsid particles, which bind to and incorporate RNA and which ultimately contain HBV DNA. Also packaged within the nucleocapsid core is a DNA polymerase, which directs replication and repair of HBV DNA. When packaging within viral proteins is complete, synthesis of the incomplete plus strand stops; this accounts for the single-strand gap and for differences in the size of the gap. HBcAg particles remain in the hepatocyte, where they are readily detectable by immunohistochemical staining, and are exported after encapsidation by an envelope of HBsAg. Therefore, naked core particles do not circulate in the serum. The secreted nucleocapsid protein, HBeAg, provides a convenient, readily detectable, qualitative marker of HBV replication and relative infectivity.

HBsAg-positive serum containing HBeAg is more likely to be highly infectious and to be associated with the presence of hepatitis B virions (and detectable HBV DNA, see later in the chapter) than HBeAg-negative or anti-HBe-positive serum. For example, HBsAg carrier mothers who are HBeAg-positive almost invariably (>90%) transmit hepatitis B infection to their offspring, whereas HBsAg carrier mothers with anti-HBe rarely (10–15%) infect their offspring.

Early during the course of acute hepatitis B, HBeAg appears transiently; its disappearance may be a harbinger of clinical improvement and resolution of infection. Persistence of HBeAg in serum beyond the first three months of acute infection may be predictive of the development of chronic infection, and the presence of HBeAg during chronic hepatitis B is associated with ongoing viral replication, infectivity, and inflammatory liver injury.

The third of the HBV genes is the largest, the P gene (Fig. 95-3), which codes for the DNA polymerase; as noted earlier, this enzyme has both DNA-dependent DNA polymerase and RNA-dependent reverse transcriptase activities. The fourth gene, X, codes for a small, nonparticulate protein, *hepatitis B x antigen* (HBxAg), that is capable of transactivating the transcription of both viral and cellular genes (Fig. 95-3). In the cytoplasm, HBxAg effects calcium release (possibly from mitochondria), which activates signal-transduction pathways that lead to stimulation of HBV reverse transcription and HBV DNA replication. Such transactivation may enhance the replication of HBV, leading to the clinical association observed between the expression of HBxAg and antibodies to it in patients with severe chronic hepatitis and hepatocellular carcinoma. The transactivating activity can enhance the transcription and replication of other viruses besides HBV, such as HIV. Cellular processes transactivated by X include the human interferon γ gene and class I major histocompatibility genes; potentially, these effects could contribute to enhanced susceptibility of HBV-infected hepatocytes to cytolytic T cells. The expression of X can also induce programmed cell death (apoptosis).

Serologic and virologic markers

After a person is infected with HBV, the first virologic marker detectable in serum within 1–12 weeks, usually between 8–12 weeks, is HBsAg **(Fig. 95-4)**. Circulating HBsAg precedes elevations of serum aminotransferase activity and clinical symptoms by 2–6 weeks and remains detectable during the entire icteric or symptomatic phase of acute hepatitis B and beyond. In typical cases, HBsAg becomes undetectable 1–2 months after the onset of jaundice and rarely persists beyond 6 months. After HBsAg disappears, antibody to HBsAg (anti-HBs) becomes detectable in serum and remains detectable indefinitely thereafter. Because HBcAg is intracellular and, when in the serum, sequestered within an HBsAg coat, naked core particles do not circulate in serum and, therefore, HBcAg is not detectable routinely in the serum of patients with HBV infection. By contrast, anti-HBc is readily demonstrable in serum, beginning within the first 1–2 weeks after the appearance of HBsAg and preceding detectable levels of anti-HBs by weeks to months. Because variability exists in the time of appearance of anti-HBs after HBV infection, occasionally a gap of several weeks or longer may separate the disappearance of HBsAg and the appearance of anti-HBs. During this "gap" or "window" period, anti-HBc may represent the only serologic evidence of current or recent HBV infection, and blood containing anti-HBc in the absence of HBsAg and anti-HBs has been implicated in the development of transfusion-associated hepatitis B. In part because the sensitivity of immunoassays for HBsAg and anti-HBs has increased, however, this window period is rarely encountered. In some persons, years after HBV infection, anti-HBc may persist in the circulation longer than anti-HBs. Therefore, isolated anti-HBc does not necessarily indicate active virus replication; most instances of isolated anti-HBc represent hepatitis B infection in the remote past. Rarely, however, isolated anti-HBc represents low-level hepatitis B viremia, with HBsAg below the detection threshold; occasionally, isolated anti-HBc represents a cross-reacting or false-positive immunologic specificity. Recent and remote HBV infections can be distinguished by determination of the immunoglobulin class of anti-HBc. Anti-HBc of the IgM class (IgM anti-HBc) predominates during the first six months after acute infection, whereas IgG anti-HBc is the predominant class of anti-HBc beyond six months. Therefore, patients with current or recent acute hepatitis B, including those in the anti-HBc window, have IgM anti-HBc in their serum. In patients who have recovered from hepatitis B in the remote past as well as those with chronic HBV infection, anti-HBc is predominantly of the IgG class. Infrequently, in ≤1–5% of patients with acute HBV infection, levels of HBsAg are too low to be detected; in such cases, the presence of IgM anti-HBc establishes the diagnosis of acute hepatitis B. When isolated anti-HBc occurs in the rare patient with chronic hepatitis B whose HBsAg level is below the sensitivity threshold of contemporary immunoassays (a low-level carrier), the anti-HBc is of the IgG class. Generally, in persons who have recovered from hepatitis B, anti-HBs and anti-HBc persist indefinitely.

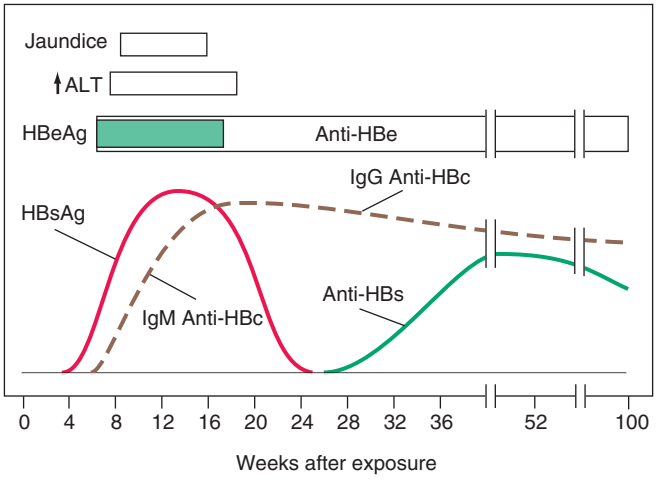


FIGURE 95-4
Scheme of typical clinical and laboratory features of acute hepatitis B.

The temporal association between the appearance of anti-HBs and resolution of HBV infection as well as the observation that persons with anti-HBs in serum are protected against reinfection with HBV suggests that *anti-HBs is the protective antibody*. Therefore, strategies for prevention of HBV infection are based on providing susceptible persons with circulating anti-HBs (see later in the chapter). Occasionally, in 10–20% of patients with chronic hepatitis B, low-level, low-affinity anti-HBs can be detected. This antibody is directed against a subtype determinant different from that represented by the patient's HBsAg; its presence is thought to reflect the stimulation of a related clone of antibody-forming cells, but it has no clinical relevance and does not signal imminent clearance of hepatitis B. These patients with HBsAg and such nonneutralizing anti-HBs should be categorized as having chronic HBV infection.

The other readily detectable serologic marker of HBV infection, HBeAg, appears concurrently with or shortly after HBsAg. Its appearance coincides temporally with high levels of virus replication and reflects the presence of circulating intact virions and detectable HBV DNA (with the notable exception of patients with precore mutations who cannot synthesize HBeAg—see "Molecular Variants"). Pre-S1 and pre-S2 proteins are also expressed during periods of peak replication, but assays for these gene products are not routinely available. In self-limited HBV infections, HBeAg becomes undetectable shortly after peak elevations in aminotransferase activity, before the disappearance of HBsAg, and anti-HBe then becomes detectable, coinciding with a period of relatively lower infectivity (Fig. 95-4). Because markers of HBV replication appear transiently during acute infection, testing for such markers is of little clinical utility in typical cases of acute HBV infection. In contrast, markers of HBV replication provide valuable information in patients with protracted infections.

Departing from the pattern typical of acute HBV infections, in chronic HBV infection, HBsAg remains detectable beyond six months, anti-HBc is primarily of the IgG class, and anti-HBs is either undetectable or detectable at low levels (see "Laboratory Features") **(Fig. 95-5)**. During early chronic HBV infection, HBV DNA can be detected both in serum and in hepatocyte nuclei, where it is present in free or episomal form. This *replicative stage* of HBV infection is the time of maximal infectivity and liver injury; HBeAg is a qualitative marker and HBV DNA a quantitative marker of this replicative phase, during which all three forms of HBV circulate, including intact virions. Over time, the replicative phase of chronic HBV infection gives way to a relatively *nonreplicative phase*. This occurs at a rate of ~10% per year and is accompanied by seroconversion from HBeAg-positive to anti-HBe-positive. In most cases, this seroconversion coincides with a transient, acute hepatitis-like elevation in aminotransferase activity, believed to reflect cell-mediated immune clearance of virus-infected hepatocytes. In the nonreplicative phase of chronic infection, when HBV DNA is demonstrable in hepatocyte nuclei, it tends to be integrated into the host genome. In this phase, only spherical and tubular forms of HBV, *not intact virions*, circulate, and liver injury tends to subside. Most such patients would be characterized as *inactive HBV carriers*. In reality, the designations *replicative* and *nonreplicative* are only relative; even in the so-called nonreplicative phase, HBV replication can be detected at levels of ~≤10^3 virions with highly sensitive amplification probes such as the polymerase chain reaction (PCR); below this replication threshold, liver injury and infectivity of HBV are limited to negligible. Still, the distinctions are pathophysiologically and clinically meaningful. Occasionally, nonreplicative HBV infection converts back to replicative infection. Such spontaneous reactivations are accompanied by re-expression of HBeAg and HBV DNA, and sometimes of IgM anti-HBc, as well as by exacerbations of liver injury. Because high-titer IgM anti-HBc can reappear during acute exacerbations of chronic hepatitis B, relying on IgM anti-HBc versus IgG anti-HBc to distinguish between acute and chronic hepatitis B infection, respectively, may not always be reliable; in such cases, patient history is invaluable in helping to distinguish de novo acute hepatitis B infection from acute exacerbation of chronic hepatitis B infection.

Molecular variants

Variation occurs throughout the HBV genome, and clinical isolates of HBV that do not express typical viral proteins have been attributed to mutations in individual or even multiple gene locations. For example, variants have been described that lack nucleocapsid proteins, envelope proteins, or both. Two categories of naturally occurring HBV variants have attracted the most attention. One of these was identified initially in Mediterranean countries among patients with an unusual serologic clinical profile. They have severe chronic HBV infection

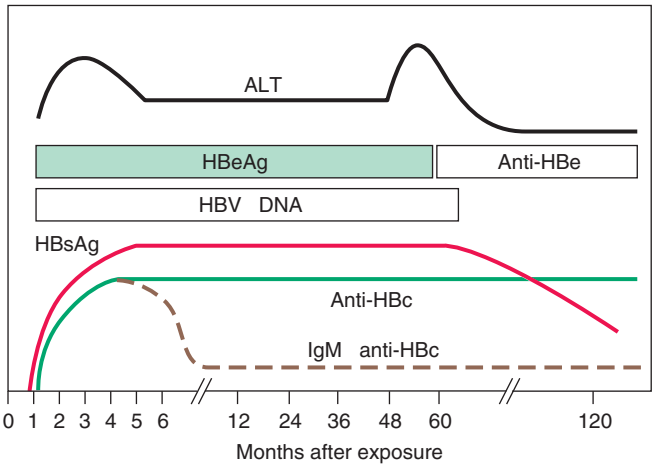


FIGURE 95-5

Scheme of typical laboratory features of wild-type chronic hepatitis B. HBeAg and HBV DNA can be detected in serum during the *replicative phase* of chronic infection, which is associated with infectivity and liver injury. Seroconversion from the replicative phase to the *nonreplicative phase* occurs at a rate of ~10% per year and is heralded by an acute hepatitis-like elevation of ALT activity; during the nonreplicative phase, infectivity and liver injury are limited. In HBeAg-negative chronic hepatitis B associated with mutations in the precore region of the HBV genome, replicative chronic hepatitis B occurs in the absence of HBeAg.

and detectable HBV DNA but with anti-HBe instead of HBeAg. These patients were found to be infected with an HBV mutant that contained an alteration in the precore region rendering the virus incapable of encoding HBeAg. Although several potential mutation sites exist in the pre-C region, the region of the C gene necessary for the expression of HBeAg (see "Virology and Etiology"), the most commonly encountered in such patients is a single base substitution, from G to A, which occurs in the second to last codon of the pre-C gene at nucleotide 1896. This substitution results in the replacement of the TGG tryptophan codon by a stop codon (T*A*G), which prevents the translation of HBeAg. Another mutation, in the core-promoter region, prevents transcription of the coding region for HBeAg and yields an HBeAg-negative phenotype. Patients with such mutations in the precore region and who are unable to secrete HBeAg tend to have severe liver disease that progresses more rapidly to cirrhosis or, alternatively, they are identified clinically later in the course of the natural history of chronic hepatitis B, when the disease is more advanced. Both "wild-type" HBV and precore-mutant HBV can coexist in the same patient, or mutant HBV may arise late during wild-type HBV infection. In addition, clusters of fulminant hepatitis B in Israel and Japan have been attributed to common-source infection with a precore mutant. Fulminant hepatitis B in North America and western Europe, however, occurs in patients infected with wild-type HBV, in the absence of precore mutants, and both precore mutants and other mutations throughout the HBV genome occur commonly,

even in patients with typical, self-limited, milder forms of HBV infection. HBeAg-negative chronic hepatitis with mutations in the precore region is now the most frequently encountered form of hepatitis B in Mediterranean countries and in Europe. In the United States, where HBV genotype A (less prone to G1896A mutation) is prevalent, precore-mutant HBV is much less common; however, as a result of immigration from Asia and Europe, the proportion of HBeAg-negative hepatitis B–infected individuals has increased in the United States, and they now represent approximately one-third of patients with chronic hepatitis B. Characteristic of such HBeAg-negative chronic hepatitis B are lower levels of HBV DNA (usually $\leq 10^5$ copies/mL) and one of several patterns of aminotransferase activity—persistent elevations, periodic fluctuations above the normal range, and periodic fluctuations between the normal and elevated range.

The second important category of HBV mutants consists of *escape mutants*, in which a single amino acid substitution, from glycine to arginine, occurs at position 145 of the immunodominant *a* determinant common to all subtypes of HBsAg. This change in HBsAg leads to a critical conformational change that results in a loss of neutralizing activity by anti-HBs. This specific HBV/*a* mutant has been observed in two situations, active and passive immunization, in which humoral immunologic pressure may favor evolutionary change ("escape") in the virus—in a small number of hepatitis B vaccine recipients who acquired HBV infection despite the prior appearance of neutralizing anti-HBs and in liver transplant recipients who underwent the procedure for hepatitis B and who were treated with a high-potency human monoclonal anti-HBs preparation. Although such mutants have not been recognized frequently, their existence raises a concern that may complicate vaccination strategies and serologic diagnosis.

Different types of mutations emerge during antiviral therapy of chronic hepatitis B with nucleoside analogues; such "YMDD" and similar mutations in the polymerase motif of HBV are described in Chap. 96.

Extrahepatic sites

Hepatitis B antigens and HBV DNA have been identified in extrahepatic sites, including lymph nodes, bone marrow, circulating lymphocytes, spleen, and pancreas. Although the virus does not appear to be associated with tissue injury in any of these extrahepatic sites, its presence in these "remote" reservoirs has been invoked (but is not necessary) to explain the recurrence of HBV infection after orthotopic liver transplantation. A more complete understanding of the clinical relevance of extrahepatic HBV remains to be defined.

Hepatitis D

The delta hepatitis agent, or HDV, the only member of the genus *Deltavirus*, is a defective RNA virus that coinfects with and requires the helper function of HBV (or other hepadnaviruses) for its replication and expression. Slightly smaller than HBV, delta is a formalin-sensitive, 35- to 37-nm virus with a hybrid structure. Its nucleocapsid expresses delta antigen, which bears no antigenic homology with any of the HBV antigens, and contains the virus genome. The delta core is "encapsidated" by an outer envelope of HBsAg, indistinguishable from that of HBV except in its relative compositions of major, middle, and large HBsAg component proteins. The genome is a small, 1700-nucleotide, circular, single-strand RNA of negative polarity that is nonhomologous with HBV DNA (except for a small area of the polymerase gene) but that has features and the rolling circle model of replication common to genomes of plant satellite viruses or viroids. HDV RNA contains many areas of internal complementarity; therefore, it can fold on itself by internal base pairing to form an unusual, very stable, rodlike structure that contains a very stable, self-cleaving and self-ligating ribozyme. HDV RNA requires host RNA polymerase II for its replication via RNA-directed RNA synthesis by transcription of genomic RNA to a complementary antigenomic (plus strand) RNA; the antigenomic RNA, in turn, serves as a template for subsequent genomic RNA synthesis. HDV RNA has only one open reading frame, and delta antigen (HDAg), a product of the antigenomic strand is the only known HDV protein; HDAg exists in two forms: a small, 195-amino-acid species, which plays a role in facilitating HDV RNA replication, and a large, 214-amino-acid species, which appears to suppress replication but is required for assembly of the antigen into virions. Delta antigens have been shown to bind directly to RNA polymerase II, resulting in stimulation of transcription. Although complete hepatitis D virions and liver injury require the cooperative helper function of HBV, intracellular replication of HDV RNA can occur without HBV. Genomic heterogeneity among HDV isolates has been described; however, pathophysiologic and clinical consequences of this genetic diversity have not been recognized. The clinical spectrum of hepatitis D is common to all seven genotypes identified, the predominant of which is genotype 1.

HDV can either infect a person simultaneously with HBV (*co-infection*) or superinfect a person already infected with HBV (*super-infection*); when HDV infection is transmitted from a donor with one HBsAg subtype to an HBsAg-positive recipient with a different subtype, the HDV agent assumes the HBsAg subtype of the recipient, rather than the donor. Because HDV relies absolutely on HBV, the duration of HDV infection is determined by the duration of (and cannot outlast) HBV infection. HDV antigen is expressed primarily in hepatocyte nuclei and is occasionally detectable in serum. During acute HDV infection, anti-HDV of the IgM class predominates, and 30–40 days may elapse after symptoms appear before anti-HDV can be detected. In self-limited infection, anti-HDV is low-titer and transient, rarely remaining detectable beyond the clearance of HBsAg and HDV antigen. In chronic HDV infection, anti-HDV circulates in high titer, and both IgM and IgG anti-HDV can be detected. HDV antigen in the liver and HDV RNA in serum and liver can be detected during HDV replication.

Hepatitis C

Hepatitis C virus, which, before its identification was labeled "non-A, non-B hepatitis," is a linear, single-strand, positive-sense, 9600-nucleotide RNA virus, the genome of which is similar in organization to that of flaviviruses and pestiviruses; HCV is the only member of the genus *Hepacivirus* in the family Flaviviridae. The HCV genome contains a single, large open reading frame (gene) that codes for a virus polyprotein of ~3000 amino acids, which is cleaved after translation to yield 10 viral proteins. The 5′ end of the genome consists of an untranslated region (containing an internal ribosomal entry site) adjacent to the genes for four structural proteins, the nucleocapsid core protein, C; two envelope glycoproteins, E1 and E2; and a membrane protein p7. The 5′ untranslated region and core gene are highly conserved among genotypes, but the envelope proteins are coded for by the hypervariable region, which varies from isolate to isolate and may allow the virus to evade host immunologic containment directed at accessible virus-envelope proteins. The 3′ end of the genome also includes an untranslated region and contains the genes for six nonstructural (NS) proteins NS2, NS3, NS4A, NS4B, NS5A, and NS5B. The NS2 cysteine protease cleaves NS3 from NS2, and the NS3-4A serine protease cleaves all the downstream proteins from the polyprotein. Important NS proteins involved in virus replication include the NS3 helicase, NS3-NS4A serine protease, and the NS5B RNA-dependent RNA polymerase **(Fig. 95-6)**. Because HCV does not replicate via a DNA intermediate, it does not integrate into the host genome. Because HCV tends to circulate in relatively low titer, 10^3–10^7 virions/mL, visualization of virus particles, estimated to be 40–60 nm in diameter, remains difficult. Still, the replication rate of HCV is very high, 10^{12} virions per day; its half-life is 2.7 hours. The chimpanzee is a helpful but cumbersome animal model. Although a robust, reproducible, small animal model is lacking, HCV replication has been documented in an immunodeficient mouse model containing explants of human liver and in transgenic mouse and rat models. Although in vitro replication has been difficult, hepatocellular carcinoma–derived cell lines have been described (replicon systems) that support replication of genetically manipulated, truncated, or full-length HCV RNA (but not intact virions). Recently, complete replication of HCV and intact 55-nm virions have been described in cell culture systems. HCV gains entry into the hepatocyte via the nonliver-specific CD81 receptor and the liver-specific tight junction protein claudin-1. Relying on the same assembly and secretion pathway as low-density lipoproteins (LPLs), HCV masquerades as a lipoprotein, which may limit its visibility to the adaptive immune system and which may explain its ability to evade immune containment and clearance.

At least six distinct major genotypes, as well as >50 subtypes within genotypes, of HCV have been identified by nucleotide sequencing. Genotypes differ one from another in sequence homology by ≥30%. Because divergence of HCV isolates within a genotype or subtype and, within the same host, may vary insufficiently to define a distinct genotype, these intragenotypic differences are referred to as *quasispecies* and differ in sequence homology by only a few percent. The genotypic and quasispecies diversity of HCV, resulting from its high mutation rate, interferes with effective humoral immunity. Neutralizing antibodies to HCV have been demonstrated, but they tend to be short lived, and HCV infection does not induce lasting immunity against reinfection with different virus isolates or even the same virus isolate. Thus, neither *heterologous* nor *homologous* immunity appears to develop commonly after acute HCV infection. Some HCV genotypes are distributed worldwide, while others are more geographically confined (see "Epidemiology and Global Features"). In addition, differences exist among genotypes in responsiveness to antiviral therapy; however, early reports of differences in pathogenicity among genotypes have not been corroborated.

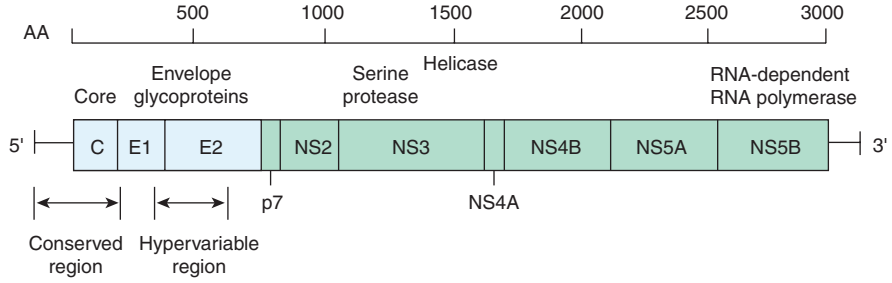


FIGURE 95-6

Organization of the hepatitis C virus genome and its associated, 3000 amino-acid (AA) proteins. The three structural genes at the 5′ end are the core region, C, which codes for the nucleocapsid, and the envelope regions, E1 and E2, which code for envelope glycoproteins. The 5′ untranslated region and the C region are highly conserved among isolates, while the envelope domain E2 contains the hypervariable region. Adjacent to the structural proteins is p7, a membrane protein that appears to function as an ion channel. At the 3′ end are six nonstructural (NS) regions: NS2, which codes for a cysteine protease; NS3, which codes for a serine protease and an RNA helicase; NS4A and NS4B; NS5A; and NS5B, which codes for an RNA-dependent RNA polymerase. After translation of the entire polyprotein, individual proteins are cleaved by both host and viral proteases.

Currently available, third-generation immunoassays, which incorporate proteins from the core, NS3, and NS5 regions, detect anti-HCV antibodies during acute infection. The most sensitive indicator of HCV infection is the presence of HCV RNA, which requires molecular amplification by PCR or transcription-mediated amplification (TMA) **(Fig. 95-7)**. To allow standardization of the quantification of HCV RNA among laboratories and commercial assays, HCV RNA is reported as international units (IUs) per milliliter; quantitative assays are available that allow detection of HCV RNA with a sensitivity as low as 5 IU/mL. HCV RNA can be detected within a few days of exposure to HCV—well before the appearance of anti-HCV—and tends to persist for the duration of HCV infection; however, occasionally in patients with chronic HCV infection, HCV RNA may be detectable only intermittently. Application of sensitive molecular probes for HCV RNA has revealed the presence of replicative HCV in peripheral blood lymphocytes of infected persons; however, as is the case for HBV in lymphocytes, the clinical relevance of HCV lymphocyte infection is not known.

Hepatitis E

Previously labeled *epidemic* or *enterically transmitted non-A, non-B hepatitis*, HEV is an enterically transmitted virus that occurs primarily in India, Asia, Africa, and Central America; in those geographic areas, HEV is the most common cause of acute hepatitis. This agent, with epidemiologic features resembling those of hepatitis A, is a 32- to 34-nm, nonenveloped, HAV-like virus with a 7600-nucleotide, single-strand, positive-sense RNA genome. HEV has three open reading frames (ORF) (genes), the largest of which, *ORF1*, encodes nonstructural proteins involved in virus replication. A middle-sized gene, *ORF2*, encodes the nucleocapsid protein, the major nonstructural protein, and the smallest, *ORF3*, encodes a structural protein whose function remains undetermined. All HEV isolates appear to belong to a single serotype, despite genomic heterogeneity of up to 25% and the existence of five genotypes, only four of which have been detected in humans; genotypes 1 and 2 appear to be more virulent, while genotypes 3 and 4 are more attenuated and account for subclinical infections. Contributing to the perpetuation of this virus are animal reservoirs, most notably in swine. There is no genomic or antigenic homology, however, between HEV and HAV or other picornaviruses; and HEV, although resembling caliciviruses, is sufficiently distinct from any known agent to merit a new classification of its own as a unique genus, *Hepevirus*, within the family Hepeviridae. The virus has been detected in stool, bile, and liver and is excreted in the stool during the late incubation period; immune responses to viral antigens occur very early during the course of acute infection. Both IgM anti-HEV and IgG anti-HEV can be detected, but both fall rapidly after acute infection, reaching low levels within 9–12 months. Currently, serologic testing for HEV infection is not available routinely.

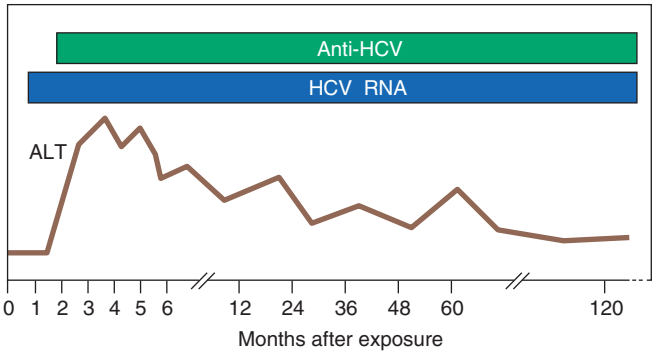


FIGURE 95-7
Scheme of typical laboratory features during acute hepatitis C progressing to chronicity. HCV RNA is the first detectable event, preceding alanine aminotransferase (ALT) elevation and the appearance of anti-HCV.

PATHOGENESIS

Under ordinary circumstances, none of the hepatitis viruses is known to be directly cytopathic to hepatocytes. Evidence suggests that the clinical manifestations and outcomes after acute liver injury associated with viral hepatitis are determined by the immunologic responses of the host. Among the viral hepatitides, the immunopathogenesis of hepatitis B and C have been studied most extensively.

Hepatitis B

For HBV, the existence of inactive hepatitis B carriers with normal liver histology and function suggests that the virus is not directly cytopathic. The fact that patients with defects in cellular immune competence are more likely to remain chronically infected rather than to clear HBV supports the role of cellular immune responses in the pathogenesis of hepatitis B–related liver injury. The model that has the most experimental support involves cytolytic T cells sensitized specifically to recognize host and hepatitis B viral antigens on the liver cell surface. Nucleocapsid proteins (HBcAg and possibly HBeAg), present on the cell membrane in minute quantities, are the viral target antigens that, with host antigens, invite cytolytic T cells to destroy HBV-infected hepatocytes. Differences in the robustness and broad polyclonality of CD8+ cytolytic T cell responsiveness and in the elaboration of antiviral cytokines by T cells have been invoked to explain differences in outcomes between those who recover after acute hepatitis, and those who progress to chronic hepatitis, or between those with mild and those with severe (fulminant) acute HBV infection.

Although a robust cytolytic T cell response occurs and eliminates virus-infected liver cells during acute hepatitis B, >90% of HBV DNA has been found in experimentally infected chimpanzees to disappear from the liver and blood before maximal T cell infiltration

of the liver and before most of the biochemical and histologic evidence of liver injury. This observation suggests that components of the innate immune system and inflammatory cytokines, independent of cytopathic antiviral mechanisms, participate in the early immune response to HBV infection; this effect has been shown to represent elimination of HBV replicative intermediates from the cytoplasm and covalently closed circular viral DNA from the nucleus of infected hepatocytes. Ultimately, HBV-HLA-specific cytolytic T cell responses of the adaptive immune system are felt to be responsible for recovery from HBV infection.

Debate continues over the relative importance of viral and host factors in the pathogenesis of HBV-associated liver injury and its outcome. As noted earlier, precore genetic mutants of HBV have been associated with the more severe outcomes of HBV infection (severe chronic and fulminant hepatitis), suggesting that, under certain circumstances, relative pathogenicity is a property of the virus, not the host. The fact that concomitant HDV and HBV infections are associated with more severe liver injury than HBV infection alone and the fact that cells transfected in vitro with the gene for HDV (delta) antigen express HDV antigen and then become necrotic in the absence of any immunologic influences are also consistent with a viral effect on pathogenicity. Similarly, in patients who undergo liver transplantation for end-stage chronic hepatitis B, occasionally, rapidly progressive liver injury appears in the new liver. This clinical pattern is associated with an unusual histologic pattern in the new liver, *fibrosing cholestatic hepatitis*, which, ultrastructurally, appears to represent a choking of the cell with overwhelming quantities of HBsAg. This observation suggests that, under the influence of the potent immunosuppressive agents required to prevent allograft rejection, HBV may have a direct cytopathic effect on liver cells, independent of the immune system.

Although the precise mechanism of liver injury in HBV infection remains elusive, studies of nucleocapsid proteins have shed light on the profound immunologic tolerance to HBV of babies born to mothers with highly replicative (HBeAg-positive), chronic HBV infection. In HBeAg-expressing transgenic mice, in utero exposure to HBeAg, which is sufficiently small to traverse the placenta, induces T cell tolerance to both nucleocapsid proteins. This, in turn, may explain why, when infection occurs so early in life, immunologic clearance does not occur, and protracted, lifelong infection ensues.

An important distinction should be drawn between HBV infection acquired at birth, common in endemic areas, such as the Far East, and infection acquired in adulthood, common in the west. Infection in the neonatal period is associated with the acquisition of immunologic tolerance to HBV, absence of an acute hepatitis illness, but the almost invariable establishment of chronic, often lifelong infection. Neonatally acquired HBV infection can culminate decades later in cirrhosis and hepatocellular carcinoma (see "Complications and Sequelae"). In contrast, when HBV infection is acquired during adolescence or early adulthood, the host immune response to HBV infected hepatocytes tends to be robust, an acute hepatitis-like illness is the rule, and failure to recover is the exception. After adulthood acquired infection, chronicity is uncommon, and the risk of hepatocellular carcinoma is very low. Based on these observations, some authorities categorize HBV infection into an "immunotolerant" phase, an "immunoreactive" phase, and an "inactive" phase. This somewhat simplistic formulation does not apply at all to the typical adult in the West with self-limited acute hepatitis B, in whom no period of immunologic tolerance occurs. Even among those with neonatally acquired HBV infection, in whom immunologic tolerance is established definitively, intermittent bursts of hepatic necroinflammatory activity punctuate the period during the early decades of life during which liver injury appears to be quiescent (labeled by some as the "immunotolerant" phase). In addition, even when clinically apparent, liver injury and progressive fibrosis emerge during later decades (the so-called immunoreactive, or immunointolerant phase), the level of immunologic tolerance to HBV remains substantial. More accurately, in patients with neonatally acquired HBV infection, a dynamic equilibrium exists between tolerance and intolerance, the outcome of which determines the clinical expression of chronic infection. Those individuals who are infected as neonates tend to have a relatively higher level of immunologic tolerance during the early decades of life and a relatively lower level (but only rarely a loss) of tolerance in the later decades of life.

Hepatitis C

Cell-mediated immune responses and elaboration by T cells of antiviral cytokines contribute to the containment of infection and pathogenesis of liver injury associated with hepatitis C. Perhaps HCV infection of lymphoid cells plays a role in moderating immune responsiveness to the virus, as well. Intrahepatic HLA class I restricted cytolytic T cells directed at nucleocapsid, envelope, and nonstructural viral protein antigens have been demonstrated in patients with chronic hepatitis C; however, such virus-specific cytolytic T cell responses do not correlate adequately with the degree of liver injury or with recovery. Yet, a consensus has emerged supporting a role in the pathogenesis of HCV-associated liver injury of virus-activated CD4 helper T cells that stimulate, via the cytokines they elaborate, HCV-specific CD8 cytotoxic T cells. These responses appear to be more robust (higher in number, more diverse in viral antigen specificity, more functionally effective, and more long lasting) in those who recover from HCV than in those who have chronic infection. Several HLA alleles have been linked with self-limited hepatitis C, the most convincing of which is the C/C haplotype of the IL28B gene. Although attention has focused on adaptive immunity, HCV proteins have been shown to interfere with innate immunity

by resulting in blocking of type 1 interferon responses and inhibition of interferon signaling and effector molecules in the interferon signaling cascade. Also shown to contribute to limiting HCV infection are natural killer cells of the innate immune system that function when HLA class 1 molecules required for successful adaptive immunity are underexpressed. Of note, the emergence of substantial viral quasispecies diversity and HCV sequence variation allow the virus to evade attempts by the host to contain HCV infection by both humoral and cellular immunity.

Finally, cross-reactivity between viral antigens (HCV NS3 and NS5A) and host autoantigens (cytochrome P450 2D6) has been invoked to explain the association between hepatitis C and a subset of patients with autoimmune hepatitis and antibodies to liver-kidney microsomal (LKM) antigen (anti-LKM) (Chap. 96).

EXTRAHEPATIC MANIFESTATIONS

Immune complex–mediated tissue damage appears to play a pathogenetic role in the extrahepatic manifestations of acute hepatitis B. The occasional prodromal serum sickness–like syndrome observed in acute hepatitis B appears to be related to the deposition in tissue blood vessel walls of HBsAg/anti-HBs circulating immune complexes, leading to activation of the complement system and depressed serum complement levels.

In patients with chronic hepatitis B, other types of immune-complex disease may be seen. Glomerulonephritis with the nephrotic syndrome is observed occasionally; HBsAg, immunoglobulin, and C3 deposition has been found in the glomerular basement membrane. While generalized vasculitis (polyarteritis nodosa) develops in considerably fewer than 1% of patients with chronic HBV infection, 20–30% of patients with polyarteritis nodosa have HBsAg in serum. In these patients, the affected small- and medium-size arterioles contain HBsAg, immunoglobulins, and complement components. Another extrahepatic manifestation of viral hepatitis, essential mixed cryoglobulinemia (EMC), was reported initially to be associated with hepatitis B. The disorder is characterized clinically by arthritis; cutaneous vasculitis (palpable purpura); and, occasionally, with glomerulonephritis and serologically by the presence of circulating cryoprecipitable immune complexes of more than one immunoglobulin class. Many patients with this syndrome have chronic liver disease, but the association with HBV infection is limited; instead, a substantial proportion has chronic HCV infection, with circulating immune complexes containing HCV RNA. Immune-complex glomerulonephritis is another recognized extrahepatic manifestation of chronic hepatitis C.

PATHOLOGY

The typical morphologic lesions of all types of viral hepatitis are similar and consist of panlobular infiltration with mononuclear cells, hepatic cell necrosis, hyperplasia of Kupffer cells, and variable degrees of cholestasis. Hepatic cell regeneration is present, as evidenced by numerous mitotic figures, multinucleated cells, and "rosette" or "pseudoacinar" formation. The mononuclear infiltration consists primarily of small lymphocytes, although plasma cells and eosinophils occasionally are present. Liver cell damage consists of hepatic cell degeneration and necrosis, cell dropout, ballooning of cells, and acidophilic degeneration of hepatocytes (forming so-called Councilman or apoptotic bodies). Large hepatocytes with a ground-glass appearance of the cytoplasm may be seen in chronic but not in acute HBV infection; these cells contain HBsAg and can be identified histochemically with orcein or aldehyde fuchsin. In uncomplicated viral hepatitis, the reticulin framework is preserved.

In hepatitis C, the histologic lesion is often remarkable for a relative paucity of inflammation, a marked increase in activation of sinusoidal lining cells, lymphoid aggregates, the presence of fat (more frequent in genotype 3 and linked to increased fibrosis), and, occasionally, bile duct lesions in which biliary epithelial cells appear to be piled up without interruption of the basement membrane. Occasionally, microvesicular steatosis occurs in hepatitis D. In hepatitis E, a common histologic feature is marked cholestasis. A cholestatic variant of slowly resolving acute hepatitis A also has been described.

A more severe histologic lesion, *bridging hepatic necrosis*, also termed *subacute* or *confluent necrosis* or *interface hepatitis*, is observed occasionally in acute hepatitis. "Bridging" between lobules results from large areas of hepatic cell dropout, with collapse of the reticulin framework. Characteristically, the bridge consists of condensed reticulum, inflammatory debris, and degenerating liver cells that span adjacent portal areas, portal to central veins, or central vein to central vein. This lesion had been thought to have prognostic significance; in many of the originally described patients with this lesion, a subacute course terminated in death within several weeks to months, or severe chronic hepatitis and cirrhosis developed; however, the association between bridging necrosis and a poor prognosis in patients with acute hepatitis has not been upheld. Therefore, although demonstration of this lesion in patients with chronic hepatitis has prognostic significance (Chap. 96), its demonstration during acute hepatitis is less meaningful, and liver biopsies to identify this lesion are no longer undertaken routinely in patients with acute hepatitis. In *massive hepatic necrosis* (fulminant hepatitis, "acute yellow atrophy"), the striking feature at postmortem examination is the finding of a small, shrunken, soft liver. Histologic examination reveals massive necrosis and dropout of liver cells of most lobules with extensive collapse and condensation of the reticulin framework. When histologic documentation is required in the management of fulminant or very severe hepatitis, a biopsy can be done by the angiographically guided transjugular route, which permits the performance of this invasive procedure in the presence of severe coagulopathy.

Immunohistochemical and electron-microscopic studies have localized HBsAg to the cytoplasm and plasma membrane of infected liver cells. In contrast, HBcAg predominates in the nucleus, but, occasionally, scant amounts are also seen in the cytoplasm and on the cell membrane. HDV antigen is localized to the hepatocyte nucleus, while HAV, HCV, and HEV antigens are localized to the cytoplasm.

EPIDEMIOLOGY AND GLOBAL FEATURES

Before the availability of serologic tests for hepatitis viruses, all viral hepatitis cases were labeled as either "infectious" or "serum" hepatitis. Modes of transmission overlap, however, and *a clear distinction among the different types of viral hepatitis cannot be made solely on the basis of clinical or epidemiologic features* **(Table 95-2)**. The most accurate means to distinguish the various types of viral hepatitis involves specific serologic testing.

Hepatitis A

This agent is transmitted almost exclusively by the fecal-oral route. Person-to-person spread of HAV is enhanced by poor personal hygiene and overcrowding; large outbreaks as well as sporadic cases have been traced to contaminated food, water, milk, frozen raspberries and strawberries, green onions imported from Mexico, and shellfish. Intrafamily and intrainstitutional spread are also common. Early epidemiologic observations supported a predilection for hepatitis A to occur in late fall and early winter. In temperate zones, epidemic waves have been recorded every 5–20 years as new segments of nonimmune population appeared; however, in developed countries, the incidence of hepatitis A has been declining, presumably as a function of improved sanitation, and these cyclic patterns are no longer observed. No HAV carrier state has been identified after acute hepatitis A; perpetuation of the virus in nature depends presumably on nonepidemic, inapparent subclinical infection, ingestion

TABLE 95-2

CLINICAL AND EPIDEMIOLOGIC FEATURES OF VIRAL HEPATITIS

FEATURE	HAV	HBV	HCV	HDV	HEV
Incubation (days)	15–45, mean 30	30–180, mean 60–90	15–160, mean 50	30–180, mean 60–90	14–60, mean 40
Onset	Acute	Insidious or acute	Insidious	Insidious or acute	Acute
Age preference	Children, young adults	Young adults (sexual and percutaneous), babies, toddlers	Any age, but more common in adults	Any age (similar to HBV)	Young adults (20–40 years)
Transmission					
Fecal-oral	+++	–	–	–	+++
Percutaneous	Unusual	+++	+++	+++	–
Perinatal	–	+++	±[a]	+	–
Sexual	±	++	±[a]	++	–
Clinical					
Severity	Mild	Occasionally severe	Moderate	Occasionally severe	Mild
Fulminant	0.1%	0.1–1%	0.1%	5–20%[b]	1–2%[e]
Progression to chronicity	None	Occasional (1–10%) (90% of neonates)	Common (85%)	Common[d]	None
Carrier	None	0.1–30%[c]	1.5–3.2%	Variable[f]	None
Cancer	None	+(Neonatal infection)	+	±	None
Prognosis	Excellent	Worse with age, debility	Moderate	Acute, good Chronic, poor	Good
Prophylaxis	IG, inactivated vaccine	HBIG, recombinant vaccine	None	HBV vaccine (none for HBV carriers)	Vaccine
Therapy	None	Interferon Lamivudine Adefovir Pegylated interferon Entecavir Telbivudine Tenofovir	Pegylated interferon plus ribavirin, telaprevir, boceprevir	Interferon or pegylated interferon (efficacy moderate)	None

[a]Primarily with HIV co-infection and high-level viremia in index case; risk ~5%.
[b]Up to 5% in acute HBV/HDV co-infection; up to 20% in HDV superinfection of chronic HBV infection.
[c]Varies considerably throughout the world and in subpopulations within countries; see text.
[d]In acute HBV/HDV co-infection, the frequency of chronicity is the same as that for HBV; in HDV superinfection, chronicity is invariable.
[e]10–20% in pregnant women.
[f]Common in Mediterranean countries, rare in North America and Western Europe.
Abbreviation: HBIG, hepatitis B immunoglobulin.

of contaminated food or water in, or imported from, endemic areas, and/or contamination linked to environmental reservoirs.

In the general population, anti-HAV, a marker for previous HAV infection, increases in prevalence as a function of increasing age and of decreasing socioeconomic status. In the 1970s, serologic evidence of prior hepatitis A infection occurred in ~40% of urban populations in the United States, most of whose members never recalled having had a symptomatic case of hepatitis. In subsequent decades, however, the prevalence of anti-HAV has been declining in the United States. In developing countries, exposure, infection, and subsequent immunity are almost universal in childhood. As the frequency of subclinical childhood infections declines in developed countries, a susceptible cohort of adults emerges. Hepatitis A tends to be more symptomatic in adults; therefore, paradoxically, as the frequency of HAV infection declines, the likelihood of clinically apparent, even severe, HAV illnesses increases in the susceptible adult population. Travel to endemic areas is a common source of infection for adults from nonendemic areas. More recently recognized epidemiologic foci of HAV infection include child-care centers, neonatal intensive care units, promiscuous men who have sex with men, and injection drug users. Although hepatitis A is rarely bloodborne, several outbreaks have been recognized in recipients of clotting-factor concentrates. In the United States, the introduction of hepatitis A vaccination programs among children from high-incidence states has resulted in a >70% reduction in the annual incidence of new HAV infections and has shifted the burden of new infections from children to young adults.

Hepatitis B

Percutaneous inoculation has long been recognized as a major route of hepatitis B transmission, but the outmoded designation "serum hepatitis" is an inaccurate label for the epidemiologic spectrum of HBV infection recognized today. As detailed next, most of the hepatitis transmitted by blood transfusion is not caused by HBV; moreover, in approximately two-thirds of patients with acute type B hepatitis, no history of an identifiable percutaneous exposure can be elicited. We now recognize that many cases of hepatitis B result from less obvious modes of nonpercutaneous or covert percutaneous transmission. HBsAg has been identified in almost every body fluid from infected persons, and at least some of these body fluids—most notably semen and saliva—are infectious, albeit less so than serum, when administered percutaneously or nonpercutaneously to experimental animals. Among the nonpercutaneous modes of HBV transmission, oral ingestion has been documented as a potential but inefficient route of exposure. By contrast, the two nonpercutaneous routes considered to have the greatest impact are intimate (especially sexual) contact and perinatal transmission.

In sub-Saharan Africa, intimate contact among toddlers is considered instrumental in contributing to the maintenance of the high frequency of hepatitis B in the population. Perinatal transmission occurs primarily in infants born to HBsAg carrier mothers or mothers with acute hepatitis B during the third trimester of pregnancy or during the early postpartum period. Perinatal transmission is uncommon in North America and Western Europe but occurs with great frequency and is the most important mode of HBV perpetuation in the Far East and developing countries. Although the precise mode of perinatal transmission is unknown, and although ~10% of infections may be acquired in utero, epidemiologic evidence suggests that most infections occur approximately at the time of delivery and are not related to breast-feeding. The likelihood of perinatal transmission of HBV correlates with the presence of HBeAg and high-level viral replication; 90% of HBeAg-positive mothers but only 10–15% of anti-HBe-positive mothers transmit HBV infection to their offspring. In most cases, acute infection in the neonate is clinically asymptomatic, but the child is very likely to remain chronically infected.

The >350–400 million HBsAg carriers in the world constitute the main reservoir of hepatitis B in human beings. Whereas serum HBsAg is infrequent (0.1–0.5%) in normal populations in the United States and western Europe, a prevalence of up to 5–20% has been found in the Far East and in some tropical countries; in persons with Down's syndrome, lepromatous leprosy, leukemia, Hodgkin's disease, polyarteritis nodosa; in patients with chronic renal disease on hemodialysis; and in injection drug users.

Other groups with high rates of HBV infection include spouses of acutely infected persons; sexually promiscuous persons (especially promiscuous men who have sex with men); health care workers exposed to blood; persons who require repeated transfusions especially with pooled blood-product concentrates (e.g., hemophiliacs); residents and staff of custodial institutions for the developmentally handicapped; prisoners; and, to a lesser extent, family members of chronically infected patients. In volunteer blood donors, the prevalence of anti-HBs, a reflection of previous HBV infection, ranges from 5–10%, but the prevalence is higher in lower socioeconomic strata, older age groups, and persons—including those just mentioned—exposed to blood products. Because of highly sensitive virologic screening of donor blood, the risk of acquiring HBV infection from a blood transfusion is 1 in 230,000.

Prevalence of infection, modes of transmission, and human behavior conspire to mold geographically different epidemiologic patterns of HBV infection. In the Far East and Africa, hepatitis B, a disease of the newborn and young children, is perpetuated by a cycle of maternal-neonatal spread. In North America and Western Europe, hepatitis B is primarily a disease of adolescence and early adulthood, the time of life when intimate sexual contact as well as recreational and occupational percutaneous exposures tend to occur. To some degree, however, this dichotomy between high-prevalence and low-prevalence geographic regions has been minimized by immigration from high-prevalence to low-prevalence areas. The introduction of hepatitis

B vaccine in the early 1980s and adoption of universal childhood vaccination policies in many countries resulted in a dramatic ~90% decline in the incidence of new HBV infections in those countries as well as in the dire consequences of chronic infection, including hepatocellular carcinoma. Populations and groups for whom HBV-infection screening is recommended are listed in **Table 95-3**.

Hepatitis D

Infection with HDV has a worldwide distribution, but two epidemiologic patterns exist. In Mediterranean countries (northern Africa, southern Europe, the Middle East), HDV infection is endemic among those with hepatitis B, and the disease is transmitted predominantly by nonpercutaneous means, especially close personal contact. In nonendemic areas, such as the United States and northern Europe, HDV infection is confined to persons exposed frequently to blood and blood products, primarily injection drug users and hemophiliacs. HDV infection can be introduced into a population through drug users or by migration of persons from endemic to nonendemic areas. Thus, patterns of population migration and human behavior facilitating percutaneous contact play important roles in the introduction and amplification of HDV infection. Occasionally, the migrating epidemiology of hepatitis D is expressed in explosive outbreaks of severe hepatitis, such as those that have occurred in remote South American villages as well as in urban centers in the United States. Ultimately, such outbreaks of hepatitis D—either of co-infections with acute hepatitis B or of superinfections in those already infected with HBV—may blur the distinctions between endemic and nonendemic areas. On a global scale, HDV infection declined at the end of the 1990s. Even in Italy, an HDV-endemic area, public health measures introduced to control HBV infection resulted during the 1990s in a 1.5%/year reduction in the prevalence of HDV infection. Still, the frequency of HDV infection during the first decade of the twenty-first century has not fallen below levels reached during the 1990s; the reservoir has been sustained by survivors infected during 1970–1980 and recent immigrants from still-endemic to less-endemic countries.

TABLE 95-3

HIGH-RISK POPULATIONS FOR WHICH HBV-INFECTION SCREENING IS RECOMMENDED

Persons born in countries/regions with a high (>8%) or intermediate (>2%) prevalence of HBV infection, including immigrants and adopted children, and persons born in the United States who were not vaccinated as infants and whose parents immigrated from areas of high HBV endemicity
Household and sexual contacts of persons with hepatitis B
Persons who have used injection drugs
Persons with multiple sexual contacts or a history of sexually transmitted disease
Men who have sex with men
Inmates of correctional facilities
Persons with elevated alanine or aspartate aminotransferase levels
Persons with HCV or HIV infection
Hemodialysis patients
Pregnant women
Persons who require immunosuppressive or cytotoxic therapy

Hepatitis C

Routine screening of blood donors for HBsAg and the elimination of commercial blood sources in the early 1970s reduced the frequency of, but did not eliminate, transfusion-associated hepatitis. During the 1970s, the likelihood of acquiring hepatitis after transfusion of voluntarily donated, HBsAg-screened blood was ~10% per patient (up to 0.9% per unit transfused); 90–95% of these cases were classified, based on serologic exclusion of hepatitis A and B, as "non-A, non-B" hepatitis. For patients requiring transfusion of pooled products, such as clotting factor concentrates, the risk was even higher, up to 20–30%.

During the 1980s, voluntary self-exclusion of blood donors with risk factors for AIDS and then the introduction of donor screening for anti-HIV reduced further the likelihood of transfusion-associated hepatitis to <5%. During the late 1980s and early 1990s, the introduction first of "surrogate" screening tests for non-A, non-B hepatitis (alanine aminotransferase [ALT] and anti-HBc, both shown to identify blood donors with a higher likelihood of transmitting non-A, non-B hepatitis to recipients) and, subsequently, after the discovery of HCV, first-generation immunoassays for anti-HCV reduced the frequency of transfusion-associated hepatitis even further. A prospective analysis of transfusion-associated hepatitis conducted between 1986 and 1990 showed that the frequency of transfusion-associated hepatitis at one urban university hospital fell from a baseline of 3.8% per patient (0.45% per unit transfused) to 1.5% per patient (0.19% per unit) after the introduction of surrogate testing and to 0.6% per patient (0.03% per unit) after the introduction of first-generation anti-HCV assays. The introduction of second-generation anti-HCV assays reduced the frequency of transfusion-associated hepatitis C to almost imperceptible levels—1 in 100,000—and these gains were reinforced by the application of third-generation anti-HCV assays and of automated PCR testing of donated blood for HCV RNA, which has resulted in a reduction in the risk of transfusion-associated HCV infection to 1 in 2.3 million transfusions.

In addition to being transmitted by transfusion, hepatitis C can be transmitted by other percutaneous routes, such as injection drug use. In addition, this virus can

be transmitted by occupational exposure to blood, and the likelihood of infection is increased in hemodialysis units. Although the frequency of transfusion-associated hepatitis C fell as a result of blood-donor screening, the overall frequency of hepatitis C remained the same until the early 1990s, when the overall frequency fell by 80%, in parallel with a reduction in the number of new cases in injection drug users. After the exclusion of anti-HCV-positive plasma units from the donor pool, rare, sporadic instances have occurred of hepatitis C among recipients of immunoglobulin (IG) preparations for intravenous (but not intramuscular) use.

Serologic evidence for HCV infection occurs in 90% of patients with a history of transfusion-associated hepatitis (almost all occurring before 1992, when second-generation HCV-screening tests were introduced); hemophiliacs and others treated with clotting factors; injection drug users; 60–70% of patients with sporadic "non-A, non-B" hepatitis who lack identifiable risk factors; 0.5% of volunteer blood donors; and, in the most recent survey conducted in the United States between 1999 and 2000, 1.6% of the general population in the United States, which translates into 4.1 million persons (3.2 million with viremia). Comparable frequencies of HCV infection occur in most countries around the world, with 170 million persons infected worldwide, but extraordinarily high prevalences of HCV infection occur in certain countries such as Egypt, where >20% of the population in some cities is infected. The high frequency in Egypt is attributable to contaminated equipment used for medical procedures and unsafe injection practices in the 1970s. In the United States, African Americans and Mexican Americans have higher frequencies of HCV infection than whites. Between 1988 and 1994, 30- to 40-year-old adult males had the highest prevalence of HCV infection; however, in a survey conducted between 1999 and 2000, the peak age decile had shifted to those age 40–49 years; an increase in hepatitis C–related mortality has paralleled this secular trend, increasing since 1995 predominantly in the 55- to 64-year age group. Thus, despite an 80% reduction in new HCV infections during the 1990s, the prevalence of HCV infection in the population was sustained by an aging cohort that had acquired their infections 2 to 3 decades earlier, during the 1960s and 1970s, as a result predominantly of self-inoculation with recreational drugs. Hepatitis C accounts for 40% of chronic liver disease, is the most frequent indication for liver transplantation, and is estimated to account for 8000–10,000 deaths per year in the United States.

The distribution of HCV genotypes varies in different parts of the world. Worldwide, genotype 1 is the most common. In the United States, genotype 1 accounts for 70% of HCV infections, while genotypes 2 and 3 account for the remaining 30%; among African Americans, the frequency of genotype 1 is even higher (i.e., 90%). Genotype 4 predominates in Egypt; genotype 5 is localized to South Africa, and genotype 6 to Hong Kong.

Most asymptomatic blood donors found to have anti-HCV and ~20–30% of persons with reported cases of acute hepatitis C do not fall into a recognized risk group; however, many such blood donors do recall risk-associated behaviors when questioned carefully.

As a bloodborne infection, HCV potentially can be transmitted sexually and perinatally; however, both of these modes of transmission are inefficient for hepatitis C. Although 10–15% of patients with acute hepatitis C report having potential sexual sources of infection, most studies have failed to identify sexual transmission of this agent. The chances of sexual and perinatal transmission have been estimated to be ~5%, well below comparable rates for HIV and HBV infections. Moreover, sexual transmission appears to be confined to such subgroups as persons with multiple sexual partners and sexually transmitted diseases; transmission of HCV infection is rare between stable, monogamous sexual partners. Breast-feeding does not increase the risk of HCV infection between an infected mother and her infant. Infection of health workers is not dramatically higher than among the general population; however, health workers are more likely to acquire HCV infection through accidental needle punctures, the efficiency of which is ~3%. Infection of household contacts is rare as well.

Other groups with an increased frequency of HCV infection include patients who require hemodialysis and organ transplantation, those who require transfusions in the setting of cancer chemotherapy, HIV-infected persons, and persons with unexplained serum aminotransferase elevations. In immunosuppressed individuals, levels of anti-HCV may be undetectable, and a diagnosis may require testing for HCV RNA. Although new acute cases of hepatitis C are rare, newly diagnosed cases are common among otherwise healthy persons who experimented briefly with injection drugs, as noted earlier, 2 or 3 decades earlier. Such instances usually remain unrecognized for years, until unearthed by laboratory screening for routine medical examinations, insurance applications, and attempted blood donation. Populations groups for whom HCV-infection screening is recommended are listed in **Table 95-4**.

TABLE 95-4

HIGH-RISK POPULATIONS FOR WHICH HCV-INFECTION SCREENING IS RECOMMENDED

Persons who have used injection drugs or those who have used illicit drugs by noninjection routes
Persons with HIV infection
Hemophiliacs treated with clotting factor concentrates prior to 1987
Hemodialysis patients
Persons with unexplained elevations of aminotransferase levels
Transfusion or transplantation recipients prior to July 1992
Children born to women with hepatitis C
Health care, public safety, and emergency medical personnel following needle injury or mucosal exposure to HCV-contaminated blood
Sexual partners of persons with hepatitis C infection

Hepatitis E

This type of hepatitis, identified in India, Asia, Africa, the Middle East, and Central America, resembles hepatitis A in its primarily enteric mode of spread. The commonly recognized cases occur after contamination of water supplies such as after monsoon flooding, but sporadic, isolated cases occur. An epidemiologic feature that distinguishes HEV from other enteric agents is the rarity of secondary person-to-person spread from infected persons to their close contacts. Infections arise in populations that are immune to HAV and favor young adults. In endemic areas, the prevalence of antibodies to HEV is ≤40%. In nonendemic areas of the world, such as the United States, clinically apparent acute hepatitis E is extremely rare; however, the prevalence of antibodies to HEV can be as high as 20% in such areas. In nonendemic areas, HEV does not account for any of the sporadic "non-A, non-B" cases of hepatitis; however, cases imported from endemic areas have been found in the United States. Several reports suggest a zoonotic reservoir for HEV in swine.

CLINICAL AND LABORATORY FEATURES

Symptoms and signs

Acute viral hepatitis occurs after an incubation period that varies according to the responsible agent. Generally, incubation periods for hepatitis A range from 15–45 days (mean, 4 weeks), for hepatitis B and D from 30–180 days (mean, 8–12 weeks), for hepatitis C from 15–160 days (mean, 7 weeks), and for hepatitis E from 14–60 days (mean, 5–6 weeks). The *prodromal symptoms* of acute viral hepatitis are systemic and quite variable. Constitutional symptoms of anorexia, nausea and vomiting, fatigue, malaise, arthralgias, myalgias, headache, photophobia, pharyngitis, cough, and coryza may precede the onset of jaundice by 1–2 weeks. The nausea, vomiting, and anorexia are frequently associated with alterations in olfaction and taste. A low-grade fever between 38° and 39°C (100°–102°F) is more often present in hepatitis A and E than in hepatitis B or C, except when hepatitis B is heralded by a serum sickness–like syndrome; rarely, a fever of 39.5°–40°C (103°–104°F) may accompany the constitutional symptoms. Dark urine and clay-colored stools may be noticed by the patient from 1–5 days before the onset of clinical jaundice.

With the onset of *clinical jaundice*, the constitutional prodromal symptoms usually diminish, but in some patients mild weight loss (2.5–5 kg) is common and may continue during the entire icteric phase. The liver becomes enlarged and tender and may be associated with right upper quadrant pain and discomfort. Infrequently, patients present with a cholestatic picture, suggesting extrahepatic biliary obstruction. Splenomegaly and cervical adenopathy are present in 10–20% of patients with acute hepatitis. Rarely, a few spider angiomas appear during the icteric phase and disappear during convalescence. During the *recovery phase*, constitutional symptoms disappear, but usually some liver enlargement and abnormalities in liver biochemical tests are still evident. The duration of the posticteric phase is variable (range, 2–12 weeks) and is usually more prolonged in acute hepatitis B and C. Complete clinical and biochemical recovery is to be expected 1–2 months after all cases of hepatitis A and E and 3–4 months after the onset of jaundice in three-quarters of uncomplicated, self-limited cases of hepatitis B and C (among healthy adults, acute hepatitis B is self-limited in 95–99% while hepatitis C is self-limited in only ~15%). In the remainder, biochemical recovery may be delayed. A substantial proportion of patients with viral hepatitis never become icteric.

Infection with HDV can occur in the presence of acute or chronic HBV infection; the duration of HBV infection determines the duration of HDV infection. When acute HDV and HBV infection occur simultaneously, clinical and biochemical features may be indistinguishable from those of HBV infection alone, although occasionally they are more severe. As opposed to patients with *acute* HBV infection, patients with *chronic* HBV infection can support HDV replication indefinitely. This can happen when acute HDV infection occurs in the presence of a nonresolving acute HBV infection. More commonly, acute HDV infection becomes chronic when it is superimposed on an underlying chronic HBV infection. In such cases, the HDV superinfection appears as a clinical exacerbation or an episode resembling acute viral hepatitis in someone already chronically infected with HBV. Superinfection with HDV in a patient with chronic hepatitis B often leads to clinical deterioration (see later in the chapter).

In addition to superinfections with other hepatitis agents, acute hepatitis-like clinical events in persons with chronic hepatitis B may accompany spontaneous HBeAg to anti-HBe seroconversion or spontaneous reactivation (i.e., reversion from nonreplicative to replicative infection). Such reactivations can occur as well in therapeutically immunosuppressed patients with chronic HBV infection when cytotoxic/immunosuppressive drugs are withdrawn; in these cases, restoration of immune competence is thought to allow resumption of previously checked cell-mediated immune cytolysis of HBV-infected hepatocytes. Occasionally, acute clinical exacerbations of chronic hepatitis B may represent the emergence of a precore mutant (see "Virology and Etiology"), and the subsequent course in such patients may be characterized by periodic exacerbations.

Laboratory features

The serum aminotransferases aspartate aminotransferase (AST) and ALT (previously designated SGOT and SGPT) show a variable increase during the prodromal phase of acute viral hepatitis and precede the rise in bilirubin level (Figs. 95-2 and 95-4). The acute level of these enzymes, however, does not correlate well with the degree of liver cell damage. Peak levels vary from 400–4000 IU or more; these levels are usually reached at the time the patient is clinically icteric and diminish progressively during the recovery phase of acute hepatitis.

The diagnosis of anicteric hepatitis is based on clinical features and on aminotransferase elevations.

Jaundice is usually visible in the sclera or skin when the serum bilirubin value is >43 μmol/L (2.5 mg/dL). When jaundice appears, the serum bilirubin typically rises to levels ranging from 85–340 μmol/L (5–20 mg/dL). The serum bilirubin may continue to rise despite falling serum aminotransferase levels. In most instances, the total bilirubin is equally divided between the conjugated and unconjugated fractions. Bilirubin levels >340 μmol/L (20 mg/dL) extending and persisting late into the course of viral hepatitis are more likely to be associated with severe disease. In certain patients with underlying hemolytic anemia, however, such as glucose-6-phosphate dehydrogenase deficiency and sickle cell anemia, a high serum bilirubin level is common, resulting from superimposed hemolysis. In such patients, bilirubin levels >513 μmol/L (30 mg/dL) have been observed and are not necessarily associated with a poor prognosis.

Neutropenia and lymphopenia are transient and are followed by a relative lymphocytosis. Atypical lymphocytes (varying between 2 and 20%) are common during the acute phase. Measurement of the prothrombin time (PT) is important in patients with acute viral hepatitis, for a prolonged value may reflect a severe hepatic synthetic defect, signify extensive hepatocellular necrosis, and indicate a worse prognosis. Occasionally, a prolonged PT may occur with only mild increases in the serum bilirubin and aminotransferase levels. Prolonged nausea and vomiting, inadequate carbohydrate intake, and poor hepatic glycogen reserves may contribute to hypoglycemia noted occasionally in patients with severe viral hepatitis. Serum alkaline phosphatase may be normal or only mildly elevated, while a fall in serum albumin is uncommon in uncomplicated acute viral hepatitis. In some patients, mild and transient steatorrhea has been noted as well as slight microscopic hematuria and minimal proteinuria.

A diffuse but mild elevation of the γ globulin fraction is common during acute viral hepatitis. Serum IgG and IgM levels are elevated in about one-third of patients during the acute phase of viral hepatitis, but the serum IgM level is elevated more characteristically during acute hepatitis A. During the acute phase of viral hepatitis, antibodies to smooth muscle and other cell constituents may be present, and low titers of rheumatoid factor, nuclear antibody, and heterophil antibody can also be found occasionally. In hepatitis C and D, antibodies to LKM may occur; however, the species of LKM antibodies in the two types of hepatitis are different from each other as well as from the LKM antibody species characteristic of autoimmune hepatitis type 2 (Chap. 96). The autoantibodies in viral hepatitis are nonspecific and can also be associated with other viral and systemic diseases. In contrast, virus-specific antibodies, which appear during and after hepatitis virus infection, are serologic markers of diagnostic importance.

As described earlier, serologic tests are available with which to establish a diagnosis of hepatitis A, B, D, and C. Tests for fecal or serum HAV are not routinely available. Therefore, a diagnosis of hepatitis A is based on detection of IgM anti-HAV during acute illness (Fig. 95-2). Rheumatoid factor can give rise to false-positive results in this test.

A diagnosis of HBV infection can usually be made by detection of HBsAg in serum. Infrequently, levels of HBsAg are too low to be detected during acute HBV infection, even with contemporary, highly sensitive immunoassays. In such cases, the diagnosis can be established by the presence of IgM anti-HBc.

The titer of HBsAg bears little relation to the severity of clinical disease. Indeed, an inverse correlation exists between the serum concentration of HBsAg and the degree of liver cell damage. For example, titers are highest in immunosuppressed patients, lower in patients with chronic liver disease (but higher in mild chronic than in severe chronic hepatitis), and very low in patients with acute fulminant hepatitis. These observations suggest that, in hepatitis B, the degree of liver cell damage and the clinical course are related to variations in the patient's immune response to HBV rather than to the amount of circulating HBsAg. In immunocompetent persons, however, a correlation exists between markers of HBV *replication* and liver injury (see later in the chapter).

Another serologic marker that may be of value in patients with hepatitis B is HBeAg. Its principal clinical usefulness is as an indicator of relative infectivity. Because HBeAg is invariably present during early acute hepatitis B, HBeAg testing is indicated primarily during follow-up of chronic infection.

In patients with hepatitis B surface antigenemia of unknown duration (e.g., blood donors found to be HBsAg-positive and referred to a physician for evaluation), testing for IgM anti-HBc may be useful to distinguish between acute or recent infection (IgM anti-HBc-positive) and chronic HBV infection (IgM anti-HBc-negative, IgG anti-HBc-positive). A false-positive test for IgM anti-HBc may be encountered in patients with high-titer rheumatoid factor.

Anti-HBs is rarely detectable in the presence of HBsAg in patients with *acute* hepatitis B, but 10–20% of persons with *chronic* HBV infection may harbor low-level anti-HBs. This antibody is directed not against the common group determinant, *a*, but against the heterotypic subtype determinant (e.g., HBsAg of subtype *ad* with anti-HBs of subtype *y*). In most cases, this serologic pattern cannot be attributed to infection with two different HBV subtypes, and the presence of this antibody is not a harbinger of imminent HBsAg clearance. When such antibody is detected, its presence is of no recognized clinical significance (see "Virology and Etiology").

After immunization with hepatitis B vaccine, which consists of HBsAg alone, anti-HBs is the only serologic marker to appear. The commonly encountered serologic patterns of hepatitis B and their interpretations are summarized in **Table 95-5**. Tests for the detection of HBV DNA in liver and serum are now available. Like HBeAg, serum HBV DNA is an indicator of HBV replication, but tests for HBV DNA are more sensitive and quantitative. First-generation hybridization assays for HBV DNA had a sensitivity of 10^5–10^6 virions/mL,

TABLE 95-5

COMMONLY ENCOUNTERED SEROLOGIC PATTERNS OF HEPATITIS B INFECTION

HBsAg	ANTI-HBs	ANTI-HBc	HBeAg	ANTI-HBe	INTERPRETATION
+	–	IgM	+	–	Acute hepatitis B, high infectivity
+	–	IgG	+	–	Chronic hepatitis B, high infectivity
+	–	IgG	–	+	1. Late acute or chronic hepatitis B, low infectivity 2. HBeAg–negative ("precore–mutant") hepatitis B (chronic or, rarely, acute)
+	+	+	+/–	+/–	1. HBsAg of one subtype and heterotypic anti–HBs (common) 2. Process of seroconversion from HBsAg to anti–HBs (rare)
–	–	IgM	+/–	+/–	1. Acute hepatitis B 2. Anti–HBc "window"
–	–	IgG	–	+/–	1. Low–level hepatitis B carrier 2. Hepatitis B in remote past
–	+	IgG	–	+/–	Recovery from hepatitis B
–	+	–	–	–	1. Immunization with HBsAg (after vaccination) 2. Hepatitis B in the remote past (?) 3. False–positive

a relative threshold below which infectivity and liver injury are limited and HBeAg is usually undetectable. Currently, testing for HBV DNA has shifted from insensitive hybridization assays to amplification assays (e.g., the PCR-based assay, which can detect as few as 10 or 100 virions/mL); among the commercially available PCR assays, the most useful are those with the highest sensitivity (5–10 IU/mL) and the largest dynamic range (10^0–10^9 IU/mL). With increased sensitivity, amplification assays remain reactive well below the threshold for infectivity and liver injury. These markers are useful in following the course of HBV replication in patients with chronic hepatitis B receiving antiviral chemotherapy (e.g., with interferon or nucleoside analogues) (Chap. 96). In immunocompetent persons with chronic hepatitis B, a general correlation does appear to exist between the level of HBV replication, as reflected by the level of HBV DNA in serum, and the degree of liver injury. High-serum HBV DNA levels, increased expression of viral antigens, and necroinflammatory activity in the liver go hand in hand unless immunosuppression interferes with cytolytic T cell responses to virus-infected cells; reduction of HBV replication with antiviral drugs tends to be accompanied by an improvement in liver histology. Among patients with chronic hepatitis B, high levels of HBV DNA increase the risk of cirrhosis, hepatic decompensation, and hepatocellular carcinoma (see "Complications and Sequelae").

In patients with hepatitis C, an episodic pattern of aminotransferase elevation is common. A specific serologic diagnosis of hepatitis C can be made by demonstrating the presence in serum of anti-HCV. When contemporary immunoassays are used, anti-HCV can be detected in acute hepatitis C during the initial phase of elevated aminotransferase activity. This antibody may never become detectable in 5–10% of patients with acute hepatitis C, and levels of anti-HCV may become undetectable after recovery (albeit rare) from acute hepatitis C. In patients with chronic hepatitis C, anti-HCV is detectable in >95% of cases. Nonspecificity can confound immunoassays for anti-HCV, especially in persons with a low prior probability of infection, such as volunteer blood donors, or in persons with circulating rheumatoid factor, which can bind nonspecifically to assay reagents; testing for HCV RNA can be used in such settings to distinguish between true-positive and false-positive anti-HCV determinations. Assays for HCV RNA are the most sensitive tests for HCV infection and represent the "gold standard" in establishing a diagnosis of hepatitis C. HCV RNA can be detected even before acute elevation of aminotransferase activity and before the appearance of anti-HCV in patients with acute hepatitis C. In addition, HCV RNA remains detectable indefinitely, continuously in most but intermittently in some, in patients with chronic hepatitis C (detectable as well in some persons with normal liver tests (i.e., inactive carriers). In the small minority of patients with hepatitis C who lack anti-HCV, a diagnosis can be supported by detection of HCV RNA. If all these tests are negative and the patient has a well-characterized case of hepatitis after percutaneous exposure to blood or blood products, a diagnosis of hepatitis caused by an unidentified agent can be entertained.

Amplification techniques are required to detect HCV RNA, and two types are available. One is a branched-chain complementary DNA (bDNA) assay, in which the detection signal (a colorimetrically detectable enzyme bound to a complementary DNA probe) is amplified. The other involves target amplification (i.e., synthesis of multiple copies of the viral genome). This can be done by PCR or TMA, in which the viral RNA is reverse transcribed to complementary DNA and then amplified by repeated cycles of DNA synthesis. Both can be used as quantitative assays and a measurement of

relative "viral load"; PCR and TMA, with a sensitivity of 10–10^2 IU/mL, are more sensitive than bDNA, with a sensitivity of 10^3 IU/mL; assays are available with a wide dynamic range (10–10^7 IU/mL). Determination of HCV RNA level is not a reliable marker of disease severity or prognosis but is helpful in predicting relative responsiveness to antiviral therapy. The same is true for determinations of HCV genotype (Chap. 96).

A proportion of patients with hepatitis C have isolated anti-HBc in their blood, a reflection of a common risk in certain populations of exposure to multiple bloodborne hepatitis agents. The anti-HBc in such cases is almost invariably of the IgG class and usually represents HBV infection in the remote past (HBV DNA undetectable), rarely current HBV infection with low-level virus carriage.

The presence of HDV infection can be identified by demonstrating intrahepatic HDV antigen or, more practically, an anti-HDV seroconversion (a rise in titer of anti-HDV or de novo appearance of anti-HDV). Circulating HDV antigen, also diagnostic of acute infection, is detectable only briefly, if at all. Because anti-HDV is often undetectable once HBsAg disappears, retrospective serodiagnosis of acute self-limited, simultaneous HBV and HDV infection is difficult. Early diagnosis of acute infection may be hampered by a delay of up to 30–40 days in the appearance of anti-HDV.

When a patient presents with acute hepatitis and has HBsAg and anti-HDV in serum, determination of the class of anti-HBc is helpful in establishing the relationship between infection with HBV and HDV. Although IgM anti-HBc does not distinguish *absolutely* between acute and chronic HBV infection, its presence is a reliable indicator of recent infection and its absence a reliable indicator of infection in the remote past. In simultaneous acute HBV and HDV infections, IgM anti-HBc will be detectable, while in acute HDV infection superimposed on chronic HBV infection, anti-HBc will be of the IgG class.

Tests for the presence of HDV RNA are useful for determining the presence of ongoing HDV replication and relative infectivity. Diagnostic tests for hepatitis E are commercially available in several countries outside the United States; in the United States, diagnostic assays can be performed at the Centers for Disease Control and Prevention.

Liver biopsy is rarely necessary or indicated in acute viral hepatitis, except when the diagnosis is questionable or when clinical evidence suggests a diagnosis of chronic hepatitis.

A diagnostic algorithm can be applied in the evaluation of cases of acute viral hepatitis. A patient with acute hepatitis should undergo four serologic tests: HBsAg, IgM anti-HAV, IgM anti-HBc, and anti-HCV **(Table 95-6)**. The presence of HBsAg, with or without IgM anti-HBc, represents HBV infection. If IgM anti-HBc is present, the HBV infection is considered acute; if IgM anti-HBc is absent, the HBV infection is considered chronic. A diagnosis of acute hepatitis B can be made in the absence of HBsAg when IgM anti-HBc is detectable. A diagnosis of acute hepatitis A is based on the presence of IgM anti-HAV. If IgM anti-HAV coexists with HBsAg, a diagnosis of simultaneous HAV and HBV infections can be made; if IgM anti-HBc (with or without HBsAg) is detectable, the patient has simultaneous acute hepatitis A and B, and if IgM anti-HBc is undetectable, the patient has acute hepatitis A superimposed on chronic HBV infection. The presence of anti-HCV supports a diagnosis of acute hepatitis C. Occasionally, testing for HCV RNA or repeat anti-HCV testing later during the illness is necessary to establish the diagnosis. Absence of all serologic markers is consistent with a diagnosis of "non-A, non-B, non-C" hepatitis, if the epidemiologic setting is appropriate.

In patients with chronic hepatitis, initial testing should consist of HBsAg and anti-HCV. Anti-HCV supports and HCV RNA testing establishes the diagnosis of chronic hepatitis C. If a serologic diagnosis of chronic hepatitis B is made, testing for HBeAg and anti-HBe is indicated to evaluate relative infectivity. Testing for HBV DNA in such patients provides a more quantitative and sensitive measure of the level of virus replication and, therefore, is very helpful during antiviral therapy (Chap. 96). In patients with chronic

TABLE 95-6

SIMPLIFIED DIAGNOSTIC APPROACH IN PATIENTS PRESENTING WITH ACUTE HEPATITIS

SEROLOGIC TESTS OF PATIENT'S SERUM				
HBsAg	IgM ANTI-HAV	IgM ANTI-HBc	ANTI-HCV	DIAGNOSTIC INTERPRETATION
+	–	+	–	Acute hepatitis B
+	–	–	–	Chronic hepatitis B
+	+	–	–	Acute hepatitis A superimposed on chronic hepatitis B
+	+	+	–	Acute hepatitis A and B
–	+	–	–	Acute hepatitis A
–	+	+	–	Acute hepatitis A and B (HBsAg below detection threshold)
–	–	+	–	Acute hepatitis B (HBsAg below detection threshold)
–	–	–	+	Acute hepatitis C

hepatitis B and normal aminotransferase activity in the absence of HBeAg, serial testing over time is often required to distinguish between inactive carriage and HBeAg-negative chronic hepatitis B with fluctuating virologic and necroinflammatory activity. In persons with hepatitis B, testing for anti-HDV is useful in those with severe and fulminant disease, with severe chronic disease, with chronic hepatitis B and acute hepatitis-like exacerbations, with frequent percutaneous exposures, and from areas where HDV infection is endemic.

PROGNOSIS

Virtually all previously healthy patients with hepatitis A recover completely with no clinical sequelae. Similarly, in acute hepatitis B, 95–99% of previously healthy adults have a favorable course and recover completely. Certain clinical and laboratory features, however, suggest a more complicated and protracted course. Patients of advanced age and with serious underlying medical disorders may have a prolonged course and are more likely to experience severe hepatitis. Initial presenting features such as ascites, peripheral edema, and symptoms of hepatic encephalopathy suggest a poorer prognosis. In addition, a prolonged PT, low-serum albumin level, hypoglycemia, and very high-serum bilirubin values suggest severe hepatocellular disease. Patients with these clinical and laboratory features deserve prompt hospital admission. The case-fatality rate in hepatitis A and B is very low (~0.1%) but is increased by advanced age and underlying debilitating disorders. Among patients ill enough to be hospitalized for acute hepatitis B, the fatality rate is 1%. Hepatitis C is less severe during the acute phase than hepatitis B and is more likely to be anicteric; fatalities are rare, but the precise case-fatality rate is not known. In outbreaks of waterborne hepatitis E in India and Asia, the case-fatality rate is 1–2% and up to 10–20% in pregnant women. Patients with simultaneous acute hepatitis B and hepatitis D do not necessarily experience a higher mortality rate than do patients with acute hepatitis B alone; however, in several recent outbreaks of acute simultaneous HBV and HDV infection among injection drug users, the case-fatality rate has been ~5%. In the case of HDV superinfection of a person with chronic hepatitis B, the likelihood of fulminant hepatitis and death is increased substantially. Although the case-fatality rate for hepatitis D has not been defined adequately, in outbreaks of severe HDV superinfection in isolated populations with a high hepatitis B carrier rate, the mortality rate has been recorded in excess of 20%.

COMPLICATIONS AND SEQUELAE

A small proportion of patients with hepatitis A experience *relapsing hepatitis* weeks to months after apparent recovery from acute hepatitis. Relapses are characterized by recurrence of symptoms, aminotransferase elevations, occasionally jaundice, and fecal excretion of HAV. Another unusual variant of acute hepatitis A is *cholestatic hepatitis*, characterized by protracted cholestatic jaundice and pruritus. Rarely, liver test abnormalities persist for many months, even up to a year. Even when these complications occur, hepatitis A remains self-limited and does not progress to chronic liver disease. During the prodromal phase of acute hepatitis B, a serum sickness-like syndrome characterized by arthralgia or arthritis, rash, angioedema, and rarely, hematuria and proteinuria may develop in 5–10% of patients. This syndrome occurs before the onset of clinical jaundice, and these patients are often diagnosed erroneously as having rheumatologic diseases. The diagnosis can be established by measuring serum aminotransferase levels, which are almost invariably elevated, and serum HBsAg. As noted earlier, EMC is an immune-complex disease that can complicate chronic hepatitis C and is part of a spectrum of B cell lymphoproliferative disorders, which, in rare instances, can evolve to B cell lymphoma. Attention has been drawn as well to associations between hepatitis C and such cutaneous disorders as porphyria cutanea tarda and lichen planus. A mechanism for these associations is unknown. Finally, related to the reliance of HCV on lipoprotein secretion and assembly pathways and on interactions of HCV with glucose metabolism, HCV infection may be complicated by hepatic steatosis, hypercholesterolemia, insulin resistance (and other manifestations of the metabolic syndrome), and type 2 diabetes mellitus; both hepatic steatosis and insulin resistance appear to accelerate hepatic fibrosis and blunt responsiveness to antiviral therapy (Chap. 96).

The most feared complication of viral hepatitis is *fulminant hepatitis* (massive hepatic necrosis); fortunately, this is a rare event. Fulminant hepatitis is primarily seen in hepatitis B and D, as well as hepatitis E, but rare fulminant cases of hepatitis A occur primarily in older adults and in persons with underlying chronic liver disease, including, according to some reports, chronic hepatitis B and C. Hepatitis B accounts for >50% of fulminant cases of viral hepatitis, a sizable proportion of which are associated with HDV infection and another proportion with underlying chronic hepatitis C. Fulminant hepatitis is hardly ever seen in hepatitis C, but hepatitis E, as noted earlier, can be complicated by fatal fulminant hepatitis in 1–2% of all cases and in up to 20% of cases in pregnant women. Patients usually present with signs and symptoms of encephalopathy that may evolve to deep coma. The liver is usually small and the PT excessively prolonged. The combination of rapidly shrinking liver size, rapidly rising bilirubin level, and marked prolongation of the PT, even as aminotransferase levels fall, together with clinical signs of confusion, disorientation, somnolence, ascites, and edema, indicates that the patient has hepatic failure with encephalopathy. Cerebral edema is common; brainstem compression, gastrointestinal bleeding, sepsis, respiratory failure, cardiovascular collapse, and renal failure are terminal events. The mortality rate is exceedingly high (>80% in patients with deep coma), but patients who survive may have a complete biochemical and histologic recovery. If a donor liver can be located in time, liver

transplantation may be life-saving in patients with fulminant hepatitis.

Documenting the disappearance of HBsAg after apparent clinical recovery from acute hepatitis B is particularly important. Before laboratory methods were available to distinguish between acute hepatitis and acute hepatitis-like exacerbations (*spontaneous reactivations*) of chronic hepatitis B, observations suggested that ~10% of previously healthy patients remained HBsAg-positive for >6 months after the onset of clinically apparent acute hepatitis B. One-half of these persons cleared the antigen from their circulations during the next several years, but the other 5% remained chronically HBsAg-positive. More recent observations suggest that the true rate of chronic infection after clinically apparent acute hepatitis B is as low as 1% in normal, immunocompetent, young adults. Earlier, higher estimates may have been confounded by inadvertent inclusion of acute exacerbations in chronically infected patients; these patients, chronically HBsAg-positive before exacerbation, were unlikely to seroconvert to HBsAg-negative thereafter. Whether the rate of chronicity is 10% or 1%, such patients have anti-HBc in serum; anti-HBs is either undetected or detected at low titer against the opposite subtype specificity of the antigen (see "Laboratory Features"). These patients may (1) be inactive carriers; (2) have low-grade, mild chronic hepatitis; or (3) have moderate to severe chronic hepatitis with or without cirrhosis. The likelihood of remaining chronically infected after acute HBV infection is especially high among neonates, persons with Down's syndrome, chronically hemodialyzed patients, and immunosuppressed patients, including persons with HIV infection.

Chronic hepatitis is an important late complication of acute hepatitis B occurring in a small proportion of patients with acute disease, but more common in those who present with chronic infection without having experienced an acute illness, as occurs typically after neonatal infection or after infection in an immunosuppressed host (Chap. 96). Certain clinical and laboratory features suggest progression of acute hepatitis to chronic hepatitis: (1) lack of complete resolution of clinical symptoms of anorexia, weight loss, fatigue, and the persistence of hepatomegaly; (2) the presence of bridging/interface or multilobular hepatic necrosis on liver biopsy during protracted, severe acute viral hepatitis; (3) failure of the serum aminotransferase, bilirubin, and globulin levels to return to normal within 6–12 months after the acute illness; and (4) the persistence of HBeAg for >3 months or HBsAg for >6 months after acute hepatitis.

Although acute hepatitis D infection does not increase the likelihood of chronicity of simultaneous acute hepatitis B, hepatitis D has the potential for contributing to the severity of chronic hepatitis B. Hepatitis D superinfection can transform inactive or mild chronic hepatitis B into severe, progressive chronic hepatitis and cirrhosis; it also can accelerate the course of chronic hepatitis B. Some HDV superinfections in patients with chronic hepatitis B lead to fulminant hepatitis. As defined in longitudinal studies over 3 decades, the annual rates of cirrhosis and hepatocellular carcinoma in patients with chronic hepatitis D are 4% and 2.8%, respectively. Although HDV and HBV infections are associated with severe liver disease, mild hepatitis and even inactive carriage have been identified in some patients, and the disease may become indolent beyond the early years of infection.

After acute HCV infection, the likelihood of remaining chronically *infected* approaches 85–90%. Although many patients with chronic hepatitis C have no symptoms, cirrhosis may develop in as many as 20% within 10–20 years of acute illness; in some series of cases reported by referral centers, cirrhosis has been reported in as many as 50% of patients with chronic hepatitis C. Although chronic hepatitis C accounts for at least 40% of cases of chronic liver disease and of patients undergoing liver transplantation for end-stage liver disease in the United States and Europe, in the majority of patients with chronic hepatitis C, morbidity and mortality are limited during the initial 20 years after the onset of infection. Progression of chronic hepatitis C may be influenced by age of acquisition, duration of infection, immunosuppression, coexisting excessive alcohol use, concomitant hepatic steatosis, other hepatitis virus infection, or HIV co-infection. In fact, instances of severe and rapidly progressive chronic hepatitis B and C are being recognized with increasing frequency in patients with HIV infection (Chap. 93). In contrast, neither HAV nor HEV causes chronic liver disease.

Rare complications of viral hepatitis include pancreatitis, myocarditis, atypical pneumonia, aplastic anemia, transverse myelitis, and peripheral neuropathy. Persons with chronic hepatitis B, particularly those infected in infancy or early childhood and especially those with HBeAg and/or high-level HBV DNA, have an enhanced risk of hepatocellular carcinoma. The risk of hepatocellular carcinoma is increased as well in patients with chronic hepatitis C, almost exclusively in patients with cirrhosis, and almost always after at least several decades, usually after 3 decades of disease. In children, hepatitis B may present rarely with anicteric hepatitis, a nonpruritic papular rash of the face, buttocks, and limbs, and lymphadenopathy (papular acrodermatitis of childhood or Gianotti-Crosti syndrome).

Rarely, autoimmune hepatitis (Chap. 96) can be triggered by a bout of otherwise self-limited acute hepatitis, as reported after acute hepatitis A, B, and C.

DIFFERENTIAL DIAGNOSIS

Viral diseases such as infectious mononucleosis; those due to cytomegalovirus, herpes simplex, and coxsackieviruses; and toxoplasmosis may share certain clinical features with viral hepatitis and cause elevations in serum aminotransferase and, less commonly, in serum bilirubin levels. Tests such as the differential heterophile and serologic tests for these agents may be helpful in the differential diagnosis if HBsAg, anti-HBc, IgM anti-HAV, and anti-HCV determinations are negative. Aminotransferase elevations can accompany almost any

systemic viral infection; other rare causes of liver injury confused with viral hepatitis are infections with *Leptospira*, *Candida*, *Brucella*, *Mycobacterium*, and *Pneumocystis* spp. A complete drug history is particularly important, for many drugs and certain anesthetic agents can produce a picture of either acute hepatitis or cholestasis. Equally important is a past history of unexplained "repeated episodes" of acute hepatitis. This history should alert the physician to the possibility that the underlying disorder is chronic hepatitis. Alcoholic hepatitis must also be considered, but usually the serum aminotransferase levels are not as markedly elevated and other stigmata of alcoholism may be present. The finding on liver biopsy of fatty infiltration, a neutrophilic inflammatory reaction, and "alcoholic hyaline" would be consistent with alcohol-induced rather than viral liver injury. Because acute hepatitis may present with right upper quadrant abdominal pain, nausea and vomiting, fever, and icterus, it is often confused with acute cholecystitis, common duct stone, or ascending cholangitis. Patients with acute viral hepatitis may tolerate surgery poorly; therefore, it is important to exclude this diagnosis, and in confusing cases, a percutaneous liver biopsy may be necessary before laparotomy. Viral hepatitis in the elderly is often misdiagnosed as obstructive jaundice resulting from a common duct stone or carcinoma of the pancreas. Because acute hepatitis in the elderly may be quite severe and the operative mortality high, a thorough evaluation including biochemical tests, radiographic studies of the biliary tree, and even liver biopsy may be necessary to exclude primary parenchymal liver disease. Another clinical constellation that may mimic acute hepatitis is right ventricular failure with passive hepatic congestion or hypoperfusion syndromes, such as those associated with shock, severe hypotension, and severe left ventricular failure. Also included in this general category is any disorder that interferes with venous return to the heart, such as right atrial myxoma, constrictive pericarditis, hepatic vein occlusion (Budd-Chiari syndrome), or veno-occlusive disease. Clinical features are usually sufficient to distinguish among these vascular disorders and viral hepatitis. Acute fatty liver of pregnancy, cholestasis of pregnancy, eclampsia, and the HELLP (*h*emolysis, *e*levated *l*iver tests, and *l*ow *p*latelets) syndrome can be confused with viral hepatitis during pregnancy. Very rarely, malignancies metastatic to the liver can mimic acute or even fulminant viral hepatitis. Occasionally, genetic or metabolic liver disorders (e.g., Wilson's disease, α_1-antitrypsin deficiency) as well as nonalcoholic fatty liver disease are confused with viral hepatitis.

TREATMENT Acute Viral Hepatitis

In hepatitis B, among previously healthy adults who present with clinically apparent acute hepatitis, recovery occurs in ~99%; therefore, antiviral therapy is not likely to improve the rate of recovery and is not required. In rare instances of severe acute hepatitis B, treatment with a nucleoside analogue at oral doses used to treat chronic hepatitis B (Chap. 96) has been attempted successfully. Although clinical trials have not been done to establish the efficacy of this approach; although severe acute hepatitis B is not an approved indication for therapy; and although the duration of therapy has not been determined; nonetheless, most authorities would recommend institution of antiviral therapy with a nucleoside analogue for severe, but not mild–moderate, acute hepatitis B. In typical cases of acute hepatitis C, recovery is rare, progression to chronic hepatitis is the rule, and meta-analyses of small clinical trials suggest that antiviral therapy with interferon alfa monotherapy (3 million units SC three times a week) is beneficial, reducing the rate of chronicity considerably by inducing sustained responses in 30–70% of patients. In a German multicenter study of 44 patients with acute symptomatic hepatitis C, initiation of intensive interferon alfa therapy (5 million units SC daily for 4 weeks, then three times a week for another 20 weeks) within an average of 3 months after infection resulted in a sustained virologic response rate of 98%. Although treatment of acute hepatitis C is recommended, the optimum regimen, duration of therapy, and time to initiate therapy remain to be determined. Many authorities now opt for a 24-week course (beginning within 2–3 months after onset) of the best regimen identified for the treatment of chronic hepatitis C, long-acting pegylated interferon plus the nucleoside analogue ribavirin, although the value of adding ribavirin has not been demonstrated (see Chap. 96 for doses). Because of the marked reduction over the past 2 decades in the frequency of acute hepatitis C, opportunities to identify and treat patients with acute hepatitis C are rare, except in injection drug users. Hospital epidemiologists, however, will encounter health workers who sustain hepatitis C-contaminated needle sticks; when monitoring for ALT elevations and HCV, RNA after these accidents identifies acute hepatitis C (risk only ~3%), therapy should be initiated.

Notwithstanding these specific therapeutic considerations, in most cases of typical acute viral hepatitis, specific treatment generally is not necessary. Although hospitalization may be required for clinically severe illness, most patients do not require hospital care. Forced and prolonged bed rest is not essential for full recovery, but many patients will feel better with restricted physical activity. A high-calorie diet is desirable, and because many patients may experience nausea late in the day, the major caloric intake is best tolerated in the morning. Intravenous feeding is necessary in the acute stage if the patient has persistent vomiting and cannot maintain oral intake. Drugs capable of producing adverse reactions such as cholestasis and drugs metabolized by the liver should be avoided. If severe pruritus is present, the use of the bile salt-sequestering resin cholestyramine is helpful. Glucocorticoid therapy has no value in acute viral hepatitis, even in severe cases associated with *bridging*

necrosis, and may be deleterious, even increasing the risk of chronicity (e.g., of acute hepatitis B).

Physical isolation of patients with hepatitis to a single room and bathroom is rarely necessary except in the case of fecal incontinence for hepatitis A and E or uncontrolled, voluminous bleeding for hepatitis B (with or without concomitant hepatitis D) and hepatitis C. Because most patients hospitalized with hepatitis A excrete little, if any, HAV, the likelihood of HAV transmission from these patients during their hospitalization is low. Therefore, burdensome *enteric precautions are no longer recommended*. Although gloves should be worn when the bedpans or fecal material of patients with hepatitis A are handled, these precautions do not represent a departure from sensible procedure and contemporary universal precautions for all hospitalized patients. For patients with hepatitis B and hepatitis C, emphasis should be placed on blood precautions (i.e., avoiding direct, ungloved hand contact with blood and other body fluids). Enteric precautions are unnecessary. The importance of simple hygienic precautions such as hand washing cannot be overemphasized. Universal precautions that have been adopted for all patients apply to patients with viral hepatitis.

Hospitalized patients may be discharged following substantial symptomatic improvement, a significant downward trend in the serum aminotransferase and bilirubin values, and a return to normal of the PT. Mild aminotransferase elevations should not be considered contraindications to the gradual resumption of normal activity.

In *fulminant hepatitis*, the goal of therapy is to support the patient by maintenance of fluid balance, support of circulation and respiration, control of bleeding, correction of hypoglycemia, and treatment of other complications of the comatose state in anticipation of liver regeneration and repair. Protein intake should be restricted, and oral lactulose or neomycin administered. Glucocorticoid therapy has been shown in controlled trials to be ineffective. Likewise, exchange transfusion, plasmapheresis, human cross-circulation, porcine liver cross-perfusion, hemoperfusion, and extracorporeal liver-assist devices have not been proven to enhance survival. Meticulous intensive care that includes prophylactic antibiotic coverage is the one factor that does appear to improve survival. Orthotopic liver transplantation is resorted to with increasing frequency, with excellent results, in patients with fulminant hepatitis.

PROPHYLAXIS

Because application of therapy for acute viral hepatitis is limited and because antiviral therapy for chronic viral hepatitis is cumbersome and costly but effective in only a proportion of patients (Chap. 96), emphasis is placed on prevention through immunization. The prophylactic approach differs for each of the types of viral hepatitis. In the past, immunoprophylaxis relied exclusively on passive immunization with antibody-containing globulin preparations purified by cold ethanol fractionation from the plasma of hundreds of normal donors. Currently, for hepatitis A and B, active immunization with vaccines is the preferable approach to prevention.

Hepatitis A

Both passive immunization with IG and active immunization with killed vaccines are available. All preparations of IG contain anti-HAV concentrations sufficient to be protective. When administered before exposure or during the early incubation period, IG is effective in preventing clinically apparent hepatitis A. For postexposure prophylaxis of intimate contacts (household, sexual, institutional) of persons with hepatitis A, the administration of 0.02 mL/kg is recommended as early after exposure as possible; it may be effective even when administered as late as 2 weeks after exposure. Prophylaxis is not necessary for those who have already received hepatitis A vaccine, casual contacts (office, factory, school, or hospital), for most elderly persons, who are very likely to be immune, or for those known to have anti-HAV in their serum. In day-care centers, recognition of hepatitis A in children or staff should provide a stimulus for immunoprophylaxis in the center and in the children's family members. By the time most common-source outbreaks of hepatitis A are recognized, it is usually too late in the incubation period for IG to be effective; however, prophylaxis may limit the frequency of secondary cases. For travelers to tropical countries, developing countries, and other areas outside standard tourist routes, IG prophylaxis had been recommended before a vaccine became available. When such travel lasted <3 months, 0.02 mL/kg was given; for longer travel or residence in these areas, a dose of 0.06 mL/kg every 4–6 months was recommended. Administration of plasma-derived globulin is safe; all contemporary lots of IG are subjected to viral inactivation steps and must be free of HCV RNA as determined by PCR testing. Administration of IM lots of IG has not been associated with transmission of HBV, HCV, or HIV.

Formalin-inactivated vaccines made from strains of HAV attenuated in tissue culture have been shown to be safe, immunogenic, and effective in preventing hepatitis A. Hepatitis A vaccines are approved for use in persons who are at least one year old and appear to provide adequate protection beginning 4 weeks after a primary inoculation. If it can be given within 4 weeks of an expected exposure, such as by travel to an endemic area, hepatitis A vaccine is the preferred approach to *pre-exposure* immunoprophylaxis. If travel is more imminent, IG (0.02 mL/kg) should be administered at a different injection site, along with the first dose of vaccine. Because vaccination provides long-lasting protection (protective levels of anti-HAV should last 20 years after vaccination), persons whose risk will be sustained (e.g., frequent travelers or those remaining in endemic areas for prolonged periods) should be vaccinated, and vaccine should supplant the need for repeated IG injections.

Shortly after its introduction, hepatitis A vaccine was recommended for children living in communities with a high incidence of HAV infection; in 1999, this recommendation was extended to include all children living in states, counties, and communities with high rates of HAV infection. As of 2006, the Advisory Committee on Immunization Practices of the U.S. Public Health Service recommended *routine hepatitis A vaccination of all children*. Other groups considered to be at increased risk for HAV infection and who are candidates for hepatitis A vaccination include military personnel, populations with cyclic outbreaks of hepatitis A (e.g., Alaskan natives), employees of day-care centers, primate handlers, laboratory workers exposed to hepatitis A or fecal specimens, and patients with chronic liver disease. Because of an increased risk of fulminant hepatitis A—observed in some experiences but not confirmed in others—among patients with chronic hepatitis C, patients with chronic hepatitis C are candidates for hepatitis A vaccination, as are persons with chronic hepatitis B. Other populations whose recognized risk of hepatitis A is increased should be vaccinated, including men who have sex with men, injection drug users, persons with clotting disorders who require frequent administration of clotting-factor concentrates, persons traveling from the United States to countries with high or intermediate hepatitis A endemicity, postexposure prophylaxis for contacts of persons with hepatitis A, and household members and other close contacts of adopted children arriving from countries with high and moderate hepatitis A endemicity. Recommendations for dose and frequency differ for the two approved vaccine preparations **(Table 95-7)**; all injections are IM. Hepatitis A vaccine has been reported to be effective in preventing secondary household cases of acute hepatitis A, but its role in other instances of postexposure prophylaxis remains to be demonstrated. In the United States, reported mortality resulting from hepatitis A declined in parallel with hepatitis A vaccine-associated reductions in the annual incidence of new infections.

TABLE 95-7

HEPATITIS A VACCINATION SCHEDULES

AGE, YEARS	NO. OF DOSES	DOSE	SCHEDULE, MONTHS
HAVRIX (GlaxoSmithKline)[a]			
1–18	2	720 ELU[b] (0.5 mL)	0, 6–12
≥19	2	1440 ELU (1 mL)	0, 6–12
VAQTA (Merck)			
1–18	2	25 units (0.5 mL)	0, 6–18
≥19	2	50 units (1 mL)	0, 6–18

[a]A combination of this hepatitis A vaccine and hepatitis B vaccine, TWINRIX, is licensed for simultaneous protection against both of these viruses among adults (age ≥18 years). Each 1-mL dose contains 720 ELU of hepatitis A vaccine and 20 μg of hepatitis B vaccine. These doses are recommended at months 0, 1, and 6.
[b]Enzyme-linked immunoassay units.

Hepatitis B

Until 1982, prevention of hepatitis B was based on *passive* immunoprophylaxis either with standard IG, containing modest levels of anti-HBs, or hepatitis B immunoglobulin (HBIG), containing high-titer anti-HBs. The efficacy of standard IG has never been established and remains questionable; even the efficacy of HBIG, demonstrated in several clinical trials, has been challenged, and its contribution appears to be in reducing the frequency of clinical *illness*, not in preventing *infection*. The first vaccine for *active* immunization, introduced in 1982, was prepared from purified, noninfectious 22-nm spherical forms of HBsAg derived from the plasma of healthy HBsAg carriers. In 1987, the plasma-derived vaccine was supplanted by a genetically engineered vaccine derived from recombinant yeast. The latter vaccine consists of HBsAg particles that are nonglycosylated but are otherwise indistinguishable from natural HBsAg; two recombinant vaccines are licensed for use in the United States. Current recommendations can be divided into those for pre-exposure and postexposure prophylaxis.

For *pre-exposure* prophylaxis against hepatitis B in settings of frequent exposure (health workers exposed to blood; hemodialysis patients and staff; residents and staff of custodial institutions for the developmentally handicapped; injection drug users; inmates of long-term correctional facilities; persons with multiple sexual partners; persons such as hemophiliacs who require long-term, high-volume therapy with blood derivatives; household and sexual contacts of HBsAg carriers; persons living in or traveling extensively in endemic areas; unvaccinated children under the age of 18; and unvaccinated children who are Alaskan natives, Pacific Islanders, or residents in households of first-generation immigrants from endemic countries), three IM (deltoid, not gluteal) injections of hepatitis B vaccine are recommended at 0, 1, and 6 months (other, optional schedules are summarized in **Table 95-8**). Pregnancy is *not* a contraindication to vaccination. In areas of low HBV endemicity such as the United States, despite the availability of safe and effective hepatitis B vaccines, a strategy of vaccinating persons in high-risk groups has not been effective. The incidence of new hepatitis B cases continued to increase in the United States after the introduction of vaccines; <10% of all targeted persons in high-risk groups have actually been vaccinated, and ~30% of persons with sporadic acute hepatitis B do not fall into any high-risk-group category. Therefore, to have an impact on the frequency of HBV infection in an area of low endemicity such as the United States, universal hepatitis B vaccination in childhood has been recommended. For unvaccinated children born after the implementation of universal infant vaccination, vaccination during early adolescence, at age 11–12 years, was recommended, and this recommendation has been extended to include all unvaccinated children age 0–19 years. In HBV-hyperendemic areas (e.g., Asia), universal vaccination of children has resulted in a marked 10- to 15-year decline in hepatitis B and its complications, including hepatocellular carcinoma.

TABLE 95-8

PREEXPOSURE HEPATITIS B VACCINATION SCHEDULES

TARGET GROUP	NO. OF DOSES	DOSE	SCHEDULE, MONTHS
RECOMBIVAX-HB (Merck)[a]			
Infants, children (<1–10 years)	3	5 µg (0.5 mL)	0, 1–2, 4–6
Adolescents (11–19 years)	3 or 4	5 µg (0.5 mL)	0–2, 1–4, 4–6 *or* 0, 12, 24 *or* 0, 1, 2, 12
	or 2	10 µg (1 mL)	0, 4–6 (age 11–15)
Adults (≥20 years)	3	10 µg (1 mL)	0–2, 1–4, 4–6
Hemodialysis patients[b]			
<20 years	3	5 µg (0.5 mL)	0, 1, 6
≥20 years	3	40 µg (4 mL)	0, 1, 6
ENGERIX-B (GlaxoSmithKline)[c]			
Infants, children (<1–10 years)	3 or 4	10 µg (0.5 mL)	0, 1–2, 4–6 *or* 0, 1, 2,12
Adolescents (10–19 years)	3 or 4	10 µg (0.5 mL)	0, 1–2, 4–6 *or* 0, 12, 24 *or* 0, 1, 2, 12
Adults (≥20 years)	3 or 4	20 µg (1 mL)	0–2, 1–4, 4–6, *or* 0, 1, 2, 12
Hemodialysis patients[b]			
<20 years	4	10 µg (0.5 mL)	0, 1, 2, 6
≥20 years	4	40 µg (2 mL)	0, 1, 2, 6

[a]This manufacturer produces a licensed combination of hepatitis B vaccine and vaccines against *Haemophilus influenzae* type b and *Neisseria meningitidis*, Comvax, for use in infants and young children. Please consult product insert for dose and schedule.

[b]This group also includes other immunocompromised persons.

[c]This manufacturer produces two licensed combination hepatitis B vaccines: (1) Twinrix, recombinant hepatitis B vaccine plus inactivated hepatitis A vaccine, is licensed for simultaneous protection against both of these viruses among adults (age ≥ 18 years). Each 1-mL dose contains 720 enzyme-linked immunoassay units of hepatitis A vaccine and 20 µg of hepatitis B vaccine. These doses are recommended at months 0, 1, and 6. (2) Pediatrix, recombinant hepatitis B vaccine plus diphtheria and tetanus toxoids, pertussis, and inactivated poliovirus, is licensed for use in infants and young children. Please consult product insert for doses and schedules.

The two available recombinant hepatitis B vaccines are comparable, one containing 10 µg of HBsAg (Recombivax-HB) and the other containing 20 µg of HBsAg (Engerix-B), and recommended doses for each injection vary for the two preparations (Table 95-8). Combinations of hepatitis B vaccine with other childhood vaccines are available as well (Table 95-8).

For unvaccinated persons sustaining an exposure to HBV, *postexposure* prophylaxis with a combination of HBIG (for rapid achievement of high-titer circulating anti-HBs) and hepatitis B vaccine (for achievement of long-lasting immunity as well as its apparent efficacy in attenuating clinical illness after exposure) is recommended. For *perinatal* exposure of infants born to HBsAg-positive mothers, a single dose of HBIG, 0.5 mL, should be administered IM in the thigh *immediately after birth*, followed by a complete course of three injections of recombinant hepatitis B vaccine (see doses mentioned earlier) to be started within the first 12 hours of life. For those experiencing a direct percutaneous inoculation or transmucosal exposure to HBsAg-positive blood or body fluids (e.g., accidental *needle stick*, other mucosal penetration, or ingestion), a single IM dose of HBIG, 0.06 mL/kg, administered as soon after exposure as possible, is followed by a complete course of hepatitis B vaccine to begin within the first week. For those exposed by *sexual* contact to a patient with acute hepatitis B, a single IM dose of HBIG, 0.06 mL/kg, should be given within 14 days of exposure, to be followed by a complete course of hepatitis B vaccine. When both HBIG and hepatitis B vaccine are recommended, they may be given at the same time but at separate sites.

The precise duration of protection afforded by hepatitis B vaccine is unknown; however, ~80–90% of immunocompetent vaccinees retain protective levels of anti-HBs for at least 5 years, and 60–80% for 10 years. Thereafter and even after anti-HBs becomes undetectable, protection persists against clinical hepatitis B, hepatitis B surface antigenemia, and chronic HBV infection. Currently, *booster* immunizations are not recommended routinely, except in immunosuppressed persons who have lost detectable anti-HBs or immunocompetent persons who sustain percutaneous HBsAg-positive inoculations after losing detectable antibody. Specifically, for hemodialysis patients, annual anti-HBs testing is recommended after vaccination; booster doses are recommended when anti-HBs levels fall to <10 mIU/mL. As noted earlier, for persons at risk of both hepatitis A and B, a combined vaccine is available containing 720 enzyme-linked immunoassay units (ELUs) of inactivated HAV and 20 µg of recombinant HBsAg (at 0, 1, and 6 months).

Hepatitis D

Infection with hepatitis D can be prevented by vaccinating susceptible persons with hepatitis B vaccine. No product is available for immunoprophylaxis to prevent HDV superinfection in HBsAg carriers; for them, avoidance of percutaneous exposures and limitation of intimate contact with persons who have HDV infection are recommended.

Hepatitis C

IG is ineffective in preventing hepatitis C and is no longer recommended for postexposure prophylaxis in cases of perinatal, needle stick, or sexual exposure. Although prototype vaccines that induce antibodies to HCV

envelope proteins have been developed, currently, hepatitis C vaccination is not feasible practically. Genotype and quasispecies viral heterogeneity, as well as rapid evasion of neutralizing antibodies by this rapidly mutating virus, conspire to render HCV a difficult target for immunoprophylaxis with a vaccine. Prevention of transfusion-associated hepatitis C has been accomplished by the following successively introduced measures: exclusion of commercial blood donors and reliance on a volunteer blood supply; screening donor blood with surrogate markers such as ALT (no longer recommended) and anti-HBc, markers that identify segments of the blood donor population with an increased risk of bloodborne infections; exclusion of blood donors in high-risk groups for AIDS and the introduction of anti-HIV screening tests; and progressively sensitive serologic and virologic screening tests for HCV infection.

In the absence of active or passive immunization, prevention of hepatitis C includes behavior changes and precautions to limit exposures to infected persons. Recommendations designed to identify patients with clinically inapparent hepatitis as candidates for medical management have as a secondary benefit the identification of persons whose contacts could be at risk of becoming infected. A so-called look-back program has been recommended to identify persons who were transfused before 1992 with blood from a donor found subsequently to have hepatitis C. In addition, anti-HCV testing is recommended for anyone who received a blood transfusion or a transplanted organ before the introduction of second-generation screening tests in 1992, those who ever used injection drugs (or took other illicit drugs by noninjection routes), chronically hemodialyzed patients, persons with clotting disorders who received clotting factors made before 1987 from pooled blood products, persons with elevated aminotransferase levels, health workers exposed to HCV-positive blood or contaminated needles, persons with HIV infection, health care and public safety personnel following a needle-stick or other nonpercutaneous exposure to HCV-infected material, sexual partners of persons with hepatitis C, and children born to HCV-positive mothers (Table 95-4).

For stable, monogamous sexual partners, sexual transmission of hepatitis C is unlikely, and sexual barrier precautions are not recommended. For persons with multiple sexual partners or with sexually transmitted diseases, the risk of sexual transmission of hepatitis C is increased, and barrier precautions (latex condoms) are recommended. A person with hepatitis C should avoid sharing such items as razors, toothbrushes, and nail clippers with sexual partners and family members. No special precautions are recommended for babies born to mothers with hepatitis C, and breast-feeding does not have to be restricted.

Hepatitis E

Whether IG prevents hepatitis E remains undetermined. A safe and effective recombinant vaccine has been developed and is available in endemic areas but not in the United States.

CHAPTER 96

CHRONIC HEPATITIS

Jules L. Dienstag

Chronic hepatitis represents a series of liver disorders of varying causes and severity in which hepatic inflammation and necrosis continue for at least 6 months. Milder forms are nonprogressive or only slowly progressive, while more severe forms may be associated with scarring and architectural reorganization, which, when advanced, lead ultimately to cirrhosis. Several categories of chronic hepatitis have been recognized. These include chronic viral hepatitis, drug-induced chronic hepatitis, and autoimmune chronic hepatitis. In many cases, clinical and laboratory features are insufficient to allow assignment into one of these three categories; these "idiopathic" cases are also believed to represent autoimmune chronic hepatitis. Finally, clinical and laboratory features of chronic hepatitis are observed occasionally in patients with such hereditary/metabolic disorders as Wilson's disease

(copper overload) and nonalcoholic fatty liver disease and even occasionally in patients with alcoholic liver injury. Although all types of chronic hepatitis share certain clinical, laboratory, and histopathologic features, chronic viral and chronic autoimmune hepatitis are sufficiently distinct to merit separate discussions. For discussion of acute hepatitis, see Chap. 95.

CLASSIFICATION OF CHRONIC HEPATITIS

Common to all forms of chronic hepatitis are histopathologic distinctions based on localization and extent of liver injury. These vary from the milder forms, previously labeled *chronic persistent hepatitis* and *chronic lobular hepatitis*, to the more severe form, formerly called *chronic active hepatitis*. When first defined, these designations were believed to have prognostic implications, which have been challenged by more recent observations. Categorization of chronic hepatitis based primarily on histopathologic features has been replaced by a more informative classification based on a combination of clinical, serologic, and histologic variables. Classification of chronic hepatitis is based on (1) its *cause*; (2) its histologic activity, or *grade*; and (3) its degree of progression, or *stage*. Thus, neither clinical features alone nor histologic features—requiring liver biopsy—alone are sufficient to characterize and distinguish among the several categories of chronic hepatitis.

CLASSIFICATION BY CAUSE

Clinical and serologic features allow the establishment of a diagnosis of *chronic viral hepatitis*, caused by hepatitis B, hepatitis B plus D, or hepatitis C; *autoimmune hepatitis*, including several subcategories, I and II (perhaps III), based on serologic distinctions; *drug-associated chronic hepatitis*; and a category of unknown cause, or *cryptogenic chronic hepatitis* **(Table 96-1)**. These are addressed in more detail next.

CLASSIFICATION BY GRADE

Grade, a histologic assessment of necroinflammatory activity, is based on examination of the liver biopsy. An assessment of important histologic features includes the degree of *periportal necrosis* and the disruption of the limiting plate of periportal hepatocytes by inflammatory cells (so-called *piecemeal necrosis* or *interface hepatitis*); the degree of confluent necrosis that links or forms bridges between vascular structures—between portal tract and portal tract or even more important bridges between portal tract and central vein—referred to as *bridging necrosis*; the degree of hepatocyte degeneration and focal necrosis within the lobule; and the degree of *portal inflammation*. Several scoring systems that take these histologic features into account have been devised, and the most popular are the histologic activity index (HAI), used commonly in the United States, and the METAVIR score, used in Europe **(Table 96-2)**. Based on the presence and degree of these features of histologic activity, chronic hepatitis can be graded as mild, moderate, or severe.

TABLE 96-1

CLINICAL AND LABORATORY FEATURES OF CHRONIC HEPATITIS

TYPE OF HEPATITIS	DIAGNOSTIC TEST(S)	AUTOANTIBODIES	THERAPY
Chronic hepatitis B	HBsAg, IgG anti-HBc, HBeAg, HBV DNA	Uncommon	IFN-α, PEG IFN-α, lamivudine, adefovir, entecavir, telbivudine, tenofovir
Chronic hepatitis C	Anti-HCV, HCV RNA	Anti-LKM1[a]	PEG IFN-α plus ribavirin Telaprevir[d] Boceprevir[d]
Chronic hepatitis D	Anti-HDV, HDV RNA, HBsAg, IgG anti-HBc	Anti-LKM3	IFN-α, PEG IFN-α[c]
Autoimmune hepatitis	ANA[b] (homogeneous), anti-LKM1 (±) hyperglobulinemia	ANA, anti-LKM1, anti-SLA[e]	Prednisone, azathioprine
Drug-associated	—	Uncommon	Withdraw drug
Cryptogenic	All negative	None	Prednisone (?), azathioprine (?)

[a]Antibodies to liver-kidney microsomes type 1 (autoimmune hepatitis type II and some cases of hepatitis C).
[b]Antinuclear antibody (autoimmune hepatitis type I).
[c]Clinical trials suggest benefit of IFN-α therapy; PEG IFN-α is as effective, if not more so.
[d]Expected approval date: 2011.
[e]Antibodies to soluble liver antigen (autoimmune hepatitis type III).
Abbreviations: HBc, hepatitis B core; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus; IFN-α, interferon-α; IgG, immunoglobulin G; LKM, liver-kidney microsome; PEG IFN-α, pegylated interferon-α; SLA, soluble liver antigen.

TABLE 96-2

HISTOLOGIC GRADING AND STAGING OF CHRONIC HEPATITIS

	HISTOLOGIC ACTIVITY INDEX (HAI)[a]		METAVIR[b]	
HISTOLOGIC FEATURE	**SEVERITY**	**SCORE**	**SEVERITY**	**SCORE**
Necroinflammatory Activity (Grade)				
Periportal necrosis, including piecemeal necrosis and/or bridging necrosis (BN)	None	0	None	0
	Mild	1	Mild	1
	Mild/moderate	2	Moderate	2
	Moderate	3	Severe	3
	Severe	4		
			Bridging necrosis	Yes
				No
Intralobular confluent necrosis	None	0	None or mild	0
	Focal	1	Moderate	1
	Zone 3—some	2	Severe	2
	Zone 3—most	3		
	Zone 3 + BN few	4		
	Zone 3 + BN multiple	5		
	Panacinar/multiacinar	6		
Focal	None	0		
	≤1 focus/10x field	1		
	2–4 foci/10x field	2		
	5–10 foci/10x field	3		
	>10 foci/10x field	4		
Portal Inflammation	None	0		
	Mild	1		
	Moderate	2		
	Moderate/marked	3		
	Marked	4		
	Total	0–18		A0–A3[c]
Fibrosis (Stage)				
None		0		F0
Portal fibrosis—some		1		F1
Portal fibrosis—most		2		F1
Bridging fibrosis—few		3		F2
Bridging fibrosis—many		4		F3
Incomplete cirrhosis		5		F4
Cirrhosis		6		F4
	Total	6		4

[a]J Hepatol 22:696, 1995.
[b]Hepatology 24:289, 1996.
[c]Necroinflammatory grade: A0 = none; A1 = mild; A2 = moderate; A3 = severe.

CLASSIFICATION BY STAGE

The stage of chronic hepatitis, which reflects the level of progression of the disease, is based on the degree of hepatic fibrosis. When fibrosis is so extensive that fibrous septa surround parenchymal nodules and alter the normal architecture of the liver lobule, the histologic lesion is defined as *cirrhosis*. Staging is based on the degree of fibrosis as categorized on a numerical scale from 0–6 (HAI) or 0–4 (METAVIR) (Table 96-2).

CHRONIC VIRAL HEPATITIS

Both the enterically transmitted forms of viral hepatitis, hepatitis A and E, are self-limited and do not cause chronic hepatitis (rare reports notwithstanding in which acute hepatitis A serves as a trigger for the onset of autoimmune hepatitis in genetically susceptible patients). In contrast, the entire clinicopathologic spectrum of chronic hepatitis occurs in patients with chronic viral hepatitis B and C as well as in patients with chronic hepatitis D superimposed on chronic hepatitis B.

CHRONIC HEPATITIS B

The likelihood of chronicity after acute hepatitis B varies as a function of age. Infection at birth is associated with clinically silent acute infection but a 90% chance of chronic infection, while infection in young adulthood in immunocompetent persons is typically associated with clinically apparent acute hepatitis but a risk of chronicity of only approximately 1%. Most cases of chronic hepatitis B among adults, however, occur in patients who never had a recognized episode of clinically apparent acute viral hepatitis. The degree of liver injury (grade) in patients with chronic hepatitis B is variable, ranging from none in inactive carriers to mild to moderate to severe. Among adults with chronic hepatitis B, histologic features are of prognostic importance. In one long-term study of patients with chronic hepatitis B, investigators found a 5-year survival rate of 97% for patients with mild chronic hepatitis, 86% for patients with moderate to severe chronic hepatitis, and only 55% for patients with chronic hepatitis and postnecrotic cirrhosis. The 15-year survival in these cohorts was 77%, 66%, and 40%, respectively. On the other hand, more recent observations do not allow us to be so sanguine about the prognosis in patients with mild chronic hepatitis; among such patients followed for 1–13 years, progression to more severe chronic hepatitis and cirrhosis has been observed in more than a quarter of cases.

More important to consider than histology alone in patients with chronic hepatitis B is the degree of hepatitis B virus (HBV) replication. As reviewed in Chap. 95, chronic HBV infection can occur in the presence or absence of serum hepatitis B e antigen (HBeAg), and generally, for both HBeAg-reactive and HBeAg-negative chronic hepatitis B, the level of HBV DNA correlates with the level of liver injury and risk of progression. In *HBeAg-reactive chronic hepatitis B*, two phases have been recognized based on the relative level of HBV replication. The relatively *replicative phase* is characterized by the presence in the serum of HBeAg and HBV DNA levels well in excess of 10^5 –10^6 virions/mL, by the presence in the liver of detectable intrahepatocyte nucleocapsid antigens [primarily hepatitis B core antigen (HBcAg)], by high infectivity, and by accompanying liver injury. In contrast, the relatively *nonreplicative phase* is characterized by the absence of the conventional serum marker of HBV replication (HBeAg), the appearance of anti-HBe, levels of HBV DNA below a threshold of ~10^3 virions/mL, the absence of intrahepatocytic HBcAg, limited infectivity, and minimal liver injury. Those patients in the replicative phase tend to have more severe chronic hepatitis, while those in the nonreplicative phase tend to have minimal or mild chronic hepatitis or to be inactive hepatitis B carriers; however, distinctions in HBV replication and in histologic category do not always coincide. The likelihood in a patient with HBeAg-reactive chronic hepatitis B of converting spontaneously from relatively replicative to nonreplicative infection is approximately 10–15% per year. In patients with HBeAg-reactive chronic HBV infection, especially when acquired at birth or in early childhood, as recognized commonly in Asian countries, a dichotomy is common between very high levels of HBV replication and negligible levels of liver injury. Yet despite the relatively immediate, apparently benign nature of liver disease for many decades in this population, patients with childhood-acquired HBV infection are the ones at ultimately increased risk later in life of cirrhosis and hepatocellular carcinoma (HCC). A discussion of the pathogenesis of liver injury in patients with chronic hepatitis B appears in Chap. 95.

HBeAg-negative chronic hepatitis B (i.e., chronic HBV infection with active virus replication, readily detectable HBV DNA but without HBeAg [anti-HBe-reactive]) is more common than HBeAg-reactive chronic hepatitis B in Mediterranean and European countries and in Asia (and, correspondingly, in HBV genotypes other than A). Compared to patients with HBeAg-reactive chronic hepatitis B, patients with HBeAg-negative chronic hepatitis B have levels of HBV DNA that are several orders of magnitude lower (no more than 10^5–10^6 virions/mL) than those observed in the HBeAg-reactive subset. Most such cases represent precore or core-promoter mutations acquired late in the natural history of the disease (mostly early-life onset; age range 40–55 years, older than that for HBeAg-reactive chronic hepatitis B); these mutations prevent translation of HBeAg from the precore component of the HBV genome (precore mutants) or are characterized by down-regulated transcription of precore mRNA (core-promoter mutants; Chap. 95). Although their levels of HBV DNA tend to be lower than among patients with HBeAg-reactive chronic hepatitis B, patients with HBeAg-negative chronic hepatitis B can have progressive liver injury (complicated by cirrhosis and HCC) and experience episodic reactivation of liver disease reflected in fluctuating levels of aminotransferase activity (“flares”). The biochemical and histologic activity of HBeAg-negative disease tends to correlate closely with levels of HBV replication, unlike the case mentioned earlier of Asian patients with HBeAg-reactive chronic hepatitis B during the early decades of their HBV infection. An important point worth reiterating is the observation that the level of HBV replication is the most important risk factor for the ultimate development of cirrhosis and HCC in both HBeAg-reactive and HBeAg-negative patients. Although levels of HBV DNA are lower and more readily suppressed by therapy to undetectable levels in HBeAg-negative (compared to HBeAg-reactive) chronic hepatitis B, achieving sustained responses that permit discontinuation of antiviral therapy is less likely in HBeAg-negative patients (see later). Inactive carriers are patients with circulating hepatitis B surface antigen (HBsAg), normal serum aminotransferase levels, undetectable HBeAg, and levels of HBV DNA that are either undetectable or present at levels ≤10^3 virions/mL. This serologic profile can occur not only in inactive carriers but also in patients with HBeAg-negative chronic hepatitis B during periods of relative inactivity; distinguishing between the two requires sequential biochemical and virologic monitoring over many months.

The spectrum of *clinical features* of chronic hepatitis B is broad, ranging from asymptomatic infection to debilitating disease or even end-stage, fatal hepatic failure. As noted earlier, the onset of the disease tends to be insidious in most patients, with the exception of the very few in whom chronic disease follows failure of resolution of clinically apparent acute hepatitis B. The clinical and laboratory features associated with progression from acute to chronic hepatitis B are discussed in Chap. 95.

Fatigue is a common symptom, and persistent or intermittent *jaundice* is a common feature in severe or advanced cases. Intermittent deepening of jaundice and recurrence of malaise and anorexia, as well as worsening fatigue, are reminiscent of acute hepatitis; such exacerbations may occur spontaneously, often coinciding with evidence of virologic reactivation; may lead to progressive liver injury; and, when superimposed on well-established cirrhosis, may cause hepatic decompensation. Complications of cirrhosis occur in end-stage chronic hepatitis and include ascites, edema, bleeding gastroesophageal varices, hepatic encephalopathy, coagulopathy, or hypersplenism. Occasionally, these complications bring the patient to initial clinical attention. Extrahepatic complications of chronic hepatitis B, similar to those seen during the prodromal phase of acute hepatitis B, are associated with deposition of circulating hepatitis B antigen–antibody immune complexes. These include arthralgias and arthritis, which are common, and the more rare purpuric cutaneous lesions (leukocytoclastic vasculitis), immune-complex glomerulonephritis, and generalized vasculitis (polyarteritis nodosa) (Chap. 95).

Laboratory features of chronic hepatitis B do not distinguish adequately between histologically mild and severe hepatitis. Aminotransferase elevations tend to be modest for chronic hepatitis B, but may fluctuate in the range of 100–1000 units. As is true for acute viral hepatitis B, alanine aminotransferase (ALT) tends to be more elevated than aspartate aminotransferase (AST); however, once cirrhosis is established, AST tends to exceed ALT. Levels of alkaline phosphatase activity tend to be normal or only marginally elevated. In severe cases, moderate elevations in serum bilirubin (51.3–171 μmol/L [3–10 mg/dL]) occur. Hypoalbuminemia and prolongation of the prothrombin time occur in severe or end-stage cases. Hyperglobulinemia and detectable circulating autoantibodies are distinctly absent in chronic hepatitis B (in contrast to autoimmune hepatitis). Viral markers of chronic HBV infection are discussed in Chap. 95.

TREATMENT Chronic Hepatitis B

Although progression to cirrhosis is more likely in severe than in mild or moderate chronic hepatitis B, all forms of chronic hepatitis B can be progressive, and progression occurs primarily in patients with active HBV replication. Moreover, in populations of patients with chronic hepatitis B who are at risk for HCC, the risk is highest for those ith continued, high-level HBV replication and lower for persons in whom initially high-level HBV DNA falls spontaneously over time. Therefore, management of chronic hepatitis B is directed at suppressing the level of virus replication. Although clinical trials tend to focus on clinical endpoints achieved over 1–2 years (e.g., suppression of HBV DNA to undetectable levels, loss of HBeAg/HBsAg, improvement in histology, normalization of ALT), these short-term gains translate into reductions in the risk of clinical progression, hepatic decompensation, and death. To date, seven drugs have been approved for treatment of chronic hepatitis B: injectable interferon (IFN) α pegylated interferon (long-acting IFN bound to polyethylene glycol [PEG], known as *PEG IFN*); and the oral agents lamivudine, adefovir dipivoxil, entecavir, telbivudine, and tenofovir.

Antiviral therapy for hepatitis B has evolved rapidly since the mid-1990s, as has the sensitivity of tests for HBV DNA. When IFN and lamivudine were evaluated in clinical trials, HBV DNA was measured by insensitive hybridization assays with detection thresholds of 10^5–10^6 virions/mL; when adefovir, entecavir, telbivudine, tenofovir, and PEG IFN were studied in clinical trials, HBV DNA was measured by sensitive amplification assays (polymerase chain reaction [PCR]) with detection thresholds of 10^1–10^3 virions/mL. Recognition of these distinctions is helpful when comparing results of clinical trials that established the efficacy of these therapies (reviewed next in chronological order of publication of these efficacy trials).

INTERFERON IFN-α was the first approved therapy for chronic hepatitis B. Although it is no longer used to treat hepatitis B, standard IFN is important historically, having provided important lessons about antiviral therapy in general. For immunocompetent adults with HBeAg-reactive chronic hepatitis B (who tend to have high-level HBV DNA [>10^5–10^6 virions/mL] and histologic evidence of chronic hepatitis on liver biopsy), a 16-week course of IFN given subcutaneously at a daily dose of 5 million units, or three times a week at a dose of 10 million units, results in a loss of HBeAg and hybridization-detectable HBV DNA (i.e., a reduction to levels below 10^5 –10^6 virions/mL) in ~30% of patients, with a concomitant improvement in liver histology. Seroconversion from HBeAg to anti-HBe occurs in approximately 20%, and, in early trials, approximately 8% lost HBsAg. Successful IFN therapy and seroconversion are often accompanied by an acute hepatitis-like elevation in aminotransferase activity, which has been postulated to result from enhanced cytolytic T cell clearance of HBV-infected hepatocytes. Relapse after successful therapy is rare (1 or 2%). The likelihood of responding to IFN is higher in patients with lower levels of HBV DNA and substantial elevations of ALT. Although children can respond as well as adults, IFN therapy has not been effective in very young children infected at birth. Similarly, IFN therapy has not been effective in immunosuppressed persons, Asian patients with minimal-to-mild ALT elevations, or patients with decompensated chronic hepatitis B (in whom such therapy can actually be detrimental, sometimes precipitating decompensation, often associated

with severe adverse effects). Among patients with HBeAg loss during therapy, long-term follow-up has demonstrated that 80% experience eventual loss of HBsAg (i.e., all serologic markers of infection) and normalization of ALT over a 9-year posttreatment period. In addition, improved long-term and complication-free survival as well as a reduction in the frequency of HCC have been documented among interferon responders, supporting the conclusion that successful interferon therapy improves the natural history of chronic hepatitis B.

Initial trials of brief-duration IFN therapy in patients with *HBeAg-negative chronic hepatitis B* were disappointing, suppressing HBV replication transiently during therapy but almost never resulting in sustained antiviral responses. In subsequent IFN trials among patients with HBeAg-negative chronic hepatitis B, however, more protracted courses, lasting up to 1½ years, have been reported to result in sustained remissions documented to last for several years, with suppressed HBV DNA and aminotransferase activity, in ~20%.

Complications of IFN therapy include systemic "flu-like" symptoms; marrow suppression; emotional lability (irritability, depression, anxiety); autoimmune reactions (especially autoimmune thyroiditis); and miscellaneous side effects such as alopecia, rashes, diarrhea, and numbness and tingling of the extremities. With the possible exception of autoimmune thyroiditis, all these side effects are reversible upon dose lowering or cessation of therapy.

Although no longer competitive with the newer generation of antivirals, IFN did represent the first successful antiviral approach and set a standard against which to measure subsequent drugs in the achievement of durable virologic, serologic, biochemical, and histologic responses; consolidation of virologic and biochemical benefit in the ensuing years after therapy; and improvement in the natural history of chronic hepatitis B. Standard IFN has been supplanted by long-acting PEG IFN (see later), and IFN nonresponders are now treated with one of the newer oral nucleoside analogues.

LAMIVUDINE The first of the nucleoside analogues to be approved, the dideoxynucleoside lamivudine, inhibits reverse transcriptase activity of both HIV and HBV and is a potent and effective agent for patients with chronic hepatitis B. Although generally superseded by newer, more potent agents, lamivudine is still used in regions of the world where newer agents are not yet approved are or not affordable. In clinical trials among patients with HBeAg-reactive chronic hepatitis B, lamivudine therapy at daily doses of 100 mg for 48–52 weeks suppressed HBV DNA by a median of approximately 5.5 $\log_{10}$ copies/mL and to undetectable levels, as measured by PCR amplification assays, in approximately 40% of patients. Therapy was associated with HBeAg loss in 32–33%; HBeAg seroconversion (i.e., conversion from HBeAg-reactive to anti-HBe-reactive) in 16–21%; normalization of ALT in 40–75%; improvement in histology in 50–60%; retardation in fibrosis in 20–30%; and prevention of progression to cirrhosis. HBeAg responses can occur even in subgroups who are resistant to IFN (e.g., those with high-level HBV DNA) or who failed in the past to respond to it. As is true for IFN therapy of chronic hepatitis B, patients with near-normal ALT activity tend not to experience HBeAg responses (despite suppression of HBV DNA), and those with ALT levels exceeding five times the upper limit of normal can expect 1-year HBeAg seroconversion rates of 50–60%. Generally, HBeAg seroconversions are confined to patients who achieve suppression of HBV DNA to $<10^4$ genomes/mL. Among patients who undergo HBeAg responses during a year-long course of therapy and in whom the response is sustained for 4–6 months after cessation of therapy, the response is durable thereafter in the vast majority, >80%; therefore, the achievement of an HBeAg response represents a viable stopping point in therapy. Reduced durability has been reported in some Asian experiences; however, in most Western and Asian patient study populations, long-term durability of HBeAg responses is the rule, which, at least in Western patients, is accompanied by a posttreatment HBsAg seroconversion rate comparable to that seen after IFN-induced HBeAg responses. To support the durability of HBeAg responses, patients receive a period of consolidation therapy (at least 6 months in Western patients, at least 1 year in Asian patients) after HBeAg seroconversion; close posttreatment monitoring is necessary to identify HBV reactivation promptly and to resume therapy. If HBeAg is unaffected by lamivudine therapy, the current approach is to continue therapy until an HBeAg response occurs, but long-term therapy may be required to suppress HBV replication and, in turn, limit liver injury; HBeAg seroconversions can increase to a level of 50% after 5 years of therapy. Histologic improvement continues to accrue with therapy beyond the first year; after a cumulative course of 3 years of lamivudine therapy, necroinflammatory activity is reduced in the majority of patients, and even cirrhosis has been shown to regress to precirrhotic stages.

Losses of HBsAg have been few during the first year of lamivudine therapy, and this observation had been cited as an advantage of IFN-based over lamivudine therapy; however, in head-to-head comparisons between standard IFN and lamivudine monotherapy, HBsAg losses were rare in both groups. Trials in which lamivudine and IFN were administered in combination failed to show a benefit of combination therapy over lamivudine monotherapy for either treatment-naïve patients or prior IFN nonresponders.

In patients with *HBeAg-negative chronic hepatitis B* (i.e., in those with precore and core-promoter HBV mutations), 1 year of lamivudine therapy results in HBV DNA suppression and normalization of ALT in three-quarters of patients and in histologic improvement in approximately two-thirds. Therapy has been shown to suppress HBV DNA by approximately 4.5 $\log_{10}$ copies/mL (baseline HBV DNA levels are lower than in patients with HBeAg-reactive hepatitis B) and to undetectable levels in approximately 70%, as measured by sensitive

PCR amplification assays. Lacking HBeAg at the outset, patients with HBeAg-negative chronic hepatitis B cannot achieve an HBeAg response—a stopping point in HBeAg-reactive patients; almost invariably, when therapy is discontinued, reactivation is the rule. Therefore, these patients require long-term therapy; with successive years, the proportion with suppressed HBV DNA and normal ALT increases.

Clinical and laboratory side effects of lamivudine are negligible, indistinguishable from those observed in placebo recipients. Still, lamivudine doses should be reduced in patients with reduced creatinine clearance. During lamivudine therapy, transient ALT elevations, resembling those seen during IFN therapy and during spontaneous HBeAg-to-anti-HBe seroconversions, occur in one-fourth of patients. These ALT elevations may result from restored cytolytic T cell activation permitted by suppression of HBV replication. Similar ALT elevations, however, occur at an identical frequency in placebo recipients, but ALT elevations associated with HBeAg seroconversion are confined to lamivudine-treated patients. When therapy is stopped after a year of therapy, two- to threefold ALT elevations occur in 20–30% of lamivudine-treated patients, representing renewed liver-cell injury as HBV replication returns. Although these posttreatment flares are almost always transient and mild, rare severe exacerbations, especially in cirrhotic patients, have been observed, mandating close and careful clinical and virologic monitoring after discontinuation of treatment. Many authorities caution against discontinuing therapy in patients with cirrhosis, in whom posttreatment flares could precipitate decompensation.

Long-term monotherapy with lamivudine is associated with methionine-to-valine (M204V) or methionine-to-isoleucine (M204I) mutations, primarily at amino acid 204 in the tyrosine-methionine-aspartate-aspartate (YMDD) motif of HBV DNA polymerase, analogous to mutations that occur in HIV-infected patients treated with this drug. During a year of therapy, YMDD mutations occur in 15–30% of patients; the frequency increases with each year of therapy, reaching 70% at year 5. Ultimately, patients with YMDD mutants experience degradation of clinical, biochemical, and histologic responses; therefore, if treatment is begun with lamivudine monotherapy, the emergence of lamivudine resistance, reflected clinically by a breakthrough from suppressed levels of HBV DNA and ALT, is managed by adding another antiviral to which YMDD variants are sensitive (e.g., adefovir, tenofovir; see later).

Currently, although lamivudine is very safe and still used widely in other parts of the world, in the United States and Europe, lamivudine has been eclipsed by more potent antivirals that have superior resistance profiles (see later). Still, as the first successful oral antiviral agent for use in hepatitis B, lamivudine has provided proof of the concept that polymerase inhibitors can achieve virologic, serologic, biochemical, and histologic benefits. In addition, lamivudine has been shown to be effective in the treatment of patients with decompensated hepatitis B (for whom IFN is contraindicated), in some of whom decompensation can be reversed. Moreover, among patients with cirrhosis or advanced fibrosis, lamivudine has been shown to be effective in reducing the risk of progression to hepatic decompensation and, marginally, the risk of HCC.

Because lamivudine monotherapy can result universally in the rapid emergence of YMDD variants in persons with HIV infection, patients with chronic hepatitis B should be tested for anti-HIV prior to therapy; if HIV infection is identified, lamivudine monotherapy at the HBV daily dose of 100 mg is contraindicated. These patients should be treated for both HIV and HBV with an HIV drug regimen that includes or is supplemented by at least two drugs active against HBV; highly active antiretroviral therapy (HAART) often contains two drugs with antiviral activity against HBV (e.g., tenofovir and emtricitabine), but if lamivudine is part of the regimen, the daily dose should be 300 mg (Chap. 93). The safety of lamivudine during pregnancy has not been established; however, the drug is not teratogenic in rodents and has been used safely in pregnant women with HIV infection and with HBV infection. Limited data even suggest that administration of lamivudine during the last months of pregnancy to mothers with high-level hepatitis B viremia ($\geq 10^8$ IU/ml) can reduce the likelihood of perinatal transmission of hepatitis B.

ADEFOVIR DIPIVOXIL At an oral daily dose of 10 mg, the acyclic nucleotide analogue adefovir dipivoxil, the prodrug of adefovir, reduces HBV DNA by approximately 3.5–4 $\log_{10}$ copies/mL and is equally effective in treatment-naïve patients and IFN nonresponders. In HBeAg-reactive chronic hepatitis B, a 48-week course of adefovir dipivoxil was shown to achieve histologic improvement (and reduce the progression of fibrosis) and normalization of ALT in just over one-half of patients, HBeAg seroconversion in 12%, HBeAg loss in 23%, and suppression to an undetectable level of HBV DNA in 13–21%, as measured by PCR. Similar to IFN and lamivudine, adefovir dipivoxil is more likely to achieve an HBeAg response in patients with high baseline ALT (e.g., among adefovir-treated patients with ALT level >5 times the upper limit of normal), HBeAg seroconversions occurred in 25%. The durability of adefovir-induced HBeAg responses is high (91% in one study); therefore, HBeAg response can be relied upon as a stopping point for adefovir therapy, after a period of consolidation therapy, as outlined earlier. Although data on the impact of additional therapy beyond 1 year are limited, biochemical, serologic, and virologic outcomes improve progressively as therapy is continued.

In patients with *HBeAg-negative chronic hepatitis B*, a 48-week course of 10 mg/d of adefovir dipivoxil resulted in histologic improvement in two-thirds, normalization of ALT in threefourths, and suppression of HBV DNA to PCR-undetectable levels in one-half to two-thirds. As was true for lamivudine, because HBeAg responses—a potential

stopping point—cannot be achieved in this group, reactivation is the rule when adefovir therapy is discontinued, and indefinite, long-term therapy is required. Treatment beyond the first year consolidates the gain of the first year; after 5 years of therapy, improvement in hepatic inflammation and regression of fibrosis was observed in three-fourths of patients, ALT was normal in 70%, and HBV DNA was undetectable in almost 70%.

Adefovir contains a flexible acyclic linker instead of the L-nucleoside ring of lamivudine, avoiding steric hindrance by mutated amino acids. In addition, the molecular structure of phosphorylated adefovir is very similar to that of its natural substrate; therefore mutations to adefovir would also affect binding of the natural substrate, dATP. Hypothetically, these are among the reasons that resistance to adefovir dipivoxil is much less likely than resistance to lamivudine; no resistance was encountered in 1 year of clinical-trial therapy. In subsequent years, however, adefovir resistance begins to emerge (asparagine to threonine at amino acid 236 [N236T] and alanine to valine or threonine at amino acid 181 [A181V/T], primarily), occurring in 2.5% after 2 years, but in 29% after 5 years of therapy (reported in HBeAg-negative patients). Among patients coinfected with HBV and HIV and who have normal CD4+ T cell counts, adefovir dipivoxil is effective in suppressing HBV dramatically (by 5 $\log_{10}$ in one study). Moreover, adefovir dipivoxil is effective in lamivudine-resistant, YMDD-mutant HBV and can be used when such lamivudine-induced variants emerge. When lamivudine resistance occurs, adding adefovir (i.e., maintaining lamivudine to preempt the emergence of adefovir resistance), is superior to switching to adefovir. Almost invariably, patients with adefovir-mutant HBV respond to lamivudine (or newer agents, such as entecavir, see later). When, in the past, adefovir had been evaluated as therapy for HIV infection, doses of 60–120 mg were required to suppress HIV, and, at these doses, the drug was nephrotoxic. Even at 30 mg/d, creatinine elevations of 44 μmol/L (0.5 mg/dL) occur in 10% of patients; however, at the HBV-effective dose of 10 mg, such elevations of creatinine are rarely encountered. If any nephrotoxicity does occur, it rarely appears before 6–8 months of therapy. Although renal tubular injury is a rare potential side effect, and although creatinine monitoring is recommended during treatment, the therapeutic index of adefovir dipivoxil is high, and the nephrotoxicity observed in clinical trials at higher doses was reversible. For patients with underlying renal disease, frequency of administration of adefovir dipivoxil should be reduced to every 48 h for creatinine clearances of 20–49 mL/min; to every 72 h for creatinine clearances of 10–19 mL/min; and once a week, following dialysis, for patients undergoing hemodialysis. Adefovir dipivoxil is very well tolerated, and ALT elevations during and after withdrawal of therapy are similar to those observed and described earlier in clinical trials of lamivudine. An advantage of adefovir is its relatively favorable resistance profile; however, it is not as potent as the other approved oral agents, it does not suppress HBV DNA as rapidly or as uniformly as the others, it is the least likely of all agents to result in HBeAg seroconversion, and 20–50% of patients fail to suppress HBV DNA by 2 $\log_{10}$ ("primary nonresponders"). For these reasons, adefovir has been supplanted in both treatment-naïve and lamivudine-resistant patients by the more potent, less resistance-prone nucleotide analogue tenofovir (see later).

PEGYLATED INTERFERON After long-acting PEG IFN was shown to be effective in the treatment of hepatitis C (see next), this more convenient drug was evaluated in the treatment of chronic hepatitis B. Once-a-week PEG IFN is more effective than the more frequently administered, standard IFN, and several large-scale trials of PEG IFN versus oral nucleoside analogues have been conducted among patients with HBeAg-reactive and HBeAg-negative chronic hepatitis B.

In HBeAg-reactive chronic hepatitis B, two large-scale studies were done, one with PEG IFN-α 2b (100 μg weekly for 32 weeks, then 50 μg weekly for another 20 weeks for a total of 52 weeks, with a comparison arm of combination PEG IFN with oral lamivudine) in 307 subjects; the other involved PEG IFN-α 2a (180 μg weekly for 48 weeks) in 814 primarily Asian patients, three-fourths of whom had ALT ≥2 × the upper limit of normal, with comparison arms of lamivudine monotherapy and combination PEG IFN plus lamivudine. At the end of therapy (48–52 weeks) in the PEG IFN monotherapy arms, HBeAg loss occurred in approximately 30%, HBeAg seroconversion in 22–27%, undetectable HBV DNA (<400 copies/mL by PCR) in 10–25%, normal ALT in 34–39%, and a mean reduction in HBV DNA of 2 $\log_{10}$ copies/mL (PEG IFN-α 2b) to 4.5 $\log_{10}$ copies/mL (PEG IFN-α 2a). Six months after completing PEG IFN monotherapy in these trials, HBeAg losses were present in approximately 35%, HBeAg seroconversion in approximately 30%, undetectable HBV DNA in 7–14%, normal ALT in 32–41%, and a mean reduction in HBV DNA of 2–2.4 $\log_{10}$ copies/mL. Although the combination of PEG IFN and lamivudine was superior at the end of therapy in one or more serologic, virologic, or biochemical outcomes, neither the combination arm (in both studies) nor the lamivudine monotherapy arm (in the PEG IFN-α 2a trial) demonstrated any benefit compared to the PEG IFN monotherapy arms 6 months after therapy. Moreover, HBsAg seroconversion occurred in 3–7% of PEG IFN recipients (with or without lamivudine); some of these seroconversions were identified by the end of therapy, but many were identified during the posttreatment follow-up period. The likelihood of HBeAg loss in PEG IFN–treated HBeAg-reactive patients is associated with HBV genotype A > B > C > D (shown for PEG IFN α-2b but not for α-2a).

Based on these results, some authorities concluded that PEG IFN monotherapy should be the first-line therapy of choice in HBeAg-reactive chronic hepatitis B; however, this conclusion has been challenged. Although a finite, 1-year course of PEG IFN results in a higher rate of sustained response (6 months after treatment) than is achieved with oral nucleoside/nucleotide

analogue therapy, the comparison is confounded by the fact that oral agents are not discontinued at the end of 1 year. Instead, taken orally and free of side effects, therapy with oral agents is extended indefinitely or until after the occurrence of an HBeAg response. The rate of HBeAg responses after 2 years of oral-agent nucleoside analogue therapy is at least as high as, if not higher than, that achieved with PEG IFN after 1 year; favoring oral agents is the absence of injections and difficult-to-tolerate side effects as well as lower direct and indirect medical costs and inconvenience. The association of HBsAg responses with PEG IFN therapy occurs in such a small proportion of patients that subjecting everyone to PEG IFN for the marginal gain of HBsAg responses during or immediately after therapy in such a very small minority is questionable. Moreover, HBsAg responses occur in a comparable proportion of patients treated with early-generation nucleoside/nucleotide analogues in the years after therapy, and, with the newer, more potent nucleoside analogues, the frequency of HBsAg loss during the first year of therapy equals that of PEG IFN and is exceeded during year 2 (see later). Of course, resistance is not an issue during PEG IFN therapy, but the risk of resistance is much lower with new agents (≤1% up to 3–5 years in previously treatment-naïve, entecavir-treated and tenofovir-treated patients; see later). Finally, the level of HBV DNA inhibition that can be achieved with the newer agents, and even with lamivudine, exceeds that which can be achieved with PEG IFN, in some cases by several orders of magnitude.

In HBeAg-negative chronic hepatitis B, a trial of PEG IFN-α 2a (180 μg weekly for 48 weeks versus comparison arms of lamivudine monotherapy and of combination therapy) in 564 patients showed that PEG IFN monotherapy resulted at the end of therapy in suppression of HBV DNA by a mean of 4.1 $\log_{10}$ copies/mL, undetectable HBV DNA (<400 copies/mL by PCR) in 63%, normal ALT in 38%, and loss of HBsAg in 4%. Although lamivudine monotherapy and combination lamivudine–PEG IFN therapy were both superior to PEG IFN at the end of therapy, no advantage of lamivudine monotherapy or combination therapy was apparent over PEG IFN monotherapy 6 months after therapy— suppression of HBV DNA by a mean of 2.3 $\log_{10}$ copies/mL, undetectable HBV DNA in 19%, and normal ALT in 59%. In subjects involved in this trial followed for up to 5 years, among the two-thirds followed who had been treated initially with PEG IFN, 17% maintained HBV DNA suppression to <400 copies/ml, but ALT remained normal in only 22%; HBsAg loss increased gradually to 12%. Among the half followed who had been treated initially with lamivudine monotherapy, HBV DNA remained <400 copies/ml in 7% and ALT normal in 16%; by year 5, 3.5% had lost HBsAg. As was the case for standard IFN therapy in HBeAg-negative patients, longer after PEG IFN treatment, although a small subset maintained their responses, the proportion who benefited was very small, raising questions about the relative value of a finite period of PEG IFN, versus a longer course with a potent, low-resistance oral nucleoside analogue in these patients.

ENTECAVIR Entecavir, an oral cyclopentyl guanosine analogue polymerase inhibitor, appears to be the most potent of the HBV antivirals and is just as well tolerated as lamivudine. In a 709-subject clinical trial among HBeAg-reactive patients, oral entecavir, 0.5 mg daily, was compared to lamivudine, 100 mg daily. At 48 weeks, entecavir was superior to lamivudine in suppression of HBV DNA, mean 6.9 versus 5.5 $\log_{10}$ copies/mL and in percent with undetectable HBV DNA (<300 copies/mL by PCR), 67% versus 36%; histologic improvement (≥2-point improvement in necroinflammatory HAI score), 72% versus 62%; and normal ALT (68% versus 60%). The two treatments were indistinguishable in percent with HBeAg loss (22% versus 20%) and seroconversion (21% versus 18%). Among patients treated with entecavir for 96 weeks, HBV DNA was undetectable cumulatively in 80% (versus 39% for lamivudine), and HBeAg seroconversions had occurred in 31% (versus 26% for lamivudine); the HBeAg seroconversion rate after 3 years of entecavir in this cohort was 39%. Similarly, in a 638-subject clinical trial among HBeAg-negative patients, at week 48, oral entecavir, 0.5 mg daily, was superior to lamivudine, 100 mg daily, in suppression of HBV DNA (mean, 5.0 versus 4.5 $\log_{10}$ copies/mL) and in percent with undetectable HBV DNA (90% versus 72%); histologic improvement (70% versus 61%); and normal ALT (78% versus 71%). No resistance mutations were encountered in previously treatment-naïve, entecavir-treated patients during 96 weeks of therapy, and in a cohort of subjects treated for up to 5 years, resistance emerged in 1.2%. Its high barrier to resistance coupled with its high potency renders entecavir a first-line drug for patients with chronic hepatitis B.

Entecavir is also effective against lamivudine-resistant HBV infection. In a trial of 286 lamivudine-resistant patients, entecavir, at a higher daily dose of 1 mg, was superior to lamivudine, as measured at week 48, in achieving suppression of HBV DNA (mean, 5.1 versus 0.48 $\log_{10}$ copies/mL); undetectable HBV DNA (72% versus 19%); normal ALT (61% versus 15%); HBeAg loss (10% versus 3%); and HBeAg seroconversion (8% versus 3%). In this population of lamivudine-experienced patients, however, entecavir resistance emerged in 7% at 48 weeks. Although entecavir resistance requires both a YMDD mutation and a second mutation at one of several other sites (e.g., T184A, S202G/I, or M250V), resistance to entecavir in lamivudine-resistant chronic hepatitis B has been recorded to increase progressively to 43% at 4 years; therefore, entecavir is not as attractive a choice as adefovir or tenofovir for patients with lamivudine-resistant hepatitis B.

At the end of 2 years of entecavir therapy in clinical trials among HBeAg-reactive patients, HBsAg seroconversion was observed in 5% (≤2% during the first year). In addition, on-treatment and posttreatment ALT flares are relatively uncommon and relatively mild in entecavir-treated patients. In clinical trials, entecavir has had an excellent safety profile; doses should be reduced for patients with reduced creatinine clearance. Entecavir does have low-level antiviral activity against HIV and

cannot be used as monotherapy to treat HBV infection in HIV/HBV-co-infected persons.

TELBIVUDINE Telbivudine, a cytosine analogue, appears to be similar in efficacy to entecavir; however, it is slightly less potent in suppressing HBV DNA (a slightly more profound median 6.4-$\log_{10}$ reduction in HBeAg-reactive disease, a similar 5.2 $\log_{10}$ reduction in HBeAg-negative disease). In its registration trial, telbivudine at an oral daily dose of 600 mg suppressed HBV DNA to <300 copies/ml in 60% of HBeAg-positive and 88% of HBeAg-negative patients, reduced ALT to normal in 77% of HBeAg-positive and 74% of HBeAg-negative patients, and improved histology in 65% of HBeAg-positive and 67% HBeAgnegative patients. Although resistance to telbivudine (M204I, not M204V mutations) was less frequent than resistance to lamivudine at the end of 1 year, resistance mutations after 2 years of treatment occurred in up to 22%. Generally well tolerated, telbivudine has been associated with a low frequency of asymptomatic creatine kinase elevations and with a very low frequency of peripheral neuropathy; frequency of administration should be reduced for patients with impaired creatinine clearance. Its excellent potency notwithstanding, the inferior resistance profile of telbivudine has limited its appeal; telbivudine is neither recommended as first-line therapy nor widely used.

TENOFOVIR Tenofovir disoproxil fumarate, an acyclic nucleotide analogue and potent antiretroviral agent used to treat HIV infection, is similar to adefovir but more potent in suppressing HBV DNA and inducing HBeAg responses; it is highly active against both wild-type and lamivudine-resistant HBV and active in patients whose response to adefovir is slow and/or limited. At an oral once-daily dose of 300 mg for 48 weeks, tenofovir suppressed HBV DNA by 6.2 $\log_{10}$ (to undetectable levels [<400 copies/ml] in 76%) in HBeAg-positive and 4.6 $\log_{10}$ (to undetectable levels in 93%) in HBeAg-negative patients; reduced ALT to normal in 68% of HBeAg-positive and 76% of HBeAg-negative patients; and improved histology in 74% of HBeAg-positive and 72% of HBeAg-negative patients. In HBeAg-positive patients, HBeAg seroconversions occurred in 21% by the end of year 1 and in 27% by the end of year 2 of tenofovir treatment; HBsAg loss occurred in 3% by the end of year 1 and 6% by the end of year 2. The safety (negligible renal toxicity and mild reduction in bone density) and resistance profile (none recorded through 3 years) of tenofovir are very favorable as well; therefore, tenofovir has supplanted adefovir both as first-line therapy for chronic hepatitis B and as add-on therapy for lamivudine-resistant chronic hepatitis B. Frequency of tenofovir administration should be reduced for patients with impaired creatinine clearance.

A comparison of the six antiviral therapies in current use appears in Table 96-3; their relative potencies in suppressing HBV DNA are shown in Fig. 96-1.

COMBINATION THERAPY Although the combination of lamivudine and PEG IFN suppresses HBV DNA more profoundly during therapy than does monotherapy with either drug alone (and is much less likely to be associated with lamivudine resistance), this combination used for a year is no better than a year of PEG IFN in achieving sustained responses. To date, combinations of oral nucleoside/nucleotide agents have not achieved an enhancement in virologic, serologic, or biochemical efficacy over that achieved by the more potent of the combined drugs given individually. On the other hand, combining agents that are not cross-resistant (e.g., lamivudine and adefovir or tenofovir) has the potential to reduce the risk or perhaps even to preempt entirely the emergence of drug resistance. In the future, the treatment paradigm may shift from the current approach of sequential monotherapy to preemptive combination therapy; however, designing and executing clinical trials that demonstrate superior efficacy and resistance profile of combination therapy over monotherapy with entecavir or tenofovir will be very challenging.

NOVEL ANTIVIRALS AND STRATEGIES In addition to the seven approved antiviral drugs for hepatitis B, emtricitabine, a fluorinated cytosine analogue very similar to lamivudine in structure, efficacy, and resistance profile, offers no advantage over lamivudine. A combination of emtricitabine and tenofovir is approved for the treatment of HIV infection and is an appealing combination therapy for hepatitis B; however, neither emtricitabine nor the combination is approved yet for hepatitis B. Several initially promising antiviral agents have been abandoned because of toxicity (e.g., clevudine, which was linked to myopathy during its clinical development). Because direct-acting antivirals have been so successful in the management of chronic hepatitis B, more unconventional approaches—e.g., immunologic or genetic manipulation—are not likely to be competitive. Finally, initial emphasis in the development of antiviral therapy for hepatitis B was placed on monotherapy; whether combination regimens will yield additive or synergistic efficacy remains to be determined.

TREATMENT RECOMMENDATIONS Several learned societies and groups of expert physicians have issued treatment recommendations for patients with chronic hepatitis B; the most authoritative and updated (and free of financial support by pharmaceutical companies) are those of the American Association for the Study of Liver Diseases (AASLD) and of the European Association for the Study of the Liver (EASL). Although the recommendations differ slightly, a consensus has emerged on most of the important points (Table 96-4). No treatment is recommended or available for inactive "nonreplicative" hepatitis B carriers (undetectable HBeAg with normal ALT and HBV DNA $\leq 10^3$ IU/ml documented serially over time). In patients with detectable HBeAg and HBV DNA levels $>2 \times 10^4$ IU/ml, treatment is recommended by the AASLD for those with ALT levels above 2 × the upper limit of

TABLE 96-3

COMPARISON OF PEGYLATED INTERFERON (PEG IFN), LAMIVUDINE, ADEFOVIR, ENTECAVIR, TELBIVUDINE, AND TENOFOVIR THERAPY FOR CHRONIC HEPATITIS B[a]

FEATURE	PEG IFN[b]	LAMIVUDINE	ADEFOVIR	ENTECAVIR	TELBIVUDINE	TENOFOVIR
Route of administration	Subcutaneous Injection	Oral	Oral	Oral	Oral	Oral
Duration of therapy[c]	48–52 weeks	≥52 weeks	≥48 weeks	≥48 weeks	≥52 weeks	≥48 weeks
Tolerability	Poorly tolerated	Well tolerated	Well tolerated; creatinine monitoring recommended	Well tolerated	Well tolerated	Well tolerated; creatinine monitoring recommended
HBeAg seroconversion						
1 yr Rx	18–20%	16–21%	12%	21%	22%	21%
>1 yr Rx	NA	up to 50% @ 5 yrs	43% @ 3 yrs[d]	31% @ 2 yrs 39% @ 3 yrs	30% @ 2 yrs	27% @ 2 yrs
Log_{10} HBV DNA reduction (mean copies/mL)						
HBeAg-reactive	4.5	5.5	Median 3.5–5	6.9	6.4	6.2
HBeAg-negative	4.1	4.4–4.7	Median 3.5–3.9	5.0	5.2	4.6
HBV DNA PCR negative (<300–400 copies/mL; <1,000 copies/mL for adefovir) end of yr 1						
HBeAg-reactive	10–25%	36–44%	13–21%	67% (91% @ 4 yrs)	60%	76%
HBeAg-negative	63%	60–73%	48–77%	90%	88%	93%
ALT normalization at end of yr 1						
HBeAg-reactive	39%	41–75%	48–61%	68%	77%	68%
HBeAg-negative	34–38%	62–79%	48–77%	78%	74%	76%
HBsAg loss yr 1	3–4%	≥1%	0%	2%	<1%	3%
yr 2	12% 5 yrs after 1 yr of Rx	No data	5% at yr 5	5%	No data	6%
Histologic improvement (≥2-point reduction in HAI) at yr 1						
HBeAg-reactive	38% 6 months after	49–62%	53–68%	72%	65%	74%
HBeAg-negative	48% 6 months after	61–66%	64%	70%	67%	72%
Viral resistance	None	15-30% @ 1 yr	None @ 1 yr	≥1% @ 1 yr[e]	up to 5% @ yr 1	0% @ yr 1
		70% @ 5 yrs	29% at 5 yrs	1.2% @ 5 yrs[e]	up to 22% @ yr 2	0% through yr 3
Cost (US$) for 1 yr	~$18,000	~$2,500	~$6,500	~$8,700[f]	~$6,000	~$6,000

[a]Generally, these comparisons are based on data on each drug tested individually versus placebo in registration clinical trials; because, with rare exception, these comparisons are not based on head-to-head testing of these drugs, relative advantages and disadvantages should be interpreted cautiously.
[b]Although standard interferon α administered daily or three times a week is approved as therapy for chronic hepatitis B, it has been supplanted by PEG IFN, which is administered once a week and is more effective. Standard interferon has no advantages over PEG IFN.
[c]Duration of therapy in clinical efficacy trials; use in clinical practice may vary.
[d]Because of a computer-generated randomization error that resulted in misallocation of drug versus placebo during the second year of clinical-trial treatment, the frequency of HBeAg seroconversion beyond the first year is an estimate (Kaplan-Meier analysis) based on the small subset in whom adefovir was administered correctly.
[e]7% during a year of therapy (43% at year 4) in lamivudine-resistant patients.
[f]~17,400 for lamivudine-refractory patients.
Abbreviations: ALT, alanine aminotransferase; HAI, histologic activity index; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; NA, not applicable; PEG IFN, pegylated interferon; PCR, polymerase chain reaction; Rx, therapy; yr, year.

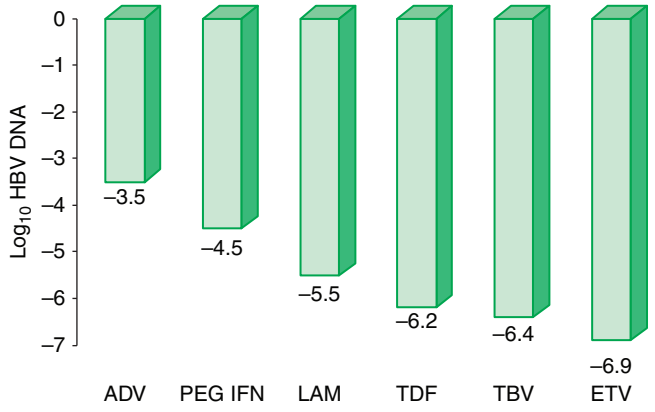


FIGURE 96-1

Relative potency of antiviral drugs for hepatitis B, as reflected by median $\log_{10}$ HBV DNA reduction in HBeAg-positive chronic hepatitis B. These data are from individual reports of large, randomized controlled registration trials that were the basis for approval of the drugs. In most instances, these data do not represent direct comparisons among the drugs, because study populations were different, baseline patient variables were not always uniform, and the sensitivity and dynamic range of the HBV DNA assays used in the trials varied. ADV, adefovir dipivoxil; PEG IFN, pegylated interferon α-2a; LAM, lamivudine; TDF, tenofovir disoproxil fumarate; TBV, telbivudine; ETV, entecavir.

normal. (The EASL recommends treatment in HBeAg-positive patients for HBV DNA levels $>2 \times 10^3$ IU/mL and ALT above the upper limit of normal.) For HBeAg-positive patients with ALT $\leq 2 \times$ the upper limit of normal, in whom sustained responses are not likely and who would require multiyear therapy, antiviral therapy is not recommended currently. This pattern is common during the early decades of life among Asian patients infected at birth; even in this group, therapy would be considered for those >40 years of age, those with ALT persistently at the high end of the twofold range, and/or those with a family history of hepatocellular carcinoma, especially if the liver biopsy shows moderate to severe necroinflammatory activity or fibrosis. In this group, when, eventually, ALT becomes elevated later in life, antiviral therapy should be instituted. For patients with HBeAg-negative chronic hepatitis B, ALT $>2 \times$ the upper limit of normal (above the upper limit of normal according to EASL) and HBV DNA $>2 \times 10^3$ IU/mL, antiviral therapy is recommended. If HBV DNA is $>2 \times 10^3$ IU/mL and ALT is 1 to $>2 \times$ the upper limit of normal, liver biopsy should be considered to help in arriving at a decision to treat if substantial liver injury is present (treatment in this subset would be recommended according to EASL guidelines, because ALT is elevated).

For patients with compensated cirrhosis, because antiviral therapy has been shown to retard clinical progression, treatment is recommended regardless of HBeAg status and ALT as long as HBV DNA is detectable at $>2 \times 10^3$ IU/ml (detectable at any level according to the EASL); monitoring without therapy is recommended for those with HBV DNA $<2 \times 10^3$ IU/ml, unless ALT is elevated. For patients with decompensated cirrhosis, treatment is recommended regardless of serologic and biochemical status, as long as HBV DNA is detectable. Patients with decompensated cirrhosis should be evaluated as candidates for liver transplantation.

Among the seven available drugs for hepatitis B, PEG IFN has supplanted standard IFN, entecavir has supplanted lamivudine, and tenofovir has supplanted adefovir. PEG IFN, entecavir, and tenofovir are recommended as first-line therapy (Table 96-3). PEG IFN requires finite-duration therapy, achieves the highest rate of HBeAg responses after a year of therapy, and does not support viral mutations, but it requires subcutaneous injections and is associated with inconvenience and intolerability. Oral nucleoside analogues require long-term therapy in most patients, and when used alone, lamivudine and telbivudine foster the emergence of viral mutations, adefovir somewhat less so, and entecavir (except in lamivudine-experienced patients) and tenofovir rarely at all. Oral agents do not require injections, are very well tolerated, lead to improved histology in 50–90% of patients, suppress HBV DNA more profoundly than PEG IFN, and are effective even in patients who fail to respond to IFN-based therapy. Although oral agents are less likely to result in HBeAg responses during the first year of therapy, as compared to PEG IFN, treatment with oral agents tends to be extended beyond the first year and, by the end of the second year, yields HBeAg responses (and even HBsAg responses) comparable in frequency to those achieved after 1 year of PEG IFN (and without the associated side effects) (Table 96-5). Although adefovir and tenofovir are safe, creatinine monitoring is recommended. Substantial experience with lamivudine during pregnancy (see earlier) has identified no teratogenicity. Although interferons do not appear to cause congenital anomalies, interferons have antiproliferative properties and should not be used during pregnancy. Adefovir during pregnancy has not been associated with birth defects; however, there may be an increased risk of spontaneous abortion. Data on the safety of entecavir during pregnancy have not been published. Sufficient data in animals and limited data in humans suggest that telbivudine and tenofovir can be used safely during pregnancy. In general, except perhaps for lamivudine, and until additional data become available, the other antivirals for hepatitis B should be avoided or used with extreme caution during pregnancy.

As noted earlier, some physicians prefer to begin with PEG IFN, while other physicians and patients prefer oral agents as first-line therapy. For patients with decompensated cirrhosis, the emergence of resistance can result in further deterioration and loss of antiviral effectiveness. Therefore, in this patient subset, the threshold for relying on therapy with a very favorable resistance profile (e.g., entecavir or tenofovir) or on combination therapy (e.g., lamivudine or telbivudine with adefovir) is low. PEG IFN should not be used in patients with compensated or decompensated cirrhosis.

TABLE 96-4

RECOMMENDATIONS FOR TREATMENT OF CHRONIC HEPATITIS B[a]

HBeAg STATUS	CLINICAL	HBV DNA (IU/mL)	ALT	RECOMMENDATION
HBeAg-reactive	[b]	>2 ×10^4	<2 × ULN[c]	No treatment; monitor. In patients >40 with family history of hepatocellular carcinoma and/or ALT persistently at the high end of the twofold range, liver biopsy may help in decision to treat
	Chronic hepatitis	>2 × 10^{4}[d]	>2 × ULN[d]	Treat[e]
	Cirrhosis, compensated	>2 × 10^3	< or > ULN	Treat[e] with oral agents, not PEG IFN
		<2 × 10^3	>ULN	Consider treatment[f]
	Cirrhosis, decompensated	Detectable	< or > ULN	Treat[e] with oral agents[g], not PEG IFN; refer for liver transplantation
		Undetectable	< or > ULN	Observe; refer for liver transplantation
HBeAg-negative	[b]	≤2 × 10^3	≤ULN	Inactive carrier; treatment not necessary
	Chronic hepatitis	>10^3	1->2 × ULN[d]	Consider liver biopsy; treat[h] if biopsy shows moderate to severe inflammation or fibrosis
	Chronic hepatitis	>10^4	>2 × ULN[d]	Treat[h,i]
	Cirrhosis, compensated	>2 × 10^3	< or > ULN	Treat[e] with oral agents, not PEG IFN
		<2 × 10^3	>ULN	Consider treatment[f]
	Cirrhosis, decompensated	Detectable	< or > ULN	Treat[h] with oral agents[g], not PEG IFN; refer for liver transplantation
		Undetectable	< or > ULN	Observe; refer for liver transplantation

[a]Based on practice guidelines of the American Association for the Study of Liver Diseases (AASLD). Except as indicated in footnotes, these guidelines are similar to those issued by the European Association for the Study of the Liver (EASL).
[b]Liver disease tends to be mild or inactive clinically; most such patients do not undergo liver biopsy.
[c]This pattern is common during early decades of life in Asian patients infected at birth.
[d]According to the EASL guidelines, treat if HBV DNA is >2 × 10^3 IU/mL and ALT >ULN.
[e]One of the potent oral drugs with a high barrier to resistance (entecavir or tenofovir) or PEG IFN can be used as first-line therapy (see text). These oral agents, but not PEG IFN, should be used for interferon-refractory/intolerant and immunocompromised patients. PEG IFN is administered weekly by subcutaneous injection for a year; the oral agents are administered daily for at least a year and continued indefinitely or until at least 6 months after HBeAg seroconversion.
[f]According to EASL guidelines, patients with compensated cirrhosis and detectable HBV DNA at any level, even with normal ALT, are candidates for therapy. Most authorities would treat indefinitely, even in HBeAg-positive disease after HBeAg seroconversion.
[g]Because the emergence of resistance can lead to loss of antiviral benefit and further deterioration in decompensated cirrhosis, a low-resistance regimen is recommended—entecavir or tenofovir monotherapy or combination therapy with the more resistance-prone lamivudine (or telbivudine) plus adefovir. Therapy should be instituted urgently.
[h]Because HBeAg seroconversion is not an option, the goal of therapy is to suppress HBV DNA and maintain a normal ALT. PEG IFN is administered by subcutaneous injection weekly for a year; caution is warranted in relying on a 6-month posttreatment interval to define a sustained response, because the majority of such responses are lost thereafter. Oral agents, entecavir or tenofovir, are administered daily, usually indefinitely or until, as very rarely occurs, virologic and biochemical responses are accompanied by HBsAg seroconversion.
[i]For older patients and those with advanced fibrosis, consider lowering the HBV DNA threshold to >2 × 10^3 IU/mL.
Abbreviations: ALT, alanine aminotransferase; AASLD, American Association for the Study of Liver Diseases; EASL, European Association for the Study of the Liver; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; PEG IFN, pegylated interferon; ULN, upper limit of normal.

TABLE 96-5

PEGYLATED INTERFERON VERSUS ORAL NUCLEOSIDE ANALOGUES FOR THE TREATMENT OF CHRONIC HEPATITIS B

	PEG IFN	NUCLEOSIDE ANALOGUES
Administration	Weekly injection	Daily, orally
Tolerability	Poorly tolerated, intensive monitoring	Well tolerated, limited monitoring
Duration of therapy	Finite 48 weeks	≥1 year, indefinite in most patients
Maximum mean HBV DNA suppression	4.5 $\log_{10}$	6.9 $\log_{10}$
Effective in high-level HBV DNA (≥10^9 IU/ml)	No	Yes
HBeAg seroconversion		
During 1 year of therapy	~30%	~20%
During >1 year of therapy	Not applicable	30% (year 2)–50% (year 5)
HBeAg-negative posttreatment HBV DNA suppression	17% @ 5 years	7% @ 4 years (lamivudine)
HBsAg loss		
During 1 year of therapy	3–4%	0–3%
During >1 year of therapy	Not applicable	3–6% @ 2 years of therapy
After 1 year of therapy–HBeAg-negative	12% @ 5 years	3.5% @ 5 years
Antiviral resistance	None	Lamivudine: ~30% year 1, ~70% year 5 Adefovir: 0 year 1, ~30% year 5 Telbivudine: up to 4% year 1, 22% year 2 Entecavir: ≤1.2% through year 5 Tenofovir: 0 through year 3
Use in cirrhosis, transplantation, immunosuppression	No	Yes
Cost, 1 year of therapy	++++	+ to ++

Abbreviations: HBV, hepatitis B virus; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; IU/mL, international units per milliliter; PEG IFN, pegylated interferon.

For patients with end-stage chronic hepatitis B who undergo liver transplantation, reinfection of the new liver is almost universal in the absence of antiviral therapy. The majority of patients become high-level viremic carriers with minimal liver injury. Before the availability of antiviral therapy, an unpredictable proportion experienced severe hepatitis B–related liver injury, sometimes a fulminant-like hepatitis, sometimes a rapid recapitulation of the original severe chronic hepatitis B (Chap. 95). Currently, however, prevention of recurrent hepatitis B after liver transplantation has been achieved definitively by *combining* hepatitis B immune globulin with one of the oral nucleoside or nucleotide analogues.

For patients treated with the more resistance-prone (lamivudine, telbivudine) or less potent (adefovir) oral agents, assessment of response at 24 weeks (48 weeks for adefovir) can identify those at high risk for inadequate response and breakthrough resistance (i.e., the presence of residual detectable viremia). When such inadequate responses are identified, a second, non-cross-resistant agent can be added or the initial agent can be replaced by a more potent agent. This "roadmap" approach has been rendered irrelevant by the use of the current generation of highly potent, low-resistant agents entecavir and tenofovir. Still, at 24 weeks, if HBV DNA exceeds 2×10^3 IU/ml, switching to a different agent or adding a second agent is advisable.

Patients with HBV/HIV co-infection can have progressive HBV-associated liver disease and, occasionally, a severe exacerbation of hepatitis B resulting from immunologic reconstitution following highly active antiretroviral therapy. Lamivudine should never be used as monotherapy in patients with HBV/HIV co-infection because HIV resistance emerges rapidly to both viruses. Adefovir has been used successfully to treat chronic hepatitis B in HBV/HIV-co-infected patients but is no longer considered a first-line agent for HBV. Entecavir has low-level activity against HIV and can result in selection of HIV resistance; therefore, it should be avoided in HBV/HIV co-infection. Tenofovir and the combination of tenofovir and emtricitabine in one pill are approved therapies for HIV and represent excellent choices for treating HBV infection in HBV/HIV-co-infected patients. Generally, even for HBV/HIV-co-infected patients who do not yet meet treatment criteria for HIV infection, treating for both HBV and HIV is recommended.

Patients with chronic hepatitis B who undergo cytotoxic chemotherapy for treatment of malignancies as well as patients treated with immunosuppressive, anticytokine, or antitumor necrosis factor therapies experience enhanced HBV replication and viral expression on hepatocyte membranes during chemotherapy coupled with suppression of cellular immunity. When chemotherapy is withdrawn, such patients are at risk for reactivation of hepatitis B, often severe and occasionally fatal. Such rebound reactivation represents restoration of cytolytic T cell function against a target organ enriched in HBV expression. Preemptive treatment with

lamivudine prior to the initiation of chemotherapy has been shown to reduce the risk of such reactivation. In all likelihood, the newer, more potent oral antiviral agents will work as well and with a lower risk of antiviral drug resistance. The optimal duration of antiviral therapy after completion of chemotherapy is not known, but a suggested approach is 6 months for inactive hepatitis B carriers and longer-duration therapy in patients with baseline HBV DNA levels >2 × 10^3 IU/ml, until standard clinical endpoints are met (Table 96-4).

CHRONIC HEPATITIS D (DELTA HEPATITIS)

Chronic infection with hepatitis D virus (HDV) may follow acute co-infection with HBV but at a rate no higher than the rate of chronicity of acute hepatitis B. That is, although HDV co-infection can increase the severity of acute hepatitis B, HDV does not increase the likelihood of progression to chronic hepatitis B. When, however, HDV super-infection occurs in a person who is already chronically infected with HBV, long-term HDV infection is the rule and a worsening of the liver disease the expected consequence. Except for severity, chronic hepatitis B plus D has similar clinical and laboratory features to those seen in chronic hepatitis B alone. Relatively severe and progressive chronic hepatitis, with or without cirrhosis, is the rule, and mild chronic hepatitis is the exception. Occasionally, mild hepatitis or even, rarely, inactive carriage occurs in patients with chronic hepatitis B plus D, and the disease may become indolent after several years of infection. A distinguishing serologic feature of chronic hepatitis D is the presence in the circulation of antibodies to liver-kidney microsomes (anti-LKMs); however, the anti-LKMs seen in hepatitis D (anti-LKM3) are directed against uridine diphosphate glucuronosyltransferase and are distinct from anti-LKM1 seen in patients with autoimmune hepatitis and in a subset of patients with chronic hepatitis C (see next). The clinical and laboratory features of chronic HDV infection are summarized in Chap. 95.

TREATMENT Chronic Hepatitis D

Management is not well defined. Glucocorticoids are ineffective and are not used. Preliminary experimental trials of IFN-α suggested that conventional doses and durations of therapy lower levels of HDV RNA and aminotransferase activity only transiently during treatment but have no impact on the natural history of the disease. In contrast, high-dose IFN-α (9 million units three times a week) for 12 months may be associated with a sustained loss of HDV replication and clinical improvement in up to 50% of patients. Moreover, the beneficial impact of treatment has been observed to persist for 15 years and to be associated with a reduction in grade of hepatic necrosis and inflammation, reversion of advanced fibrosis (improved stage), and clearance of HDV RNA in some patients. A suggested approach to therapy has been high-dose, long-term IFN for at least a year and, in responders, extension of therapy until HDV RNA and HBsAg clearance. PEG IFN has also been shown to be effective in the treatment of chronic hepatitis D and is likely to become a more convenient replacement for standard IFN. None of the nucleoside analogue antiviral agents for hepatitis B is effective in hepatitis D. In patients with end-stage liver disease secondary to chronic hepatitis D, liver transplantation has been effective. If hepatitis D recurs in the new liver without the expression of hepatitis B (an unusual serologic profile in immunocompetent persons but common in transplant patients), liver injury is limited. In fact, the outcome of transplantation for chronic hepatitis D is superior to that for chronic hepatitis B; in such patients, combination hepatitis B immune globulin and nucleoside analogue therapy for hepatitis B is indicated.

CHRONIC HEPATITIS C

Regardless of the epidemiologic mode of acquisition of hepatitis C virus (HCV) infection, chronic hepatitis follows acute hepatitis C in 50–70% of cases; chronic infection is common even in those with a return to normal in aminotransferase levels after acute hepatitis C, adding up to an 85% likelihood of chronic HCV infection after acute hepatitis C. Few clues had emerged to explain host differences associated with chronic infection until recently, when variation in a single-nucleotide polymorphism (SNP) on chromosome 19, IL28B (which codes for interferon-λ3), was identified that distinguished between responders and nonresponders to antiviral therapy (see later in the chapter). The same variants correlated with spontaneous resolution after acute infection: 53% in genotype C/C, 30% in genotype C/T, but only 23% in genotype T/T.

In patients with chronic hepatitis C followed for 20 years, progression to cirrhosis occurs in about 20–25%. Such is the case even for patients with relatively clinically mild chronic hepatitis, including those without symptoms, with only modest elevations of aminotransferase activity and with mild chronic hepatitis on liver biopsy. Even in cohorts of well-compensated patients with chronic hepatitis C referred for clinical research trials (no complications of chronic liver disease and normal hepatic synthetic function), the prevalence of cirrhosis may be as high as 50%. Most cases of hepatitis C are identified initially in asymptomatic patients who have no history of acute hepatitis C (e.g., those discovered while attempting to donate blood, while undergoing lab testing as part of an application for life insurance, or as a result of routine laboratory tests). The source of HCV infection in many of these cases is not defined, although a long-forgotten percutaneous exposure in the remote past can be elicited in a substantial proportion and probably accounts for most infections; most of these infections were acquired in the 1960s and 1970s, coming to clinical attention decades later.

Approximately one-third of patients with chronic hepatitis C have normal or near-normal aminotransferase activity; although one-third to one-half of these patients have chronic hepatitis on liver biopsy, the grade of liver injury and stage of fibrosis tend to be mild in the vast majority. In some cases, more severe liver injury has been reported—even, rarely, cirrhosis, most likely the result of previous histologic activity. Among patients with persistent normal aminotransferase activity sustained over ≥5–10 years, histologic progression has been shown to be rare; however, approximately one-fourth of patients with normal aminotransferase activity experience subsequent aminotransferase elevations, and histologic injury can be progressive once abnormal biochemical activity resumes. Therefore, continued clinical monitoring is indicated, even for patients with normal aminotransferase activity.

Despite this substantial rate of progression of chronic hepatitis C, and despite the fact that liver failure can result from end-stage chronic hepatitis C, the long-term prognosis for chronic hepatitis C in a majority of patients is relatively benign. Mortality over 10–20 years among patients with transfusion-associated chronic hepatitis C has been shown not to differ from mortality in a matched population of transfused patients in whom hepatitis C did not develop. Although death in the hepatitis group is more likely to result from liver failure, and although hepatic decompensation may occur in ~15% of such patients over the course of a decade, the majority (almost 60%) of patients remain asymptomatic and well compensated, with no clinical sequelae of chronic liver disease. Overall, chronic hepatitis C tends to be very slowly and insidiously progressive, if at all, in the vast majority of patients, while in approximately one-fourth of cases, chronic hepatitis C will progress eventually to end-stage cirrhosis. In fact, because HCV infection is so prevalent, and because a proportion of patients progress inexorably to end-stage liver disease, hepatitis C is the most frequent indication for liver transplantation. Referral bias may account for the more severe outcomes described in cohorts of patients reported from tertiary care centers (20-year progression of ≥20%) versus the more benign outcomes in cohorts of patients monitored from initial blood-product-associated acute hepatitis or identified in community settings (20-year progression of only 4–7%). Still unexplained, however, are the wide ranges in reported progression to cirrhosis, from 2% over 17 years in a population of women with hepatitis C infection acquired from contaminated anti-D immune globulin to 30% over ≤11 years in recipients of contaminated intravenous immune globulin.

Progression of liver disease in patients with chronic hepatitis C has been reported to be more likely in patients with older age, longer duration of infection, advanced histologic stage and grade, genotype 1, more complex quasispecies diversity, increased hepatic iron, concomitant other liver disorders (alcoholic liver disease, chronic hepatitis B, hemochromatosis, α_1-antitrypsin deficiency, and steatohepatitis), HIV infection, and obesity. Among these variables, however, duration of infection appears to be one of the most important, and some of the others probably reflect disease duration to some extent (e.g., quasispecies diversity, hepatic iron accumulation). No other epidemiologic or clinical features of chronic hepatitis C (e.g., severity of acute hepatitis, level of aminotransferase activity, level of HCV RNA, presence or absence of jaundice during acute hepatitis) are predictive of eventual outcome. Despite the relatively benign nature of chronic hepatitis C over time in many patients, cirrhosis following chronic hepatitis C has been associated with the late development, after several decades, of HCC; the annual rate of HCC in cirrhotic patients with hepatitis C is 1–4%, occurring primarily in patients who have had HCV infection for 30 years or more.

Perhaps the best prognostic indicator in chronic hepatitis C is liver histology; the rate of hepatic fibrosis may be slow, moderate, or rapid. Patients with mild necrosis and inflammation as well as those with limited fibrosis have an excellent prognosis and limited progression to cirrhosis. In contrast, among patients with moderate to severe necroinflammatory activity or fibrosis, including septal or bridging fibrosis, progression to cirrhosis is highly likely over the course of 10–20 years. Among patients with compensated cirrhosis associated with hepatitis C, the 10-year survival rate is close to 80%; mortality occurs at a rate of 2–6% per year; decompensation at a rate of 4–5% per year; and, as previously noted, HCC at a rate of 1–4% per year. A discussion of the pathogenesis of liver injury in patients with chronic hepatitis C appears in Chap. 95.

Clinical features of chronic hepatitis C are similar to those just described for chronic hepatitis B. Generally, fatigue is the most common symptom; jaundice is rare. Immune complex–mediated extrahepatic complications of chronic hepatitis C are less common than in chronic hepatitis B (despite the fact that assays for immune complexes are often positive in patients with chronic hepatitis C), with the exception of essential mixed cryoglobulinemia (Chap. 95), which is linked to cutaneous vasculitis and membranoproliferative glomerulonephritis as well as lymphoproliferative disorders such as B-cell lymphoma and unexplained monoclonal gammopathy. In addition, chronic hepatitis C has been associated with extrahepatic complications unrelated to immune-complex injury. These include Sjögren's syndrome, lichen planus, porphyria cutanea tarda, type 2 diabetes mellitus, and the metabolic syndrome (including insulin resistance and steatohepatitis).

Laboratory features of chronic hepatitis C are similar to those in patients with chronic hepatitis B, but aminotransferase levels tend to fluctuate more (the characteristic episodic pattern of aminotransferase activity) and to be lower, especially in patients with long-standing disease. An interesting and occasionally confusing finding in patients with chronic hepatitis C is the presence of autoantibodies. Rarely, patients with autoimmune hepatitis (see later) and hyperglobulinemia have false-positive immunoassays for anti-HCV. On the other hand, some patients with serologically confirmable chronic hepatitis C have circulating anti-LKM. These antibodies are anti-LKM1, as seen in patients with autoimmune hepatitis type 2 (see

later), and are directed against a 33-amino acid sequence of cytochrome P450 IID6. The occurrence of anti-LKM1 in some patients with chronic hepatitis C may result from the partial sequence homology between the epitope recognized by anti-LKM1 and two segments of the HCV polyprotein. In addition, the presence of this autoantibody in some patients with chronic hepatitis C suggests that autoimmunity may be playing a role in the pathogenesis of chronic hepatitis C.

Histopathologic features of chronic hepatitis C, especially those that distinguish hepatitis C from hepatitis B, are described in Chap. 95.

TREATMENT Chronic Hepatitis C

Therapy for chronic hepatitis C has evolved substantially in the two decades since IFN-α was introduced for this indication. When first approved, IFN-α was administered via subcutaneous injection three times a week for 6 months but achieved a sustained virologic response, SVR (Fig. 96-2) (a reduction of HCV RNA to undetectable levels by PCR when measured ≥6 months after completion of therapy) below 10%. Doubling the duration of therapy—but not increasing the dose or changing IFN preparations—increased the SVR rate to ~20%, and addition to the regimen of daily ribavirin, an oral guanosine nucleoside, increased the SVR rate to 40%. When used alone, ribavirin is ineffective and does not reduce HCV RNA levels, but ribavirin enhances the efficacy of IFN by reducing the likelihood of virologic relapse after the achievement of an end-treatment response (ETR) (Fig. 96-2) (response measured during, and maintained to the end of, treatment). Proposed mechanisms to explain the role of ribavirin include subtle direct reduction of HCV replication, inhibition of host inosine monophosphate dehydrogenase activity (and associated depletion of guanosine pools), immune modulation, induction of virologic mutational catastrophe, and enhancement of interferon-stimulated gene expression. Interferon therapy results in activation of the JAK-STAT signal transduction pathway, which culminates in the intracellular elaboration of genes and their protein products that have antiviral properties. Hepatitis C proteins inhibit JAK-STAT signaling at several steps along the pathway, and exogenous interferon restores expression of interferon-stimulated genes and their antiviral effects.

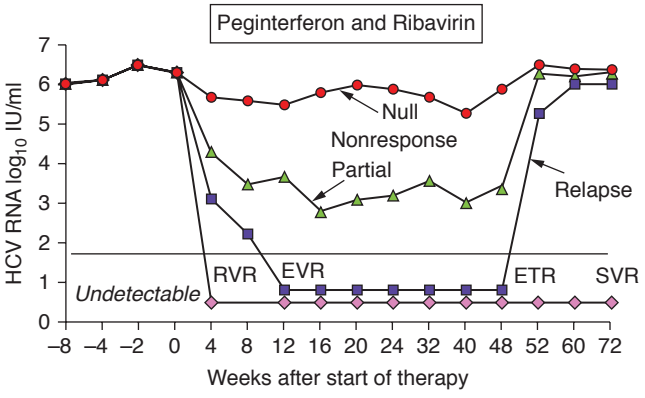


FIGURE 96-2

Virologic responses during a 48-week course of antiviral therapy in patients with hepatitis C, genotype 1 or 4 (for genotypes 2 or 3, the course would be 24 weeks). Nonresponders can be classified as null responders (HCV RNA reduction of <2 $\log_{10}$ IU/mL) or partial responders (HCV RNA reduction, ≥2 $\log_{10}$ IU/mL but not suppressed to undetectable) by week 24 of therapy. In responders, HCV RNA can become undetectable, as shown with sensitive amplification assays, within 4 weeks (RVR, rapid virologic response); can be reduced by ≥2 $\log_{10}$ IU/mL within 12 weeks (early virologic response, EVR; if HCV RNA is undetectable at 12 weeks, the designation is "complete" EVR); or at the end of therapy (48 weeks) (ETR, end-treatment response). In responders, if HCV RNA remains undetectable for 24 weeks after ETR (week 72), the patient has a sustained virologic response (SVR), but if HCV RNA becomes detectable again, the patient is considered to have relapsed. (*Reproduced with permission, courtesy of Marc G. Ghany, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health and the American Association for the Study of Liver Diseases, Hepatology 49:1335, 2009.*)

The current standard of care is the combination of longacting pegylated IFN (PEG IFN) and ribavirin, which has increased responsiveness (frequency of SVR) to as high as 55% overall, >40% in genotypes 1 and 4 and to >80% in genotypes 2 and 3. Still, many important lessons about antiviral therapy for chronic hepatitis C were learned from the experience with IFN monotherapy and combination IFN-ribavirin therapy. Even in the absence of biochemical and virologic responses, histologic improvement occurs in approximately three-fourths of all treated patients. In chronic hepatitis C, unlike the case in hepatitis B, responses to therapy are not accompanied by transient, acute hepatitis–like aminotransferase elevations. Instead, ALT levels fall precipitously during therapy. Up to 90% of virologic responses are achieved within the first 12 weeks of therapy; responses thereafter are rare. Most relapses occur within the first 12 weeks after treatment. Sustained virologic responses are very durable; normal ALT, improved histology, and absence of HCV RNA in serum and liver have been documented a decade after successful therapy, and "relapses" 2 years after sustained responses are almost unheard of. Thus, an SVR to antiviral therapy of chronic hepatitis C is tantamount to a cure.

Patient variables that tend to correlate with sustained virologic responsiveness to IFN-based therapy include favorable genotype (genotypes 2 and 3 as opposed to genotypes 1 and 4), low baseline HCV RNA level (<2 million copies/mL, which is equivalent to ~800,000 IU/mL, the current convention of quantitation), histologically mild hepatitis and minimal fibrosis, age <40, absence of obesity as well as insulin resistance and type 2 diabetes mellitus, and female gender. Patients with cirrhosis can respond, but they are less likely to do so. Studies of combination IFN-ribavirin therapy have shown that in patients with genotype 1, therapy should last a full 48 weeks,

while in those with genotypes 2 and 3, a 24-week course of therapy suffices (although more recent observations allow refined tailoring of treatment duration based on rapidity of response, see later). The response rate in African Americans is disappointingly low for reasons that are not fully understood. Potentially contributing to, but not explaining entirely, low responsiveness in African Americans are a higher proportion with genotype 1, slower early viral kinetics during therapy, impaired HCV-specific immunity, and recently recognized host genetic differences in IL28B alleles, described later. The response rate in Latino patients is also low, despite the fact that the frequency of the favorable IL28B C allele is as common in Hispanic patients as in whites. Moreover, the likelihood of a sustained response is best if adherence to the treatment regimen is high (i.e., if patients receive ≥80% of the IFN and ribavirin doses and if they continue treatment for ≥80% of the anticipated duration of therapy). Other variables reported to correlate with increased responsiveness include brief duration of infection, low HCV quasispecies diversity, immunocompetence, absence of hepatic steatosis and insulin resistance, and low liver iron levels. High levels of HCV RNA, more histologically advanced liver disease, and high quasispecies diversity all go hand in hand with advanced duration of infection, which may be the single most important clinical variable determining IFN responsiveness. The ironic fact, then, is that patients whose disease is least likely to progress are the ones *most* likely to respond to interferon and vice versa.

Genetic changes in the virus may explain differences in treatment responsiveness in some patients (e.g., among patients with genotype 1b, responsiveness to IFN is enhanced in those with amino-acid-substitution mutations in the nonstructural protein 5A gene). As described in the discussion of spontaneous recovery from acute hepatitis C, interferon gene variants discovered recently in gene-wide association studies have been shown to have a substantial impact on responsiveness of patients with genotype 1 to antiviral therapy. In studies of patients treated with PEG IFN and ribavirin, variants of the IL28B SNP that code for IFN-λ3 (a type-III IFN, the receptors for which are more discretely distributed than IFN α receptors and more concentrated in hepatocytes) correlate significantly with responsiveness. Patients homozygous for the C allele at this locus have the highest frequency of achieving an SVR (~80%), those homozygous for the T allele at this locus are least likely to achieve an SVR (~25%), and those heterozygous at this locus (C/T) have an intermediate level of responsiveness (SVRs in ~35%). The fact that C/C is common in whites of European ancestry and even more so in Japanese persons but rare in African Americans helps explain the differences in observed responsiveness among these population groups.

Side effects of IFN therapy are described earlier in the section on treatment of chronic hepatitis B. The most pronounced side effect of ribavirin therapy is hemolysis; a reduction in hemoglobin of up to 2–3 g or in hematocrit of 5–10% can be anticipated. A small, unpredictable proportion of patients experience profound, brisk hemolysis, resulting in symptomatic anemia; therefore, close monitoring of blood counts is crucial, and ribavirin should be avoided in patients with anemia or hemoglobinopathies and in patients with coronary artery disease or cerebrovascular disease, in whom anemia can precipitate an ischemic event. When symptomatic anemia occurs, ribavirin dose reductions or addition of erythropoietin to boost red blood cell levels may be required; erythropoietin has been shown to improve patients' quality of life but not the likelihood of achieving an SVR. If ribavirin is stopped during therapy, SVR rates fall, but responsiveness can be maintained as long as the ribavirin is not stopped and the total ribavirin dose exceed 60% of the planned dose. In addition, ribavirin, which is renally excreted, should not be used in patients with renal insufficiency; the drug is teratogenic, precluding its use during pregnancy and mandating the scrupulous use of efficient contraception during therapy (interferons, too, because of their antiproliferative properties, are contraindicated during pregnancy).

Ribavirin can also cause nasal and chest congestion, pruritus, and precipitation of gout. Combination IFN-ribavirin therapy is more difficult to tolerate than IFN monotherapy. In one large clinical trial of combination therapy versus monotherapy, among those in the 1-year treatment group, 21% of the combination group (but only 14% of the monotherapy group) had to discontinue treatment, while 26% of the combination group (but only 9% of the monotherapy group) required dose reductions.

Studies of viral kinetics have shown that despite a virion half-life in serum of only 2–3 h, the level of HCV is maintained by a high replication rate of 10^{12} hepatitis C virions per day. IFN-α blocks virion production or release with an efficacy that increases with increasing drug doses; moreover, the calculated death rate for infected cells during IFN therapy is inversely related to viral load; patients with the most rapid death rate of infected hepatocytes are more likely to achieve undetectable HCV RNA at 3 months; in practice, failure to achieve an early virologic response (EVR), a ≥2-$\log_{10}$ reduction in HCV RNA by week 12, predicts failure to experience a subsequent SVR. Similarly, patients in whom HCV RNA becomes undetectable within 4 weeks (i.e., who achieve a rapid virologic response [RVR]), have a very high likelihood of achieving a sustained virologic response (Fig. 96-2). Therefore, to achieve rapid viral clearance from serum and the liver, *high-dose induction therapy* has been advocated. In practice, however, high-dose induction with IFN-based therapy has not yielded higher sustained response rates.

TREATMENT OF CHOICE For the treatment of chronic hepatitis C, standard IFNs have now been supplanted by PEG IFNs. These have elimination times up to sevenfold longer than standard IFNs (i.e., a substantially longer half-life), and achieve prolonged concentrations,

permitting administration once (rather than three times) a week. Instead of the frequent drug peaks (linked to side effects) and troughs (when drug is absent) associated with frequent administration of short-acting IFNs, administration of PEG IFNs results in drug concentrations that are more stable and sustained over time. Once-a-week PEG IFN monotherapy is twice as effective as monotherapy with its standard IFN counterpart, approaches the efficacy of combination standard IFN plus ribavirin, and is as well tolerated as standard IFNs, without more difficult-to-manage thrombocytopenia and leukopenia than standard IFNs. The current standard of care, however, is a combination of PEG IFN plus ribavirin.

Two PEG IFNs are available: PEG IFN α-2b and α-2a. PEG IFN α-2b consists of a 12-kD, linear PEG molecule bound to IFN α-2b, while PEG IFN α-2a consists of a larger, 40-kD, branched PEG molecule bound to IFN α-2a; because of its larger size and smaller volume of extravascular distribution, PEG IFN α-2a can be given at a uniform dose independent of weight, while the dose of the smaller PEG IFN α-2b, which has a much wider volume distribution, must be weight-based (Table 96-6). In the registration trial for PEG IFN α-2b plus ribavirin, the best regimen was 48 weeks of 1.5 μg/kg of PEG IFN once a week plus 800 mg of ribavirin daily. A post hoc analysis suggested that weight-based dosing of ribavirin would have been more effective than the fixed 800-mg dose used in the study. In the first registration trial for PEG IFN α-2a plus ribavirin, the best regimen was 48 weeks of 180 μg of PEG IFN plus 1000 mg (for patients <75 kg) to 1200 mg (for patients ≥75 kg) of ribavirin. Sustained virologic responses of 54 and 56% were reported in these two studies, respectively. A subsequent study of PEG IFN α-2a plus ribavirin showed that, for patients with genotypes 2 and 3, a duration of 24 weeks and a ribavirin dose of 800 mg were sufficient. Among the three studies, for patients in the optimal treatment arm, SVR rates for patients with genotype 1 were 42–51% and for patients with genotypes 2 and 3 rates were 76–82%. Between genotypes 2 and 3, genotype 3 is somewhat more refractory, and some authorities would extend therapy for a full 48 weeks in patients with genotype 3, especially if they have advanced hepatic fibrosis or cirrhosis and/or high-level HCV RNA.

In the initial registration trials for combination PEG IFN plus ribavirin, both combination PEG IFN regimens were compared to standard IFN α-2b plus ribavirin. Side effects of the combination PEG IFN α-2b regimen were comparable to those for the combination standard IFN regimen; however, when the combination PEG IFN α-2a regimen was compared to the combination standard IFN α-2b regimen, flu-like symptoms and depression were less common in the combination PEG IFN group. Although ascertainment of side effects differed between studies of the two drugs, when each was tested against standard IFN α-2b plus ribavirin, combination PEG IFN α-2a plus ribavirin appeared to be better tolerated. In a recent head-to-head trial of the two PEG IFNs (the "IDEAL" trial), the two PEG IFNs were found to be comparable in efficacy (achievement of SVR)

TABLE 96-6

PEGYLATED INTERFERON α-2A AND α-2B FOR CHRONIC HEPATITIS C

	PEG IFN α-2B	PEG IFN α-2A
PEG size	12 kD linear	40 kD branched
Elimination half-life	54 hours	65 hours
Clearance	725 mL/hour	60 mL/hour
Dose	1.5 μg/kg (weight-based)	180 μg
Storage	Room temperature	Refrigerated
Ribavirin dose		
Genotype 1	800–1400 mg[a]	1000–1200 mg[b]
Genotype 2/3	800 mg	800 mg
Duration of therapy		
Genotype 1	48 weeks	48 weeks
Genotype 2/3	48 weeks[c]	24 weeks
Efficacy of combination Rx[d]	54%	56%
Genotype 1	40–42%	41–51%
Genotype 2/3	82%	76–78%

[a]In the registration trial for PEG IFN α-2b plus ribavirin, the optimal regimen was 1.5 μg of PEG IFN plus 800 mg of ribavirin; however, a post hoc analysis of this study suggested that higher ribavirin doses are better. In subsequent trials of PEG IFN α-2b with ribavirin in patients with genotype 1, the following daily ribavirin doses have been validated: 800 mg for patients weighing <65 kg, 1000 mg for patients weighing >65-85 kg, 1200 for patients weighing >85–105 kg, and 1400 mg for patients weighing >105 kg.

[b]1000 mg for patients weighing <75 kg; 1200 mg for patients weighing ≥75 kg.

[c]In the registration trial for PEG IFN α-2b plus ribavirin, all patients were treated for 48 weeks; however, data from other trials of standard interferons and the other PEG IFN demonstrated that 24 weeks suffices for patients with genotypes 2 and 3. For patients with genotype 3 who have advanced fibrosis/cirrhosis and/or high-level HCV RNA, a full 48 weeks is preferable.

[d]Attempts to compare the two PEG IFN preparations based on the results of registration clinical trials are confounded by differences between trials of the two agents in methodological details (different ribavirin doses, different methods for recording depression, and other side effects) and study-population composition (different proportion with bridging fibrosis/cirrhosis, proportion from the United States versus international, mean weight, proportion with genotype 1, and proportion with high-level HCV RNA). In the head-to-head comparison of the two PEG IFN preparations in the "IDEAL" trial reported in 2009, the two drugs were comparable in tolerability and efficacy. PEG IFN α-2b was administered at a weekly weight-based dose of 1.0 μg/kg or 1.5 μg/kg, and PEG IFN α-2a was administered at a weekly fixed dose of 180 μg. For PEG IFN α-2b, daily ribavirin weight-based doses ranged between 800–1400 mg based on weight criteria (see footnote a, above), while for PEG IFN α-2a, daily ribavirin weight-based doses ranged between 1000–1200 mg (footnote b, above). For the two PEG IFN α-2b study arms, ribavirin dose reductions for ribavirin-associated adverse effects were done in 200–400-mg decrements; for PEG IFN α-2a, the ribavirin dose was reduced to 600 mg for intolerability. Sustained virologic responses occurred in 38.0% of the low-dose PEG IFN α-2b group; 39.8% of the standard, full-dose PEG IFN α-2b group; and 40.9% of the PEG IFN α-2a group.

Abbreviations: PEG, polyethylene glycol; PEG IFN, pegylated interferon; HCV RNA, hepatitis C virus RNA.

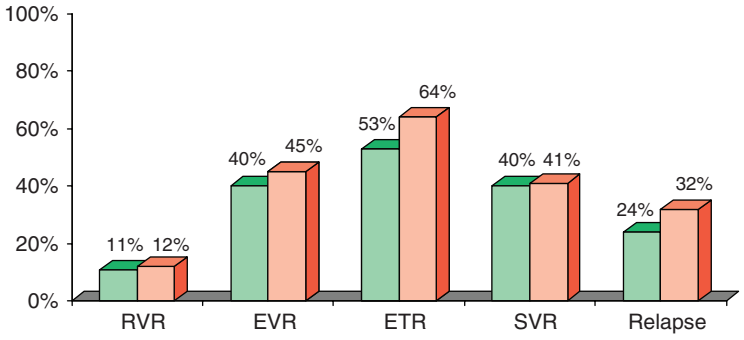


FIGURE 96-3

Head-to-head comparison of standard-dose PEG IFN α-2b 1.5 μg/kg weekly and PEG IFN α-2a 180 μg weekly administered with daily ribavirin in the "IDEAL" trial. Percent achieving treatment milestones for PEG IFN α-2b (green boxes) and PEG IFN α-2a (orange boxes). RVR, rapid virologic response, HCV RNA undetectable at week 4; EVR, early virologic response, HCV RNA undetectable at week 12; ETR, end-treatment response, HCV RNA undetectable at end of treatment week 48; SVR, sustained virologic response, HCV RNA remaining undetectable 24 weeks after completing 48 weeks of therapy. Relapse, reappearance of detectable HCV RNA by week 72 in patients with an end-treatment response at week 48. PEG IFN α-2a suppressed HCV RNA in a higher proportion of patients at weeks 12 and 48 but, because of a higher relapse rate at week 72, resulted in the same SVR rate as PEG IFN α-2b.

(Fig. 96-3) and tolerability, although headache, nausea, fever, myalgia, depression, and drug discontinuation for any reason were less frequent in patients treated with PEG IFN α-2a than standard-dose PEG IFN α-2b. In contrast, neutropenia and rash were more frequent in patients treated with PEG IFN α-2a than standard-dose PEG IFN α-2b. In two subsequent head-to-head trials and a systematic review of randomized trials, PEG IFN α–2a was more effective than α–2b (SVR in genotype 1-4: 48–55% versus 32–40%, respectively). In trials of PEG IFN α-2b among patients with HCV genotype 1, a broader range of weight-based daily ribavirin doses has been validated: 800 mg for weight <65 kg, 1000 mg for weight 65–85 kg, 1200 mg for weight >85–105 kg, and 1400 mg for weight >105 kg. Recommended doses for the two PEG IFNs plus ribavirin and other comparisons between the two therapies are shown in Table 96-6.

Unless ribavirin is contraindicated (see earlier), combination PEG IFN plus ribavirin is the recommended course of therapy—24 weeks for genotypes 2 and 3 and 48 weeks for genotype 1. Measurement of quantitative HCV RNA levels at 12 weeks is helpful in guiding therapy; if a 2-$\log_{10}$ drop in HCV RNA has not been achieved by this time, chances for an SVR are negligible. If the 12-week HCV RNA has fallen by two logs 10 (EVR), the chances for an SVR at the end of therapy are approximately two-thirds; if the 12-week HCV RNA is undetectable ("complete" EVR), the chances for a sustained virologic response exceed 80% (Fig. 96-2). Because absence of an EVR is such a strong predictor of the absence of an ultimate sustained virologic response, failure to achieve a 12-week 2-$\log_{10}$ drop in HCV RNA (EVR) may be used as a signal to discontinue therapy.

Studies have suggested that the frequency of an SVR to PEG IFN/ribavirin therapy can be increased in patients with baseline variables weighing against a response (e.g., HCV RNA >8×10^5 IU/ml, weight >85 kg) by raising the dose of PEG IFN (e.g., to as high as 270 μg of PEG IFN α-2a) and/or the dose of ribavirin to as high as 1600 mg daily (if tolerated or supplemented by erythropoietin) or by tailoring treatment based on viral response to prolong the duration of viral clearance before discontinuing therapy—that is, extending therapy from 48 to 72 weeks for patients with genotype 1 and a slow virologic response (i.e., those whose HCV RNA has not fallen rapidly to undetectable levels within 4 weeks; absence of "rapid virologic response"). Tailoring therapy based on the kinetics of HCV RNA reduction has also been applied to abbreviating the duration of therapy in patients with genotype 1 (and 4). The results of several clinical trials suggest that, in patients with genotype 1 (and 4) who have a 4-week RVR (which occurs in ≤20%), especially in the subset with a baseline low level of HCV RNA, 24 weeks of therapy with PEG IFN and weight-based ribavirin suffices, yielding SVR rates of ~90% and comparable to those achieved in this cohort with 48 weeks of therapy. Although initial reports suggested that, for patients with genotype 2 and (somewhat less so) genotype 3, in rapid virologic responders with undetectable HCV RNA at week 4, the total duration of therapy required to achieve an SVR could be as short as 12–16 weeks, a very sizable, definitive subsequent trial showed that relapse is increased if treatment duration is curtailed and that a full 24 weeks is superior for these genotypes (except for the minority with very low baseline levels of HCV RNA).

Persons with chronic HCV infection have been shown to suffer increased liver-related mortality. On the other hand, successful antiviral therapy for chronic hepatitis C resulting in an SVR has been shown to improve survival, to lower the risk of liver failure and liver-related death, to slow the progression of chronic hepatitis C, and to reverse fibrosis and even cirrhosis. Although successful treatment reduces mortality in cirrhotic patients (and those with advanced fibrosis) and reduces the likelihood of hepatocellular carcinoma, the risk of decompensation,

death, and liver cancer persists, albeit at a much reduced level, necessitating continued clinical monitoring and cancer surveillance after SVR in cirrhotics. On the other hand, in the absence of an SVR, IFN-based therapy does not reduce the risk of hepatocellular carcinoma. Similarly, for nonresponders to PEG IFN/ribavirin therapy, three trials of long-term maintenance therapy with PEG IFN have shown no benefit in reducing the risk of histologic progression or clinical decompensation, including the development of hepatocellular carcinoma. For PEG IFN/ribavirin nonresponders who have had a full, adequate course of therapy, the benefit of re-treatment—with higher doses or a longer course of the original PEG IFN regimen or the alternative PEG IFN regimen or with a different type of IFN preparation (e.g., consensus IFN)—is marginal at best.

INDICATIONS FOR ANTIVIRAL THERAPY

Patients with chronic hepatitis C who have detectable HCV RNA in serum, whether or not aminotransferase levels are increased, and chronic hepatitis of at least moderate grade and stage (portal or bridging fibrosis) are candidates for antiviral therapy with PEG IFN plus ribavirin. Most authorities recommend 800 mg of ribavirin for patients with genotypes 2 and 3 for both types of PEG IFN and weight-based 1000–1200 mg (when used with PEG IFN α-2a) or 800–1400 mg (when used with PEG IFN α-2b) ribavirin for patients with genotype 1 (and 4), unless ribavirin is contraindicated (Table 96-7). Although patients with persistently normal ALT activity tend to progress histologically very slowly or not at all, they respond to antiviral therapy just as well as do patients with elevated ALT levels; therefore, while observation without therapy is an option, such patients are potential candidates for antiviral therapy. As previously noted, therapy with IFN has been shown to improve survival and complication-free survival and to slow progression of fibrosis.

Prior to therapy, HCV genotype should be determined, and the genotype dictates the duration of therapy: 48 weeks for patients with genotype 1, 24 weeks for those with genotypes 2 and 3. For patients with genotype 1 (and 4), especially those with low baseline HCV RNA, 24 weeks of PEG IFN/ribavirin therapy may suffice if HCV RNA becomes undetectable within 4 weeks (RVR); for patients with genotypes 2 and 3, a full, 24-week course is most effective, although the duration may be reduced to 12–16 weeks for patients with genotype 2, a low baseline level of viremia, and an RVR, especially to be considered for patients who tolerate therapy poorly. As noted earlier, the absence of a 2-$\log_{10}$ drop in HCV RNA at week 12 (EVR) weighs heavily against the likelihood of an SVR; therefore, measuring HCV RNA at 12 weeks is recommended routinely (Fig. 96-2), especially for patients with genotype 1, and therapy can be discontinued if an EVR is not achieved. Among patients with an EVR (≥2-$\log_{10}$ HCV RNA reduction) but with HCV RNA still detectable at week 24, an SVR is unlikely, and therapy can be discontinued. Although response rates are lower in patients with certain pretreatment variables, selection for treatment should not be based on symptoms, genotype, HCV RNA level, mode of acquisition of hepatitis C, or advanced hepatic fibrosis. Patients with cirrhosis can respond and should not be excluded as candidates for therapy.

Patients who have relapsed (Fig. 96-2) after a course of IFN monotherapy are candidates for re-treatment with PEG IFN plus ribavirin (i.e., a more effective treatment regimen is required). For nonresponders to a prior course of IFN monotherapy, re-treatment with IFN monotherapy or combination IFN plus ribavirin therapy is unlikely to achieve a sustained virologic response; however, a trial of combination PEG IFN plus ribavirin may be worthwhile. End-treatment virologic responses as high as 40% can occur in this setting, but an SVR is the outcome in <15–20% of patients. Sustained virologic responses to retreatment of nonresponders are more frequent in those who had never received ribavirin in the past, those with genotypes 2 and 3, those with low pretreatment HCV RNA levels, and noncirrhotics, but less frequent in African Americans, those who failed to achieve a substantial reduction in HCV RNA during their previous course of therapy (null responders, Fig. 96-2), and those who required ribavirin-dose reductions. Potential approaches to improving responsiveness to PEG IFN/ribavirin in prior nonresponders include longer duration of treatment; higher doses of either PEG IFN, ribavirin, or both; and switching to a different IFN preparation; however, as noted earlier, none of these approaches achieves more than a marginal benefit.

Early treatment is indicated for persons with acute hepatitis C (Chap. 95). In patients with biochemically and histologically mild chronic hepatitis C, the rate of progression is slow, and monitoring without therapy is an option; however, such patients respond just as well to combination PEG IFN plus ribavirin therapy as those with elevated ALT and more histologically severe hepatitis. Therefore, therapy for these patients should be considered and the decision made based on such factors as patient motivation, genotype, stage of fibrosis, age, and comorbid conditions. A pretreatment liver biopsy to assess histologic grade and stage provides substantial information about progression of hepatitis C in the past, has prognostic value for future progression, and can identify such histologic factors as steatosis and stage of fibrosis, which can influence responsiveness to therapy. As therapy has improved for patients with a broad range of histologic severity, and as noninvasive laboratory markers and imaging correlates of fibrosis have gained popularity, some authorities, especially in Europe, have placed less value on, and do not recommend, pretreatment liver biopsies. On the other hand, serum markers of fibrosis are not considered sufficiently accurate, and histologic findings provide important prognostic information to physician and patient. Therefore, although the contemporary role of a pretreatment liver biopsy commands less of a consensus, a pretreatment liver biopsy still provides useful information and should be considered.

TABLE 96-7

INDICATIONS AND RECOMMENDATIONS FOR ANTIVIRAL THERAPY FOR CHRONIC HEPATITIS C

Standard Indications for Therapy

Detectable HCV RNA (with or without elevated ALT)
Portal/bridging fibrosis or moderate to severe hepatitis on liver biopsy (The necessity of a pretreatment biopsy is being debated.)
These indications apply to adults as well as to children aged 2–17, in whom treatment may be considered at reduced weight-based doses (see product inserts).

Re-treatment Recommended

Relapsers after a previous course of standard interferon monotherapy or combination standard interferon/ribavirin therapy:
A course of PEG IFN plus ribavirin (re-treatment not recommended with PEG IFN/ribavirin if relapse occurred after a full course of PEG IFN/ribavirin).
Nonresponders to a previous course of standard IFN monotherapy or combination standard IFN/ribavirin therapy:
A course of PEG IFN plus ribavirin—more likely to achieve a sustained virologic response in white patients without previous ribavirin therapy, with low baseline HCV RNA levels, with a ≥2-$\log_{10}$ reduction in HCV RNA during previous therapy, with genotypes 2 and 3, and without reduction in ribavirin dose re-treatment not recommended with PEG IFN/ribavirin if nonresponse occurred to a full course of PEG IFN/ribavirin)

Antiviral Therapy Not Recommended Routinely but Management Decisions Made on an Individual Basis

Age >60
Mild hepatitis on liver biopsy
Persons with severe renal insufficiency (glomerular filtration rate <60 mL/min) who do not require hemodialysis (reduced-dose PEG IFN and ribavirin). Antiviral therapy in patients requiring hemodialysis is more complicated, less successful, and associated with more adverse effects; if treatment is pursued, either standard doses of standard interferon 3 times a week or reduced doses of weekly PEG IFN in combination with reduced doses of daily ribavirin should be used.

Long-Term Maintenance Therapy Recommended

Cutaneous vasculitis and glomerulonephritis associated with chronic hepatitis C

Long-Term Maintenance Therapy in Nonresponders Not Recommended

Antiviral Therapy Not Recommended

Decompensated cirrhosis (except, perhaps, in transplantation centers with experience in graded escalation, low-dose treatment to achieve undetectable HCV RNA prior to transplantation; results are mixed)
Pregnancy (teratogenicity of ribavirin)
Contraindications to use of interferon or ribavirin

Standard Therapeutic Regimens

First-line treatment: PEG IFN subcutaneously once a week plus daily ribavirin orally
HCV genotypes 1 and 4—48 weeks of therapy
PEG IFN α-2a 180 μg weekly plus ribavirin 1000 mg/day (weight <75 kg) to 1200 mg/day (weight <75 kg) or
PEG IFN α-2b 1.5 μg/kg weekly plus daily oral ribavirin 800 mg for weight <65 kg, 1000 mg for weight 65–85 kg, 1200 mg for weight >85–105 kg, and 1400 mg for weight >105 kg
HCV genotypes 2 and 3—24 weeks of therapy
PEG IFN α-2a 180 μg weekly plus ribavirin 800 mg/day or
PEG IFN α-2b 1.5 μg/kg weekly plus ribavirin 800 mg/day (For patients with genotype 3 who have advanced fibrosis and/or high-level HCV RNA, a full 48 weeks of therapy may be preferable.)
Alternative regimen: PEG IFN (α-2a 180 μg or α-2b 1.0 μg/kg) subcutaneously once a week (primarily for patients in whom ribavirin is contraindicated or not tolerated) for 24 (genotypes 2 and 3) or 48 (genotypes 1 and 4) weeks.
Early discontinuation: Failure to achieve an EVR (i.e., ≥2 $\log_{10}$ HCV RNA reduction by week 12) or, if EVR is achieved, failure to achieve suppression of HCV RNA to undetectable by week 24

"Tailored" Therapeutic Regimens Based on Rapid-Treatment Milestones

HCV genotypes 1 and 4
For RVR (i.e., undetectable HCV RNA at week 4), especially in patients with low baseline HCV RNA, consider truncating the course of therapy to 24 weeks.
For patients with slow, delayed response (i.e., those who clear detectable HCV RNA between weeks 12 and 24), consider prolonging the course of therapy to 72 weeks.

"Tailored" Therapeutic Regimens Based on Baseline Variables Associated with Reduced Responsiveness

HCV genotypes 1 and 4
For patients with HCV RNA >8×10^5 IU/mL and weighing >85 kg, consider increasing the weekly PEG IFN dose (e.g., for PEG IFN α-2a, up to 270 μg) and the daily ribavirin dose (e.g., up to 1600 mg).
For HCV/HIV-co-infected patients: 48 weeks, regardless of genotype, of weekly PEG IFN α-2a (180 μg) or PEG IFN α-2b (1.5 μg/kg) plus a daily ribavirin dose of at least 600–800 mg, up to full weight-based dosing, at doses comparable to those for HCV-monoinfected patients, if tolerated

(*continued*)

TABLE 96-7

INDICATIONS AND RECOMMENDATIONS FOR ANTIVIRAL THERAPY FOR CHRONIC HEPATITIS C (*CONTINUED*)

Features Associated with Reduced Responsiveness
Single-nucleotide polymorphism (SNP) T allele (as opposed to C allele) at IL28B locus
Genotype 1
High-level HCV RNA (>2×10^6 copies/mL or >8×10^5 IU/mL)
Advanced fibrosis (bridging fibrosis, cirrhosis)
Long-duration disease
Age >40
High HCV quasispecies diversity
Immunosuppression
African-American ethnicity
Latino ethnicity
Obesity
Hepatic steatosis
Insulin resistance, type 2 diabetes mellitus
Reduced adherence (lower drug doses and reduced duration of therapy)

Abbreviations: ALT, alanine aminotransferase; HCV, hepatitis C virus; IFN, interferon; PEG IFN, pegylated interferon; IU, international units (1 IU/mL is equivalent to ~2.5 copies/mL).

Patients with compensated cirrhosis can respond to therapy, although their likelihood of a sustained response is lower than in noncirrhotics; moreover, survival has been shown to improve after successful antiviral therapy in cirrhotics. Similarly, although several retrospective studies have suggested that antiviral therapy in cirrhotics with chronic hepatitis C, independent of treatment outcome per se, reduces the frequency of HCC, less advanced disease in the treated cirrhotics, not treatment itself (i.e., lead-time bias), may have accounted for the reduced frequency of HCC observed in the treated cohorts in these reports; prospective studies to address this question have failed to demonstrate benefit, unless a sustained virologic response is achieved. Patients with decompensated cirrhosis are not candidates for IFN-based antiviral therapy, but should be referred for liver transplantation. Some liver-transplantation centers have evaluated progressively escalated, low-dose antiviral therapy in an attempt to eradicate hepatitis C viremia prior to transplantation; however, such therapy has been shown to reduce but not to prevent the risk of HCV reinfection after transplantation. After liver transplantation for end-stage liver disease caused by hepatitis C, recurrent hepatitis C is the rule, and the pace of disease progression is more accelerated than in immunocompetent patients. Current therapy with PEG IFN and ribavirin after liver transplantation is unsatisfactory in most patients, but attempts to minimize immunosuppression are beneficial. The cutaneous and renal vasculitis of HCV-associated essential mixed cryoglobulinemia (Chap. 95) may respond to antiviral therapy, but sustained responses are rare after discontinuation of therapy; therefore, prolonged, perhaps indefinite, therapy is recommended in this group. Anecdotal reports suggest that antiviral therapy may be effective in porphyria cutanea tarda or lichen planus associated with hepatitis C.

In patients with HCV/HIV co-infection, hepatitis C is more progressive and severe than in HCV-monoinfected patients. Although patients with HCV/HIV co-infection respond to antiviral therapy for hepatitis C, they do not respond as well as patients with HCV infection alone. Four large national and international trials of antiviral therapy among patients with HCV/HIV co-infection have shown that PEG IFN (both α-2a and α-2b) plus ribavirin (daily doses ranging from flat-dosed 600–800 mg to weight-based 1000/1200 mg) is superior to standard IFN regimens; however, SVR rates were lower than in HCV-monoinfected patients, ranging from 14 to 38% for patients with genotypes 1 and 4 and from 44 to 73% for patients with genotypes 2 and 3. In the three largest trials, all patients, including those with genotypes 2 and 3, were treated for a full 48 weeks. In addition, tolerability of therapy was lower than in HCV-monoinfected patients; therapy was discontinued because of side effects in 12–39% of patients in these clinical trials. Based on these trials, weekly PEG IFN plus daily ribavirin at a daily dose of at least 600–800 mg, up to full weight-based doses, at doses recommended for HCV-monoinfected patients, if tolerated, is recommended for a full 48 weeks, regardless of genotype. An alternative recommendation for ribavirin doses was issued by a European Consensus Conference and consisted of standard, weight-based 1000–1200 mg for genotypes 1 and 4, but 800 mg for genotypes 2 and 3. A head-to-head trial of combination PEG IFN/ribavirin therapy in HCV/HIV co-infection demonstrated statistically indistinguishable efficacy of the two types of PEG IFN, despite a small advantage for PEG IFN α-2a: for PEG IFN α-2b and α-2a, SVRs occurred in 28% versus 32%, respectively, of patients with genotypes 1 and 4 and in 62% versus 71%, respectively, of patients with genotypes 2 and 3.

In HCV/HIV-infected patients, ribavirin can potentiate the toxicity of didanosine (e.g., lactic acidosis) and the lipoatrophy of stavudine, and zidovudine can exacerbate ribavirin-associated hemolytic anemia; therefore, these drug combinations should be avoided.

Patients with a history of injection-drug use and alcoholism can be treated successfully for chronic hepatitis C, preferably in conjunction with drug- and alcohol-treatment programs. Because ribavirin is excreted renally, patients with end-stage renal disease, including those undergoing dialysis (which does not clear ribavirin), are not ideal candidates for ribavirin therapy. Rare reports suggest that reduced-dose ribavirin can be used, but the frequency of anemia is very high and data on efficacy are limited. If patients with renal failure (glomerular filtration rate <60 ml/min) are treated, the PEG IFN α-2a dose should be reduced from 180 to 135 μg weekly and the PEG IFN α-2b dose reduced from 1.5 to 1 μg/kg weekly; similarly, the daily ribavirin dose in this population should be reduced to 200–800 mg (but not used or used cautiously at very low doses) if hemodialysis is required. Neither the optimal regimen nor the efficacy of therapy is well established in this population.

NOVEL ANTIVIRALS To date, attempts to develop better-tolerated ribavirin successors or improved types of IFN α or longer acting IFNs than PEG IFN have not been successful. The demonstration that responsiveness to antiviral therapy is influenced by genetic variation in IL28B, which codes for IFN-λ (as noted earlier), raises the possibility that IFN-λ might be an effective or even more effective IFN for treating hepatitis C; early trials are in progress. Among the most exciting new approaches to antiviral therapy are orally administered direct antivirals that target HCV polymerase or protease. Two protease inhibitors in late stages of development were expected to be approved in 2011. The NS3-4A serine protease inhibitors telaprevir and boceprevir suppress HCV RNA profoundly and, when used together with PEG IFN and ribavirin in patients with genotype-1 HCV infection, can increase RVR rates to as high as 80% (telaprevir) and SVR rates from those achieved with current standard-of-care therapy by 20–30% to ~65–75%, in most patients with only half the duration of current therapy. These triple-drug combinations appear to yield even higher rates of SVR in >50% of prior relapsers (>70–90%) but also to achieve SVR in prior nonresponders, even in null responders to PEG IFN/ribavirin therapy (~30%). Although these new drugs add elements of additional toxicity (severe rash in ~5% of telaprevir-treated patients and anemia in half of boceprevir-treated patients), they represent an opportunity for curing a substantially larger proportion of patients with shorter treatment courses. Because resistance to these oral agents used alone has been both anticipated and observed, polymerase and protease inhibitors are being evaluated in combinations with PEG IFN and ribavirin to preempt the emergence of resistance. Potentially, in the future, combinations of direct antiviral agents will be used in drug cocktails that may replace IFN-based regimens entirely.

AUTOIMMUNE HEPATITIS

DEFINITION

Autoimmune hepatitis is a chronic disorder characterized by continuing hepatocellular necrosis and inflammation, usually with fibrosis, which can progress to cirrhosis and liver failure. When fulfilling criteria of severity, this type of chronic hepatitis, when untreated, may have a 6-month mortality of as high as 40%. Based on contemporary estimates of the natural history of treated autoimmune hepatitis, the 10-year survival is 80–90%. The prominence of extrahepatic features of autoimmunity as well as seroimmunologic abnormalities in this disorder supports an autoimmune process in its pathogenesis; this concept is reflected in the labels *lupoid*, *plasma cell*, or *autoimmune hepatitis*. Autoantibodies and other typical features of autoimmunity, however, do not occur in all cases; among the broader categories of "idiopathic" or cryptogenic chronic hepatitis, many, perhaps the majority, are probably autoimmune in origin. Cases in which hepatotropic viruses, metabolic/genetic derangements, and hepatotoxic drugs have been excluded represent a spectrum of heterogeneous liver disorders of unknown cause, a proportion of which are most likely autoimmune hepatitis.

IMMUNOPATHOGENESIS

The weight of evidence suggests that the progressive liver injury in patients with autoimmune hepatitis is the result of a cell-mediated immunologic attack directed against liver cells. In all likelihood, predisposition to autoimmunity is inherited, while the liver specificity of this injury is triggered by environmental (e.g., chemical or viral) factors. For example, patients have been described in whom apparently self-limited cases of acute hepatitis A, B, or C led to autoimmune hepatitis, presumably because of genetic susceptibility or predisposition. Evidence to support an autoimmune pathogenesis in this type of hepatitis includes the following: (1) In the liver, the histopathologic lesions are composed predominantly of cytotoxic T cells and plasma cells; (2) circulating autoantibodies (nuclear, smooth muscle, thyroid, etc.; see later in the chapter), rheumatoid factor, and hyperglobulinemia are common; (3) other autoimmune disorders—such as thyroiditis, rheumatoid arthritis, autoimmune hemolytic anemia, ulcerative colitis, membranoproliferative glomerulonephritis, juvenile diabetes mellitus, celiac disease, and Sjögren's syndrome—occur with increased frequency in patients and in their relatives who have autoimmune hepatitis; (4) histocompatibility haplotypes associated with autoimmune diseases, such as HLA-B1, -B8, -DR3, and -DR4 as well as extended haplotype DRB1 alleles, are common in patients with autoimmune hepatitis; and (5) this type of chronic hepatitis is responsive to glucocorticoid/immunosuppressive therapy, effective in a variety of autoimmune disorders.

Cellular immune mechanisms appear to be important in the pathogenesis of autoimmune hepatitis. In vitro studies have suggested that in patients with this disorder, lymphocytes are capable of becoming sensitized

to hepatocyte membrane proteins and of destroying liver cells. Abnormalities of immunoregulatory control over cytotoxic lymphocytes (impaired regulatory CD4+CD25+ T cell influences) may play a role as well. Studies of genetic predisposition to autoimmune hepatitis demonstrate that certain haplotypes are associated with the disorder, as enumerated earlier. The precise triggering factors, genetic influences, and cytotoxic and immunoregulatory mechanisms involved in this type of liver injury remain incompletely defined.

Intriguing clues into the pathogenesis of autoimmune hepatitis come from the observation that circulating autoantibodies are prevalent in patients with this disorder. Among the autoantibodies described in these patients are antibodies to nuclei (so-called antinuclear antibodies [ANAs], primarily in a homogeneous pattern) and smooth muscle (so-called anti-smooth-muscle antibodies, directed at actin), anti-LKM (see later in the chapter), antibodies to "soluble liver antigen/liver pancreas antigen" (directed against a uracil-guanine-adenine transfer RNA suppressor protein), as well as antibodies to the liver-specific asialoglycoprotein receptor (or "hepatic lectin") and other hepatocyte membrane proteins. Although some of these provide helpful diagnostic markers, their involvement in the pathogenesis of autoimmune hepatitis has not been established.

Humoral immune mechanisms have been shown to play a role in the extrahepatic manifestations of autoimmune and idiopathic hepatitis. Arthralgias, arthritis, cutaneous vasculitis, and glomerulonephritis occurring in patients with autoimmune hepatitis appear to be mediated by the deposition of circulating immune complexes in affected tissue vessels, followed by complement activation, inflammation, and tissue injury. While specific viral antigen-antibody complexes can be identified in acute and chronic viral hepatitis, the nature of the immune complexes in autoimmune hepatitis has not been defined.

Many of the *clinical features* of autoimmune hepatitis are similar to those described for chronic viral hepatitis. The onset of disease may be insidious or abrupt; the disease may present initially like, and be confused with, acute viral hepatitis; a history of recurrent bouts of what had been labeled *acute hepatitis* is not uncommon. A subset of patients with autoimmune hepatitis has distinct features. Such patients are predominantly young to middle-aged women with marked hyperglobulinemia and high-titer circulating ANAs. This is the group with positive lupus erythematosus (LE) preparations (initially labeled "lupoid" hepatitis) in whom other autoimmune features are common. Fatigue, malaise, anorexia, amenorrhea, acne, arthralgias, and jaundice are common. Occasionally arthritis, maculopapular eruptions (including cutaneous vasculitis), erythema nodosum, colitis, pleurisy, pericarditis, anemia, azotemia, and sicca syndrome (keratoconjunctivitis, xerostomia) occur. In some patients, complications of cirrhosis, such as ascites and edema (associated with hypoalbuminemia), encephalopathy, hypersplenism, coagulopathy, or variceal bleeding may bring the patient to initial medical attention.

The course of autoimmune hepatitis may be variable. In those with mild disease or limited histologic lesions (e.g., piecemeal necrosis without bridging), progression to cirrhosis is limited. In those with severe symptomatic autoimmune hepatitis (aminotransferase levels >10 times normal, marked hyperglobulinemia, "aggressive" histologic lesions—bridging necrosis or multilobular collapse, cirrhosis), the 6-month mortality without therapy may be as high as 40%. Such severe disease accounts for only 20% of cases; the natural history of milder disease is variable, often accentuated by spontaneous remissions and exacerbations. Especially poor prognostic signs include the presence histologically of multilobular collapse at the time of initial presentation and failure of the bilirubin to improve after 2 weeks of therapy. Death may result from hepatic failure, hepatic coma, other complications of cirrhosis (e.g., variceal hemorrhage), and intercurrent infection. In patients with established cirrhosis, HCC may be a late complication but occurs less frequently than in cirrhosis associated with viral hepatitis.

Laboratory features of autoimmune hepatitis are similar to those seen in chronic viral hepatitis. Liver biochemical tests are invariably abnormal but may not correlate with the clinical severity or histopathologic features in individual cases. Many patients with autoimmune hepatitis have normal serum bilirubin, alkaline phosphatase, and globulin levels with only minimal aminotransferase elevations. Serum AST and ALT levels are increased and fluctuate in the range of 100–1000 units. In severe cases, the serum bilirubin level is moderately elevated (51–171 μmol/L [3–10 mg/dL]). Hypoalbuminemia occurs in patients with very active or advanced disease. Serum alkaline phosphatase levels may be moderately elevated or near normal. In a small proportion of patients, marked elevations of alkaline phosphatase activity occur; in such patients, clinical and laboratory features overlap with those of primary biliary cirrhosis. The prothrombin time is often prolonged, particularly late in the disease or during active phases.

Hypergammaglobulinemia (>2.5 g/dL) is common in autoimmune hepatitis. Rheumatoid factor is common as well. As noted earlier, circulating autoantibodies are also prevalent. The most characteristic are ANAs in a homogeneous staining pattern. Smoothmuscle antibodies are less specific, seen just as frequently in chronic viral hepatitis. Because of the high levels of globulins achieved in the circulation of some patients with autoimmune hepatitis, occasionally the globulins may bind nonspecifically in solid-phase binding immunoassays for viral antibodies. This has been recognized most commonly in tests for antibodies to hepatitis C virus, as previously noted. In fact, studies of autoantibodies in autoimmune hepatitis have led to the recognition of new categories of autoimmune hepatitis. *Type I autoimmune hepatitis* is the classic syndrome occurring in young women, associated with marked hyperglobulinemia, lupoid features, circulating ANAs, and HLA-DR3 or HLA-DR4 (especially B8-DRB1*03). Also associated with type I autoimmune hepatitis are autoantibodies against actin as well

as atypical perinuclear antineutrophilic cytoplasmic antibodies (pANCA).

Type II autoimmune hepatitis, often seen in children, more common in Mediterranean populations, and linked to HLA-DRB1 and HLA-DQB1 haplotypes, is associated not with ANA but with anti-LKM. Actually, anti-LKM represent a heterogeneous group of antibodies. In type II autoimmune hepatitis, the antibody is anti-LKM1, directed against cytochrome P450 2D6. This is the same anti-LKM seen in some patients with chronic hepatitis C. Anti-LKM2 is seen in drug-induced hepatitis, and anti-LKM3 is seen in patients with chronic hepatitis D. Another autoantibody observed in type II autoimmune hepatitis is directed against liver cytosol formiminotransferase cyclodeaminase (anti-liver cytosol 1). More controversial is whether or not a third category of autoimmune hepatitis exists, *type III autoimmune hepatitis*. These patients lack ANA and anti-LKM1 but have circulating antibodies to soluble liver antigen/liver pancreas antigen. Most of these patients are women and have clinical features similar to, perhaps more severe than, those of patients with type I autoimmune hepatitis. Type III autoimmune hepatitis does not appear to represent a distinct category but, instead, is part of the spectrum of type I autoimmune hepatitis; this subcategory has not been adopted by a consensus of international experts.

Liver biopsy abnormalities are similar to those described for chronic viral hepatitis. Expanding portal tracts and extending beyond the plate of periportal hepatocytes into the parenchyma (designated *interface hepatitis* or *piecemeal necrosis*) is a mononuclear cell infiltrate that, in autoimmune hepatitis, may include the presence of plasma cells. Necroinflammatory activity characterizes the lobular parenchyma, and evidence of hepatocellular regeneration is reflected by "rosette" formation, the occurrence of thickened liver cell plates, and regenerative "pseudolobules." Septal fibrosis, bridging fibrosis, and cirrhosis are frequent. Bile duct injury and granulomas are uncommon; however, a subgroup of patients with autoimmune hepatitis has histologic, biochemical, and serologic features overlapping those of primary biliary cirrhosis.

DIAGNOSTIC CRITERIA

An international group has suggested a set of criteria for establishing a diagnosis of autoimmune hepatitis. Exclusion of liver disease caused by genetic disorders, viral hepatitis, drug hepatotoxicity, and alcohol are linked with such inclusive diagnostic criteria as hyperglobulinemia, autoantibodies, and characteristic histologic features. This international group has also suggested a comprehensive diagnostic scoring system that, rarely required for typical cases, may be helpful when typical features are not present. Factors that weigh in favor of the diagnosis include female gender; predominant aminotransferase elevation; presence and level of globulin elevation; presence of nuclear, smooth muscle, LKM1, and other autoantibodies; concurrent other autoimmune diseases; characteristic histologic features (interface hepatitis, plasma cells, rosettes); HLA DR3 or DR4 markers; and response to treatment (see later). Weighing against the diagnosis are predominant alkaline phosphatase elevation, mitochondrial antibodies, markers of viral hepatitis, history of hepatotoxic drugs or excessive alcohol, histologic evidence of bile duct injury, or such atypical histologic features as fatty infiltration, iron overload, and viral inclusions.

DIFFERENTIAL DIAGNOSIS

Early during the course of chronic hepatitis, autoimmune hepatitis may resemble typical *acute viral hepatitis* (Chap. 95). Without histologic assessment, severe chronic hepatitis cannot be readily distinguished based on clinical or biochemical criteria from mild chronic hepatitis. In adolescence, *Wilson's disease* may present with features of chronic hepatitis long before neurologic manifestations become apparent and before the formation of Kayser-Fleischer rings. In this age group, serum ceruloplasmin and serum and urinary copper determinations plus measurement of liver copper levels will establish the correct diagnosis. *Postnecrotic* or *cryptogenic cirrhosis* and *primary biliary cirrhosis* share clinical features with autoimmune hepatitis, and both alcoholic hepatitis and nonalcoholic steatohepatitis may present with many features common to autoimmune hepatitis; historic, biochemical, serologic, and histologic assessments are usually sufficient to allow these entities to be distinguished from autoimmune hepatitis. Of course, the distinction between autoimmune and chronic viral hepatitis is not always straightforward, especially when viral antibodies occur in patients with autoimmune disease or when autoantibodies occur in patients with viral disease. Furthermore, the presence of extrahepatic features such as arthritis, cutaneous vasculitis, or pleuritis—not to mention the presence of circulating autoantibodies—may cause confusion with *rheumatologic disorders* such as rheumatoid arthritis and systemic lupus erythematosus. The existence of clinical and biochemical features of progressive necroinflammatory liver disease distinguishes chronic hepatitis from these other disorders, which are not associated with severe liver disease.

Finally, occasionally, features of autoimmune hepatitis overlap with features of autoimmune biliary disorders such as primary biliary cirrhosis, primary sclerosing cholangitis, or, even more rarely, mitochondrial antibody-negative autoimmune cholangitis. Such overlap syndromes are difficult to categorize, and often response to therapy may be the distinguishing factor that establishes the diagnosis.

TREATMENT Autoimmune Hepatitis

The mainstay of management in autoimmune hepatitis is glucocorticoid therapy. Several controlled clinical trials have documented that such therapy leads

to symptomatic, clinical, biochemical, and histologic improvement as well as increased survival. A therapeutic response can be expected in up to 80% of patients. Unfortunately, therapy has not been shown to prevent ultimate progression to cirrhosis; however, instances of reversal of fibrosis and cirrhosis have been reported in patients responding to treatment. Although some advocate the use of prednisolone (the hepatic metabolite of prednisone), prednisone is just as effective and is favored by most authorities. Therapy may be initiated at 20 mg/d, but a popular regimen in the United States relies on an initiation dose of 60 mg/d. This high dose is tapered successively over the course of a month down to a maintenance level of 20 mg/d. An alternative, but equally effective, approach is to begin with half the prednisone dose (30 mg/d) along with azathioprine (50 mg/d). With azathioprine maintained at 50 mg/d, the prednisone dose is tapered over the course of a month down to a maintenance level of 10 mg/d. The advantage of the combination approach is a reduction, over the span of an 18-month course of therapy, in serious, life-threatening complications of steroid therapy from 66% down to under 20%. In combination regimens, 6-mercaptopurine may be substituted for its prodrug azathioprine, but this is rarely required. Azathioprine alone, however, is not effective in achieving remission, nor is alternate-day glucocorticoid therapy. Limited experience with budesonide in noncirrhotic patients suggests that this steroid side effect–sparing drug may be effective. Although therapy has been shown to be effective for severe autoimmune hepatitis (AST ≥10 times the upper limit of normal or ≥5 times the upper limit of normal in conjunction with serum globulin greater than or equal to twice normal; bridging necrosis or multilobular necrosis on liver biopsy; presence of symptoms), therapy is not indicated for mild forms of chronic hepatitis, and the efficacy of therapy in mild or asymptomatic autoimmune hepatitis has not been established.

Improvement of fatigue, anorexia, malaise, and jaundice tends to occur within days to several weeks; biochemical improvement occurs over the course of several weeks to months, with a fall in serum bilirubin and globulin levels and an increase in serum albumin. Serum aminotransferase levels usually drop promptly, but improvements in AST and ALT alone do not appear to be reliable markers of recovery in individual patients; histologic improvement, characterized by a decrease in mononuclear infiltration and in hepatocellular necrosis, may be delayed for 6–24 months. Still, if interpreted cautiously, aminotransferase levels are valuable indicators of relative disease activity, and many authorities do *not* advocate for serial liver biopsies to assess therapeutic success or to guide decisions to alter or stop therapy. Rapidity of response is more common in older patients (≥69 years) and those with HLA DBR1*04; although rapid responders may progress less slowly to cirrhosis and liver transplantation, they are no less likely than slower responders to relapse after therapy. Therapy should continue for at least 12–18 months. After tapering and cessation of therapy, the likelihood of relapse is at least 50%, even if posttreatment histology has improved to show mild chronic hepatitis, and the majority of patients require therapy at maintenance doses indefinitely. Continuing azathioprine alone (2 mg/kg body weight daily) after cessation of prednisone therapy may reduce the frequency of relapse.

In medically refractory cases, an attempt should be made to intensify treatment with high-dose glucocorticoid monotherapy (60 mg daily) or combination glucocorticoid (30 mg daily) plus high-dose azathioprine (150 mg daily) therapy. After a month, doses of prednisone can be reduced by 10 mg a month, and doses of azathioprine can be reduced by 50 mg a month toward ultimate, conventional maintenance doses. Patients refractory to this regimen may be treated with cyclosporine, tacrolimus, or mycophenolate mofetil; however, to date, only limited anecdotal reports support these approaches. If medical therapy fails, or when chronic hepatitis progresses to cirrhosis and is associated with life-threatening complications of liver decompensation, liver transplantation is the only recourse; failure of the bilirubin to improve after 2 weeks of therapy should prompt early consideration of the patient for liver transplantation. Recurrence of autoimmune hepatitis in the new liver occurs rarely in most experiences, but in as many as 35–40% of cases in others.

Acknowledgment

Kurt J. Isselbacher, MD, contributed to this chapter in previous editions of Harrison's Principles of Internal Medicine.

CHAPTER 97

ENTEROVIRUSES AND REOVIRUSES

Jeffrey I. Cohen

ENTEROVIRUSES

CLASSIFICATION AND CHARACTERIZATION

Enteroviruses are so named because of their ability to multiply in the gastrointestinal tract. Despite their name, these viruses are not a prominent cause of gastroenteritis. Enteroviruses encompass 96 human serotypes: 3 serotypes of poliovirus, 21 serotypes of coxsackievirus A, 6 serotypes of coxsackievirus B, 28 serotypes of echovirus, enteroviruses 68–71, and 34 new enteroviruses (beginning with enterovirus 73) that have been identified by molecular techniques. Echoviruses 22 and 23 have been reclassified as parechoviruses 1 and 2; 12 additional human parechoviruses have been identified. These viruses cause disease similar to that caused by echoviruses. Enterovirus surveillance conducted in the United States by the Centers for Disease Control and Prevention (CDC) in 2007–2008 showed that the most common serotype, coxsackievirus B1, was followed in frequency by echoviruses 18, 9, and 6; together, these four viruses accounted for 52% of all isolates.

Human enteroviruses contain a single-stranded RNA genome surrounded by an icosahedral capsid comprising four viral proteins. These viruses have no lipid envelope and are stable in acidic environments, including the stomach. They are susceptible to chlorine-containing cleansers but resistant to inactivation by standard disinfectants (e.g., alcohol, detergents) and can persist for days at room temperature.

PATHOGENESIS AND IMMUNITY

Much of what is known about the pathogenesis of enteroviruses has been derived from studies of poliovirus infection. After ingestion, poliovirus is thought to infect epithelial cells in the mucosa of the gastrointestinal tract and then to spread to and replicate in the submucosal lymphoid tissue of the tonsils and Peyer's patches. The virus next spreads to the regional lymph nodes, a viremic phase ensues, and the virus replicates in organs of the reticuloendothelial system. In some cases, a second viremia occurs and the virus replicates further in various tissues, sometimes causing symptomatic disease.

It is uncertain whether poliovirus reaches the central nervous system (CNS) during viremia or whether it also spreads via peripheral nerves. Since viremia precedes the onset of neurologic disease in humans, it has been assumed that the virus enters the CNS via the bloodstream. The poliovirus receptor is a member of the immunoglobulin superfamily. Poliovirus infection is limited to primates, largely because their cells express the viral receptor. Studies demonstrating the poliovirus receptor in the end-plate region of muscle at the neuromuscular junction suggest that, if the virus enters the muscle during viremia, it could travel across the neuromuscular junction up the axon to the anterior horn cells. Studies of monkeys and of transgenic mice expressing the poliovirus receptor show that, after IM injection, poliovirus does not reach the spinal cord if the sciatic nerve is cut. Taken together, these findings suggest that poliovirus can spread directly from muscle to the CNS by neural pathways. Intercellular adhesion molecule 1 (ICAM-1) is a receptor for coxsackieviruses A13, A18, and A21; CAR for coxsackievirus B; VLA-2 integrin for echovirus types 1 and 8; CD55 for enterovirus 70 and some serotypes of coxsackievirus A and B and echovirus; and P-selectin glycoprotein ligand-1 and scavenger receptor B2 for enterovirus 71.

Poliovirus can usually be cultured from the blood 3–5 days after infection, before the development of neutralizing antibodies. While viral replication at secondary sites begins to slow 1 week after infection, it continues in the gastrointestinal tract. Poliovirus is shed from the oropharynx for up to 3 weeks after infection and from the gastrointestinal tract for as long as 12 weeks; hypogammaglobulinemic patients can shed poliovirus for >20 years. During replication in the gastrointestinal tract, attenuated oral poliovirus can mutate, reverting to a more neurovirulent phenotype within a few days; however, additional mutations are probably required for full neurovirulence.

Humoral and secretory immunity in the gastrointestinal tract is important for the control of enterovirus infections. Enteroviruses induce specific IgM, which usually

persists for <6 months, and specific IgG, which persists for life. Capsid protein VP1 is the predominant target of neutralizing antibody, which generally confers lifelong protection against subsequent disease caused by the same serotype but does not prevent infection or virus shedding. Enteroviruses also induce cellular immunity whose significance is uncertain. Patients with impaired cellular immunity are not known to develop unusually severe disease when infected with enteroviruses. In contrast, the severe infections in patients with agammaglobulinemia emphasize the importance of humoral immunity in controlling enterovirus infections. Disseminated enterovirus infections have occurred in hematopoietic cell transplant recipients. IgA antibodies are instrumental in reducing poliovirus replication in and shedding from the gastrointestinal tract. Breast milk contains IgA specific for enteroviruses and can protect humans from infection.

EPIDEMIOLOGY

Enteroviruses have a worldwide distribution. More than 50% of nonpoliovirus enterovirus infections and more than 90% of poliovirus infections are subclinical. When symptoms do develop, they are usually nonspecific and occur in conjunction with fever; only a minority of infections are associated with specific clinical syndromes. The incubation period for most enterovirus infections ranges from 2 to 14 days but usually is <1 week.

Enterovirus infection is more common in socioeconomically disadvantaged areas, especially in those where conditions are crowded and in tropical areas where hygiene is poor. Infection is most common among infants and young children; serious illness develops most often during the first few days of life and in older children and adults. In developing countries, where children are infected at an early age, poliovirus infection has less often been associated with paralysis; in countries with better hygiene, older children and adults are more likely to be seronegative, become infected, and develop paralysis. Passively acquired maternal antibody reduces the risk of symptomatic infection in neonates. Young children are the most frequent shedders of enteroviruses and are usually the index cases in family outbreaks. In temperate climates, enterovirus infections occur most often in the summer and fall; no seasonal pattern is apparent in the tropics.

Most enteroviruses are transmitted primarily by the fecal-oral or oral-oral route. Patients are most infectious shortly before and after the onset of symptomatic disease, when virus is present in the stool and throat. The ingestion of virus-contaminated food or water can also cause disease. Certain enteroviruses (such as enterovirus 70, which causes acute hemorrhagic conjunctivitis) can be transmitted by direct inoculation from the fingers to the eye. Airborne transmission is important for some viruses that cause respiratory tract disease, such as coxsackievirus A21. Enteroviruses can be transmitted across the placenta from mother to fetus, causing severe disease in the newborn. The transmission of enteroviruses through blood transfusions or insect bites has not been documented. Nosocomial spread of coxsackievirus and echovirus has taken place in hospital nurseries.

CLINICAL FEATURES

Poliovirus infection

Most infections with poliovirus are asymptomatic. After an incubation period of 3–6 days, ~5% of patients present with a minor illness (abortive poliomyelitis) manifested by fever, malaise, sore throat, anorexia, myalgias, and headache. This condition usually resolves in 3 days. About 1% of patients present with aseptic meningitis (nonparalytic poliomyelitis). Examination of cerebrospinal fluid (CSF) reveals lymphocytic pleocytosis, a normal glucose level, and a normal or slightly elevated protein level; CSF polymorphonuclear leukocytes may be present early. In some patients, especially children, malaise and fever precede the onset of aseptic meningitis.

Paralytic poliomyelitis

The least common presentation is that of paralytic disease. After one or several days, signs of aseptic meningitis are followed by severe back, neck, and muscle pain and by the rapid or gradual development of motor weakness. In some cases the disease appears to be biphasic, with aseptic meningitis followed first by apparent recovery but then (1–2 days later) by the return of fever and the development of paralysis; this form is more common among children than among adults. Weakness is generally asymmetric, is proximal more than distal, and may involve the legs (most commonly); the arms; or the abdominal, thoracic, or bulbar muscles. Paralysis develops during the febrile phase of the illness and usually does not progress after defervescence. Urinary retention may also occur. Examination reveals weakness, fasciculations, decreased muscle tone, and reduced or absent reflexes in affected areas. Transient hyperreflexia sometimes precedes the loss of reflexes. Patients frequently report sensory symptoms, but objective sensory testing usually yields normal results. Bulbar paralysis may lead to dysphagia, difficulty in handling secretions, or dysphonia. Respiratory insufficiency due to aspiration, involvement of the respiratory center in the medulla, or paralysis of the phrenic or intercostal nerves may develop, and severe medullary involvement may lead to circulatory collapse. Most patients with paralysis recover some function weeks to months after infection. About two-thirds of patients have residual neurologic sequelae.

Paralytic disease is more common among older individuals, pregnant women, and persons exercising strenuously or undergoing trauma at the time of CNS symptoms. Tonsillectomy predisposes to bulbar poliomyelitis, and IM injections increase the risk of paralysis in the involved limb(s).

Vaccine-associated poliomyelitis

Until recently, poliomyelitis due to live poliovirus vaccine occurred in the United States. The risk of developing poliomyelitis after oral vaccination is estimated at 1 case per 2.5 million doses. The risk is ~2000 times

higher among immunodeficient persons, especially in persons with hypo- or agammaglobulinemia. Before 1997, an average of eight cases of vaccine-associated poliomyelitis occurred—in both vaccinees and their contacts—in the United States each year. With the change in recommendations first to a sequential regimen of inactivated poliovirus vaccine (IPV) and oral poliovirus vaccine (OPV) in 1997 and then to an all-IPV regimen in 2000, the number of cases of vaccine-associated polio declined. From 1997 to 1999, six such cases were reported in the United States; no cases have been reported since 1999.

Postpolio syndrome

The *postpolio syndrome* presents as a new onset of weakness, fatigue, fasciculations, and pain with additional atrophy of the muscle group involved during the initial paralytic disease 20–40 years earlier. The syndrome is more common among women and with increasing time after acute disease. The onset is usually insidious, and weakness occasionally extends to muscles that were not involved during the initial illness. The prognosis is generally good; progression to further weakness is usually slow, with plateau periods of 1–10 years. The postpolio syndrome is thought to be due to progressive dysfunction and loss of motor neurons that compensated for the neurons lost during the original infection and not to persistent or reactivated poliovirus infection.

Other enteroviruses

An estimated 5–10 million cases of symptomatic disease due to enteroviruses other than poliovirus occur in the United States each year. Among neonates, enteroviruses are the most common cause of aseptic meningitis and nonspecific febrile illnesses. Certain clinical syndromes are more likely to be caused by certain serotypes **(Table 97-1)**.

Nonspecific febrile illness (summer grippe)

The most common clinical manifestation of enterovirus infection is a nonspecific febrile illness. After an incubation period of 3–6 days, patients present with an acute onset of fever, malaise, and headache. Occasional cases are associated with upper respiratory symptoms, and some cases include nausea and vomiting. Symptoms often last for 3–4 days, and most cases resolve in a week. While infections with other respiratory viruses occur more often from late fall to early spring, enterovirus febrile illness frequently occurs in the summer and early fall.

Generalized disease of the newborn

Most serious enterovirus infections in infants develop during the first week of life, although severe disease can occur up to 3 months of age. Neonates often present with an illness resembling bacterial sepsis, with fever, irritability, and lethargy. Laboratory abnormalities include leukocytosis with a left shift, thrombocytopenia, elevated values in liver function tests, and CSF pleocytosis. The illness can be complicated by myocarditis and hypotension, fulminant hepatitis and disseminated intravascular coagulation, meningitis or meningoencephalitis, or pneumonia. It may be difficult to distinguish neonatal enterovirus infection from bacterial sepsis, although a history of a recent virus-like illness in the mother provides a clue.

Aseptic meningitis and encephalitis

In children and young adults, enteroviruses are the cause of up to 90% of cases of aseptic meningitis in which an etiologic agent can be identified. Patients with aseptic meningitis typically present with an acute onset of fever, chills, headache, photophobia, and pain on eye movement. Nausea and vomiting are also common. Examination reveals meningismus without localizing neurologic signs; drowsiness or irritability may also be apparent. In some cases, a febrile illness may be reported that remits

TABLE 97-1

MANIFESTATIONS COMMONLY ASSOCIATED WITH ENTEROVIRUS SEROTYPES

	SEROTYPE(S) OF INDICATED VIRUS	
MANIFESTATION	**COXSACKIEVIRUS**	**ECHOVIRUS (E) AND ENTEROVIRUS (ENT)**
Acute hemorrhagic conjunctivitis	A24	E70
Aseptic meningitis	A2, 4, 7, 9, 10; B1–5	E4, 6, 7, 9, 11, 13, 16, 18, 19, 30, 33; Ent70, 71
Encephalitis	A9; B1–5	E3, 4, 6, 7, 9, 11, 18, 25, 30; Ent71
Exanthem	A4, 5, 9, 10, 16; B1, 3–5	E4–7, 9, 11, 16–19, 25, 30; Ent71
Generalized disease of the newborn	B1–5	E4–6, 7, 9, 11, 14, 16, 18, 19
Hand-foot-and-mouth disease	A5, 7, 9, 10, 16; B1, 2, 5	Ent71
Herpangina	A1–10, 16, 22; B1–5	E6, 9, 11, 16, 17, 25, 30; Ent71
Myocarditis, pericarditis	A4, 9, 16; B1–5	E6, 9, 11, 22
Paralysis	A4, 7, 9; B1–5	E2–4, 6, 7, 9, 11, 18, 30; Ent70, 71
Pleurodynia	A1, 2, 4, 6, 9, 10, 16; B1–6	E1–3, 6, 7, 9, 11, 12, 14, 16, 19, 24, 25, 30
Pneumonia	A9, 16; B1–5	E6, 7, 9, 11, 12, 19, 20, 30; Ent68, 71

but returns several days later in conjunction with signs of meningitis. Other systemic manifestations may provide clues to an enteroviral cause, including diarrhea, myalgias, rash, pleurodynia, myocarditis, and herpangina. Examination of the CSF invariably reveals pleocytosis; the CSF cell count shows a shift from neutrophil to lymphocyte predominance within 1 day of presentation, and the total cell count does not exceed 1000/μL. The CSF glucose level is usually normal (in contrast to the low CSF glucose level in mumps) with a normal or slightly elevated protein concentration. Partially treated bacterial meningitis may be particularly difficult to exclude in some instances. Enteroviral meningitis is more frequent in summer and fall in temperate climates, while viral meningitis of other etiologies is more common in winter and spring. Symptoms ordinarily resolve within a week, although CSF abnormalities can persist for several weeks. Enteroviral meningitis is often more severe in adults than in children. Neurologic sequelae are rare, and most patients have an excellent prognosis.

Enteroviral encephalitis is much less common than enteroviral aseptic meningitis. Occasional highly inflammatory cases of enteroviral meningitis may be complicated by a mild form of encephalitis that is recognized on the basis of progressive lethargy, disorientation, and sometimes seizures. Less commonly, severe primary encephalitis may develop. An estimated 10–35% of cases of viral encephalitis are due to enteroviruses. Immunocompetent patients generally have a good prognosis.

Patients with hypogammaglobulinemia or agammaglobulinemia or severe combined immunodeficiency may develop chronic meningitis or encephalitis; about half of these patients have a dermatomyositis-like syndrome, with peripheral edema, rash, and myositis. They may also have chronic hepatitis. Patients may develop neurologic disease while receiving immunoglobulin replacement therapy. Echoviruses (especially echovirus 11) are the most common pathogens in this situation.

Paralytic disease due to enteroviruses other than poliovirus occurs sporadically and is usually less severe than poliomyelitis. Most cases are due to enterovirus 70 or 71 or to coxsackievirus A7 or A9. Guillain-Barré syndrome is also associated with enterovirus infection. While some studies have suggested a link between enteroviruses and the chronic fatigue syndrome, most recent studies have not demonstrated such an association.

Pleurodynia (Bornholm disease)

Patients with pleurodynia present with an acute onset of fever and spasms of pleuritic chest or upper abdominal pain. Chest pain is more common in adults, and abdominal pain is more common in children. Paroxysms of severe, knifelike pain usually last 15–30 min and are associated with diaphoresis and tachypnea. Fever peaks within an hour after the onset of paroxysms and subsides when pain resolves. The involved muscles are tender to palpation, and a pleural rub may be detected. The white blood cell count and chest x-ray are usually normal. Most cases are due to coxsackievirus B and occur during epidemics. Symptoms resolve in a few days, and recurrences are rare. Treatment includes the administration of nonsteroidal anti-inflammatory agents or the application of heat to the affected muscles.

Myocarditis and pericarditis

Enteroviruses are estimated to cause up to one-third of cases of acute myocarditis. Coxsackievirus B and its RNA have been detected in pericardial fluid and myocardial tissue in some cases of acute myocarditis and pericarditis. Most cases of enteroviral myocarditis or pericarditis occur in newborns, adolescents, or young adults. More than two-thirds of patients are male. Patients often present with an upper respiratory tract infection that is followed by fever, chest pain, dyspnea, arrhythmias, and occasionally heart failure. A pericardial friction rub is documented in half of cases, and the electrocardiogram shows ST-segment elevations or ST- and T-wave abnormalities. Serum levels of myocardial enzymes are often elevated. Neonates commonly have severe disease, while most older children and adults recover completely. Up to 10% of cases progress to chronic dilated cardiomyopathy. Chronic constrictive pericarditis may also be a sequela.

Exanthems

Enterovirus infection is the leading cause of exanthems in children in the summer and fall. While exanthems are associated with many enteroviruses, certain types have been linked to specific syndromes. Echoviruses 9 and 16 have frequently been associated with exanthem and fever. Rashes may be discrete or confluent, beginning on the face and spreading to the trunk and extremities. Echovirus 9 is the most common cause of a rubelliform (discrete) rash. Unlike the rash of rubella, the enteroviral rash occurs in the summer and is not associated with lymphadenopathy. Roseola-like rashes develop after defervescence, with macules and papules on the face and trunk. The Boston exanthem, caused by echovirus 16, is a roseola-like rash. A variety of other rashes have been associated with enteroviruses, including erythema multiforme (see Fig. 11-25) and vesicular, urticarial, petechial, or purpuric lesions. Enanthems also occur, including lesions that resemble the Koplik's spots seen with measles (see Fig. 11-2).

Hand-foot-and-mouth disease

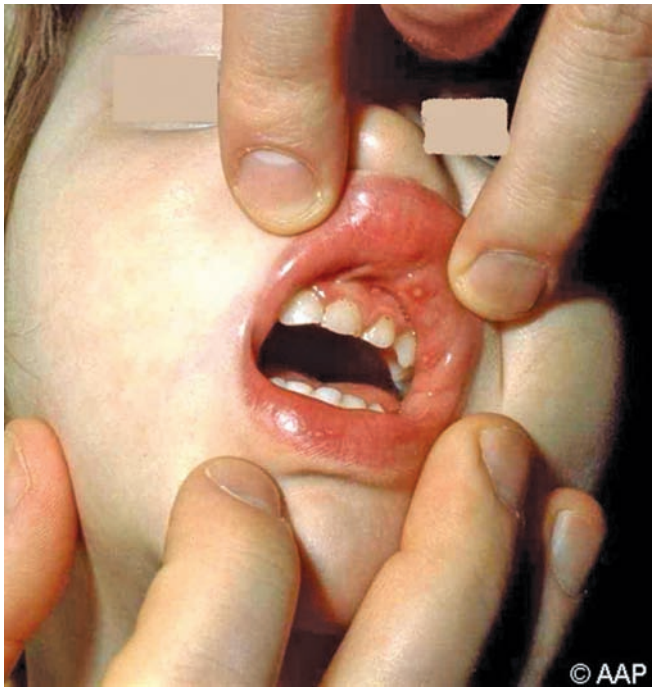
After an incubation period of 4–6 days, patients with hand-foot-and-mouth disease present with fever, anorexia, and malaise; these manifestations are followed by the development of sore throat and vesicles (**Fig. 97-1*A***; see also Fig. 11-23) on the buccal mucosa and often on the tongue and then by the appearance of tender vesicular lesions on the dorsum of the hands, sometimes with involvement of the palms. The vesicles may form bullae and quickly ulcerate. About one-third of patients also have lesions on the palate, uvula, or tonsillar pillars, and one-third have a rash on the feet (including the soles) or on the buttocks (Fig. 97-1*B*). The disease is highly infectious, with attack rates of close to 100% among

young children. The lesions usually resolve in 1 week. Most cases are due to coxsackievirus A16 or enterovirus 71.

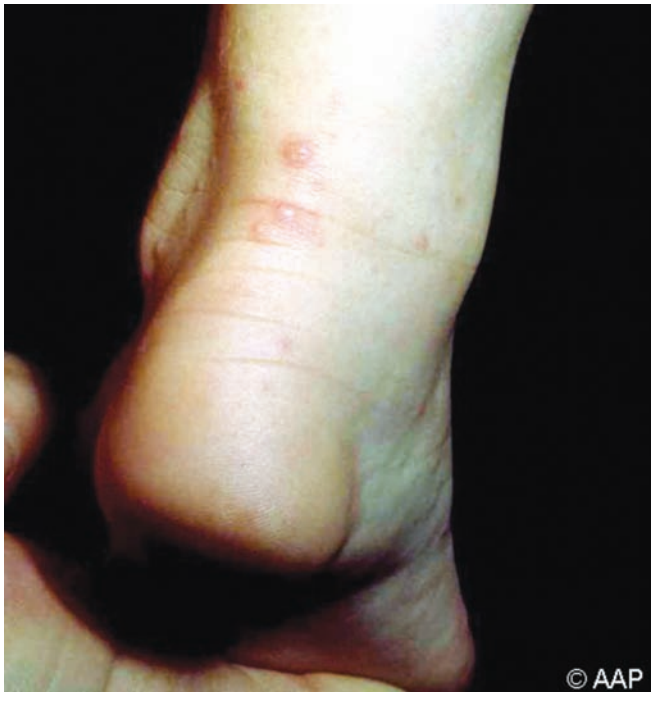
An epidemic of enterovirus 71 infection in Taiwan in 1998 resulted in thousands of cases of hand-foot-and-mouth disease or herpangina. Severe complications included CNS disease, myocarditis, and pulmonary hemorrhage. About 90% of those who died were children ≥5 years old, and death was associated with pulmonary edema or pulmonary hemorrhage. CNS disease included aseptic meningitis, flaccid paralysis (similar to that seen in poliomyelitis), or rhombencephalitis with myoclonus and tremor or ataxia. The mean age of patients with CNS complications was 2.5 years, and MRI in cases with encephalitis usually showed brain-stem lesions. Follow-up of children at 6 months showed persistent dysphagia, cranial nerve palsies, hypoventilation, limb weakness, and atrophy; at 3 years, persistent neurologic sequelae were documented, with delayed development and impaired cognitive function.

Herpangina

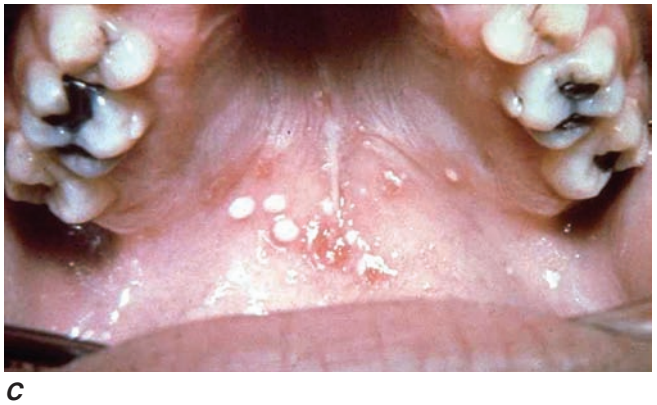
Herpangina is usually caused by coxsackievirus A and presents as acute-onset fever, sore throat, odynophagia, and grayish-white papulovesicular lesions on an



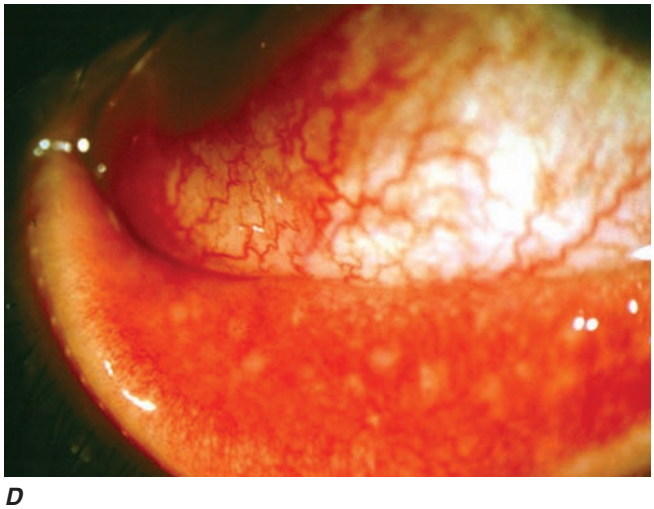
A



B



C



D

FIGURE 97-1

A. Tender vesicles in the mouth of a patient with hand-foot-and-mouth disease. ***B.*** Vesicles over the Achilles tendon in a patient with hand-foot-and-mouth disease. ***C.*** Soft-palate lesions of herpangina due to coxsackievirus. ***D.*** Acute hemorrhagic conjunctivitis due to enterovirus 71. (*Images are reprinted with permission from Red Book 2009: Committee on Infectious Diseases, 28th ed. Used with permission of the American Academy of Pediatrics.*)

erythematous base that ulcerate (Fig. 97-1*C*). The lesions can persist for weeks; are present on the soft palate, anterior pillars of the tonsils, and uvula; and are concentrated in the posterior portion of the mouth. In contrast to herpes stomatitis, enteroviral herpangina is not associated with gingivitis. Acute lymphonodular pharyngitis associated with coxsackievirus A10 presents as white or yellow nodules surrounded by erythema in the posterior oropharynx. The lesions do not ulcerate.

Acute hemorrhagic conjunctivitis

Patients with acute hemorrhagic conjunctivitis present with an acute onset of severe eye pain, blurred vision, photophobia, and watery discharge from the eye. Examination reveals edema, chemosis, and subconjunctival hemorrhage and often shows punctate keratitis and conjunctival follicles as well (Fig. 97-1*D*). Preauricular adenopathy is often found. Epidemics and nosocomial spread have been associated with enterovirus 70 and coxsackievirus A24. Systemic symptoms, including headache and fever, develop in 20% of cases, and recovery is usually complete in 10 days. The sudden onset and short duration of the illness help to distinguish acute hemorrhagic conjunctivitis from other ocular infections, such as those due to adenovirus and *Chlamydia trachomatis*. Paralysis has been associated with some cases of acute hemorrhagic conjunctivitis due to enterovirus 70 during epidemics.

Other manifestations

Enteroviruses are an infrequent cause of childhood pneumonia and the common cold. Coxsackievirus B has been isolated at autopsy from the pancreas of a few children presenting with type 1 diabetes mellitus; however, most attempts to isolate the virus have been unsuccessful. Other diseases that have been associated with enterovirus infection include parotitis, bronchitis, bronchiolitis, croup, infectious lymphocytosis, polymyositis, acute arthritis, and acute nephritis.

DIAGNOSIS

Isolation of enterovirus in cell culture is the traditional diagnostic procedure. While cultures of stool, nasopharyngeal, or throat samples from patients with enterovirus diseases are often positive, isolation of the virus from these sites does not prove that it is directly associated with disease because these sites are frequently colonized for weeks in patients with subclinical infections. Isolation of virus from the throat is more likely to be associated with disease than isolation from the stool since virus is shed for shorter periods from the throat. Cultures of CSF, serum, fluid from body cavities, or tissues are positive less frequently, but a positive result is indicative of disease caused by enterovirus. In some cases, the virus is isolated only from the blood or only from the CSF; therefore, it is important to culture multiple sites. Cultures are more likely to be positive earlier than later in the course of infection. Most human enteroviruses can be detected within a week after inoculation of cell cultures. Cultures may be negative because of the presence of neutralizing antibody, lack of susceptibility of the cells used, or inappropriate handling of the specimen. Coxsackievirus A may require inoculation into special cell-culture lines or into suckling mice.

Identification of the enterovirus serotype is useful primarily for epidemiologic studies and, with a few exceptions, has little clinical utility. It is important to identify serious infections with enterovirus during epidemics and to distinguish the vaccine strain of poliovirus from the other enteroviruses in the throat or in the feces. Stool and throat samples for culture as well as acute- and convalescent-phase serum specimens should be obtained from all patients with suspected poliomyelitis. In the absence of a positive CSF culture, a positive culture of stool obtained within the first 2 weeks after the onset of symptoms is most often used to confirm the diagnosis of poliomyelitis. If poliovirus infection is suspected, two or more fecal and throat swab samples should be obtained at least 1 day apart and cultured for enterovirus as soon as possible. If poliovirus is isolated, it should be sent to the CDC for identification as either wild-type or vaccine virus.

The polymerase chain reaction (PCR) has been used to amplify viral nucleic acid from CSF, serum, urine, throat swabs, and tissues. A pan-enterovirus PCR assay can detect all human enteroviruses. With the proper controls, PCR of the CSF is highly sensitive (70–100%) and specific (>80%) and is more rapid than culture. PCR of the CSF is less likely to be positive when patients present ≥3 days after the onset of meningitis or with enterovirus 71 infection; in these cases, PCR of throat or rectal swabs—although less specific than PCR of CSF—should be considered.

PCR of serum is also highly sensitive and specific in the diagnosis of disseminated disease. PCR may be particularly helpful for the diagnosis and follow-up of enterovirus disease in immunodeficient patients receiving immunoglobulin therapy, whose viral cultures may be negative. Antigen detection is less sensitive than PCR.

Serologic diagnosis of enterovirus infection is limited by the large number of serotypes and the lack of a common antigen. Demonstration of seroconversion may be useful in rare cases for confirmation of culture results, but serologic testing is usually limited to epidemiologic studies. Serum should be collected and frozen soon after the onset of disease and again ~4 weeks later. Measurement of neutralizing titers is the most accurate method for antibody determination; measurement of complement-fixation titers is usually less sensitive. Titers of virus-specific IgM are elevated in both acute and chronic infection.

TREATMENT Enterovirus Infections

Most enterovirus infections are mild and resolve spontaneously; however, intensive supportive care may be needed for cardiac, hepatic, or CNS disease. IV,

intrathecal, or intraventricular immunoglobulin has been used with apparent success in some cases for the treatment of chronic enterovirus meningoencephalitis and dermatomyositis in patients with hypogammaglobulinemia or agammaglobulinemia. The disease may stabilize or resolve during therapy; however, some patients decline inexorably despite therapy. IV immunoglobulin often prevents severe enterovirus disease in these patients. IV administration of immunoglobulin with high titers of antibody to the infecting virus has been used in some cases of life-threatening infection in neonates, who may not have maternally acquired antibody. In one trial involving neonates with enterovirus infections, immunoglobulin containing very high titers of antibody to the infecting virus reduced rates of viremia; however, the study was too small to show a substantial clinical benefit. The level of enteroviral antibodies varies with the immunoglobulin preparation. Although a phase 2 trial of pleconaril for severe neonatal enterovirus disease is in progress, the drug is no longer available on a compassionate-use basis. Glucocorticoids are contraindicated.

Good hand-washing practices and the use of gowns and gloves are important in limiting nosocomial transmission of enteroviruses during epidemics. Enteric precautions are indicated for 7 days after the onset of enterovirus infections.

PREVENTION AND ERADICATION OF POLIOVIRUS

(See also Chap. 4) After a peak of 57,879 cases of poliomyelitis in the United States in 1952, the introduction of inactivated vaccine in 1955 and of oral vaccine in 1961 ultimately eradicated disease due to wild-type poliovirus in the Western Hemisphere. Such disease has not been documented in the United States since 1979, when cases occurred among religious groups who had declined immunization. In the Western Hemisphere, paralysis due to wild-type poliovirus was last documented in 1991.

In 1988, the World Health Organization adopted a resolution to eradicate poliomyelitis by the year 2000. From 1988 to 2001, the number of cases worldwide decreased by >99%, with fewer than 1000 confirmed cases reported in 2001. In 2002, however, there were ~1900 cases of polio, with ~1500 reported in India. Wild-type poliovirus type 2 has not been detected in the world since 1999. The Americas were certified free of indigenous wild-type poliovirus transmission in 1994, the Western Pacific Region in 2000, and the European Region in 2002. The total number of cases worldwide fell to a nadir of 498 in 2001. However, from 2002 to 2005, 21 countries previously free of polio reported cases imported from 6 polio-endemic countries. By 2006, polio transmission had been reduced in most of these 21 countries. In 2009, 1781 cases of polio were reported; 80% were from India, Nigeria, Pakistan, and Afghanistan, the only countries where polio remains endemic **(Table 97-2)**. Polio is a source of concern for unimmunized or partially immunized travelers. Importation of poliovirus into 20 countries accounted for 20% of cases in 2009. The number of cases of wild-type polio remained relatively constant from 2005 through 2009, with 1315–1997 cases per year. Countries that reported cases of wild-type polio in 2010 but not in 2009 included Tajikistan, Senegal, and Nepal. Outbreaks of polio in Europe and North America have been traced to cases imported from the Indian subcontinent. Clearly, global eradication of polio is necessary to eliminate the risk of importation of wild-type virus. Outbreaks are thought to have been facilitated by suboptimal rates of vaccination, isolated pockets of unvaccinated children, poor sanitation and crowding, improper vaccine-storage conditions, and a reduced level of response to one of the serotypes in the vaccine. While the global eradication campaign has markedly reduced the number of cases of endemic polio, doubts have been raised as to whether eradication is a realistic goal given the large number of asymptomatic infections and the political instability in developing countries.

The occurrence of outbreaks of poliomyelitis due to circulating vaccine-derived poliovirus of all three types has been increasing, especially in areas with low vaccination rates. In Egypt, 32 cases of vaccine-derived polio occurred in 1983–1993; in the Dominican Republic and Haiti, 22 cases occurred in 2000–2001;

TABLE 97-2

LABORATORY-CONFIRMED CASES OF POLIOMYELITIS IN 2009

COUNTRY	TYPE OF TRANSMISSION	NO. OF CASES
India	Endemic	752[a]
Nigeria	Endemic	541[b]
Pakistan	Endemic	89
Chad	Imported	66
Sudan	Imported	45
Guinea	Imported	43[c]
Afghanistan	Endemic	38
Angola	Imported	29
Cote d'Ivoire	Imported	26
Others[d]	Imported	142
Others[e]	Vaccine-derived	10
Total		1781

[a]Of these cases, 11 were vaccine-derived.
[b]Of these cases, 153 were vaccine-derived.
[c]Of these cases, 1 was vaccine-derived.
[d]Benin, 20; Kenya, 19; Burkina Faso, 15; Niger, 15; Central African Republic, 14; Mauritania, 13; Liberia, 11; Sierra Leone, 11; Uganda, 8; Togo, 6; Cameroon, 3; Democratic Republic of the Congo, 3; Burundi, 2; Mali, 2.
[e]Democratic Republic of the Congo, 4; Somalia, 4; Ethiopia, 2.
Source: World Health Organization.

in Indonesia, 46 cases were reported in 2005; in Nigeria, 292 cases occurred in 2005–2009; in the Democratic Republic of the Congo, 20 cases were reported in 2005–2009; and fewer cases have occurred in other countries. These OPV-derived viruses reverted to a more neurovirulent phenotype after undetected circulation (probably for >2 years). The epidemic in Hispaniola was rapidly terminated after intensive vaccination with OPV. In 2005, a case of vaccine-derived polio occurred in an unvaccinated U.S. woman returning from a visit to Central and South America. In the same year, an unvaccinated immunocompromised infant in Minnesota was found to be shedding vaccine-derived poliovirus; further investigation identified 4 of 22 infants in the same community who were shedding the virus. All 5 infants were asymptomatic. These outbreaks emphasize the need for maintaining high levels of vaccine coverage and continued surveillance for circulating virus.

IPV is used in most industrialized countries and OPV in most developing countries, including those in which polio still is or recently was endemic. After several doses of OPV alone, the seropositivity rate for individual poliovirus serotypes may still be suboptimal for children in developing countries; one or more supplemental doses of IPV can increase the rate of seropositivity for these serotypes. Against a given serotype, monovalent OPV containing only that serotype is more immunogenic than trivalent vaccine because of a lack of interference from other serotypes. While IM injections of other vaccines (live or attenuated) can be given concurrently with OPV, unnecessary IM injections should be avoided during the first month after vaccination because they increase the risk of vaccine-associated paralysis. Since 1988, an enhanced-potency inactivated poliovirus vaccine has been available in the United States.

OPV and IPV induce antibodies that persist for at least 5 years. Both vaccines induce IgG and IgA antibodies. Compared with recipients of IPV, recipients of OPV shed less virus and less frequently develop reinfection with wild-type virus after exposure to poliovirus. Although IPV is safe and efficacious, OPV offers the advantages of ease of administration, lower cost, and induction of intestinal immunity resulting in a reduction in the risk of community transmission of wild-type virus. Because of progress toward global eradication of polio (with a reduced risk of imported cases) and the continued occurrence of cases of vaccine-associated polio, an all-IPV regimen was recommended in 2000 for childhood poliovirus vaccination in the United States, with vaccine administration at 2, 4, and 6–18 months and 4–6 years of age. The risk of vaccine-associated polio should be discussed before OPV is administered. Recommendations for vaccination of adults are listed in Table 97-3.

There are concerns about discontinuing vaccination in the event that endemic spread of poliovirus is eliminated. Among the reasons for these concerns are that poliovirus is shed from some immunocompromised persons for >10 years, that vaccine-derived poliovirus can circulate and cause disease, and that wild-type poliovirus is present in a large number of laboratories. A national survey began in October 2002 to encourage laboratories to dispose of all unneeded wild-type poliovirus materials and to identify laboratories that have wild-type poliovirus or specimens that may contain virus.

TABLE 97-3

RECOMMENDATIONS FOR POLIOVIRUS VACCINATION OF ADULTS

1. Most adults in the United States have been vaccinated during childhood and have little risk of exposure to wild-type virus in the United States. Immunization is recommended for those with a higher risk of exposure than the general population, including:
   a. travelers to areas where poliovirus is or may be epidemic or endemic;
   b. members of communities or population groups with disease caused by wild-type polioviruses;
   c. laboratory workers handling specimens that may contain wild-type polioviruses; and
   d. health care workers in close contact with patients who may be excreting wild-type polioviruses.
2. Three doses of IPV are recommended for adults who need to be immunized. The second dose should be given 1–2 months after the first dose; the third dose should be given 6–12 months after the second dose.
3. Adults who are at increased risk of exposure to wild-type poliovirus and who have previously completed primary immunization should receive a single dose of IPV. Adults who did not complete primary immunization should receive the remaining vaccinations with IPV.

Abbreviations: IPV, inactivated poliovirus vaccine.
Source: Data from LK Pickering (ed): *Red Book 2012: Committee on Infectious Diseases*, 29th ed.

REOVIRUSES

Reoviruses are double-stranded RNA viruses encompassing three serotypes. Serologic studies indicate that most humans are infected with reoviruses during childhood. Most infections either are asymptomatic or cause very mild disease. One outbreak of reovirus infection in children resulted in minor upper respiratory tract symptoms. Reovirus is considered a rare cause of mild gastroenteritis in infants and children. Speculation regarding an association of reovirus type 3 with idiopathic neonatal hepatitis and extrahepatic biliary atresia is based on an elevated prevalence of antibody to reovirus among some of these patients and the detection of viral RNA by PCR in hepatobiliary tissues in some studies. Two new orthoreoviruses (Melaka and Kampar viruses) have been associated with fever and acute respiratory disease in Malaysia.

CHAPTER 98

MEASLES (RUBEOLA)

William J. Moss

DEFINITION

Measles is a highly contagious viral disease that is characterized by a prodromal illness of fever, cough, coryza, and conjunctivitis followed by the appearance of a generalized maculopapular rash. Before the widespread use of measles vaccines, it was estimated that measles caused between 5 million and 8 million deaths worldwide each year.

GLOBAL CONSIDERATIONS

Remarkable progress has been made in reducing global measles incidence and mortality rates through measles vaccination. In the Americas, intensive vaccination and surveillance efforts—based in part on the successful Pan American Health Organization strategy of periodic nationwide measles vaccination campaigns (supplementary immunization activities, or SIAs)—and high routine measles vaccine coverage have interrupted endemic transmission of measles virus. In the United States, high coverage with two doses of measles vaccine eliminated endemic measles virus transmission in 2000. More recently, progress has been made in reducing measles incidence and mortality rates in sub-Saharan Africa as a consequence of increasing routine measles vaccine coverage and provision of a second opportunity for measles vaccination through mass measles vaccination campaigns.

In 2003, the World Health Assembly endorsed a resolution urging member countries to reduce the number of deaths attributed to measles by 50% (compared with 1999 estimates) by the end of 2005. This target was met. Global measles mortality rates were further reduced in 2008; during that year, there were an estimated 164,000 deaths due to measles (uncertainty bounds: 115,000 and 222,000 deaths). These achievements attest to the enormous public-health significance of measles vaccination. The revised global goal, as stated in the Global Immunization Vision and Strategy 2006–2015 of the World Health Organization and United Nations Children's Fund, is to reduce global measles deaths by 90% (compared with the estimated 757,000 deaths in 2000) by 2010.

ETIOLOGY

Measles virus is a spherical, nonsegmented, single-stranded, negative-sense RNA virus and a member of the *Morbillivirus* genus in the family of Paramyxoviridae. Measles was originally a zoonotic infection, arising from cross-species transmission from animals to humans by an ancestral morbillivirus ~10,000 years ago, when human populations attained sufficient size to sustain virus transmission. Although RNA viruses typically have high mutation rates, measles virus is considered to be an antigenically monotypic virus; i.e., the surface proteins responsible for inducing protective immunity have retained their antigenic structure across time and space. The public health significance of this stability is that measles vaccines developed decades ago from a single strain of measles virus remain protective worldwide. Measles virus is killed by ultraviolet light and heat, and attenuated measles vaccine viruses retain these characteristics, necessitating a cold chain for vaccine transport and storage.

EPIDEMIOLOGY

Measles virus is one of the most highly contagious directly transmitted pathogens. Outbreaks can occur in populations in which <10% of persons are susceptible. Chains of transmission are common among household contacts, school-age children, and health care workers. There are no latent or persistent measles virus infections that result in prolonged contagiousness, nor are there animal reservoirs for the virus. Thus, measles virus can be maintained in human populations only by an unbroken chain of acute infections, which requires a continuous supply of susceptible individuals. Newborns become susceptible to measles virus infection when passively acquired maternal antibody is lost and, when not vaccinated, account for the bulk of new susceptible individuals.

Endemic measles has a typical temporal pattern characterized by yearly seasonal epidemics superimposed on longer epidemic cycles of 2–5 years or more. In temperate climates, annual measles outbreaks typically occur

in the late winter and early spring. These annual outbreaks are probably attributable to social networks facilitating transmission (e.g., congregation of children at school) and environmental factors favoring the viability and transmission of measles virus. Measles cases continue to occur during interepidemic periods in large populations, but at low incidence. The longer cycles occurring every several years result from the accumulation of susceptible persons over successive birth cohorts and the subsequent decline in the number of susceptibles following an outbreak.

Secondary attack rates in susceptible household and institutional contacts generally exceed 90%. The average age at which measles occurs depends on rates of contact with infected persons, protective maternal antibody decline, and vaccine coverage. In densely populated urban settings with low vaccination coverage, measles is a disease of infants and young children. The cumulative distribution can reach 50% by 1 year of age, with a significant proportion of children acquiring measles before 9 months—the age of routine vaccination in many countries, in line with the schedule recommended by the Expanded Programme on Immunization. As measles vaccine coverage increases or population density decreases, the age distribution shifts toward older children. In such situations, measles cases predominate in school-age children. Infants and young children, although susceptible if not protected by vaccination, are not exposed to measles virus at a rate sufficient to cause a large disease burden in this age group. As vaccination coverage increases further, the age distribution of cases may be shifted into adolescence and adulthood; this distribution is seen in measles outbreaks in the United States and necessitates targeted measles vaccination programs for these older age groups.

Persons with measles are infectious for several days before and after the onset of rash, when levels of measles virus in blood and body fluids are highest and when cough, coryza, and sneezing, which facilitate virus spread, are most severe. The contagiousness of measles before the onset of recognizable disease hinders the effectiveness of quarantine measures. Measles virus can be isolated from urine as late as 1 week after rash onset, and viral shedding by children with impaired cell-mediated immunity can be prolonged.

Medical settings are well-recognized sites of measles virus transmission. Children may present to health care facilities during the prodrome, when the diagnosis is not obvious although the child is infectious and is likely to infect susceptible contacts. Health care workers can acquire measles from infected children and transmit measles virus to others. Nosocomial transmission can be reduced by maintenance of a high index of clinical suspicion, use of appropriate isolation precautions when measles is suspected, administration of measles vaccine to susceptible children and health care workers, and documentation of health care workers' immunity to measles (i.e., proof of receipt of two doses of measles vaccine or detection of antibodies to measles virus).

As efforts at measles control are increasingly successful, public perceptions of the risk of measles as a disease diminish and are replaced by concerns about possible adverse events associated with measles vaccine. As a consequence, numerous measles outbreaks have occurred because of opposition to vaccination on religious or philosophical grounds or unfounded fears of serious adverse events (see "Active Immunization," later).

PATHOGENESIS

Measles virus is transmitted primarily by respiratory droplets over short distances and, less commonly, by small-particle aerosols that remain suspended in the air for long periods. Airborne transmission appears to be important in certain settings, including schools, physicians' offices, hospitals, and enclosed public places. The virus can be transmitted by direct contact with infected secretions but does not survive for long on fomites.

The incubation period for measles is ~10 days to fever onset and 14 days to rash onset. This period may be shorter in infants and longer (up to 3 weeks) in adults. Infection is initiated when measles virus is deposited on epithelial cells in the respiratory tract, oropharynx, or conjunctivae **(Fig. 98-1*A*)**. During the first 2–4 days after infection, measles virus proliferates locally in the respiratory mucosa and spreads to draining lymph nodes. Virus then enters the bloodstream in infected leukocytes (primarily monocytes), producing the primary viremia that disseminates infection throughout the reticuloendothelial system. Further replication results in secondary viremia that begins 5–7 days after infection and disseminates measles virus throughout the body. Replication of measles virus in these target organs, together with the host's immune response, is responsible for the signs and symptoms of measles that occur 8–12 days after infection and mark the end of the incubation period (Fig. 98-1*B*).

IMMUNE RESPONSES

Host immune responses to measles virus are essential for viral clearance, clinical recovery, and the establishment of long-term immunity (Fig. 98-1*C*). Early nonspecific (innate) immune responses during the prodromal phase include activation of natural killer (NK) cells and increased production of the antiviral proteins interferon (IFN) α and IFN-γ. The adaptive immune responses consist of measles virus–specific antibody and cellular responses. The protective efficacy of antibodies to measles virus is illustrated by the immunity conferred to infants from passively acquired maternal antibodies and the protection of exposed, susceptible individuals after administration of anti–measles virus immunoglobulin. The first measles virus–specific antibodies produced after infection are of the IgM subtype, with a subsequent

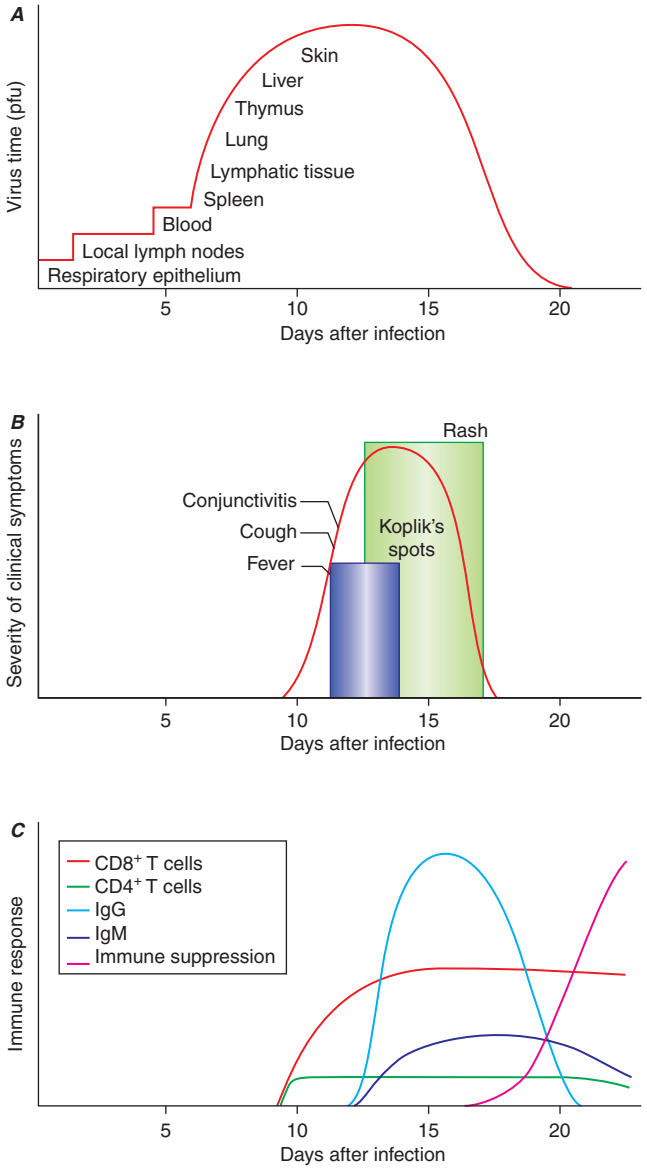


FIGURE 98-1

Measles virus infection: pathogenesis, clinical features, and immune responses. *A*: Spread of measles virus, from initial infection of the respiratory tract through dissemination to the skin. ***B*:** Appearance of clinical signs and symptoms, including Koplik's spots and rash. ***C*:** Antibody and T cell responses to measles virus. The signs and symptoms of measles arise coincident with the host immune response. (*Source: WJ Moss, DE Griffin: Nat Rev Microbiol 4:900, 2006.*)

switch to predominantly IgG1 and IgG4 isotypes. The IgM antibody response is typically absent following reexposure or revaccination and serves as a marker of primary infection.

The importance of cellular immunity to measles virus is demonstrated by the ability of children with agammaglobulinemia (congenital inability to produce antibodies) to recover fully from measles and the contrasting picture for children with severe defects in T lymphocyte function, who often develop severe or fatal disease. The initial predominant T_H1 response (characterized by IFN-γ) is essential for viral clearance, and the later T_H2 response (characterized by interleukin 4) promotes the development of measles virus–specific antibodies that are critical for protection against reinfection.

The duration of protective immunity following wild-type measles virus infection is generally thought to be lifelong. Immunologic memory to measles virus includes both continued production of measles virus–specific antibodies and circulation of measles virus–specific $CD4^+$ and $CD8^+$ T lymphocytes.

However, the intense immune responses induced by measles virus infection are paradoxically associated with depressed responses to unrelated (nonmeasles virus) antigens, which persist for several weeks to months beyond resolution of the acute illness. This state of immune suppression enhances susceptibility to secondary infections with bacteria and viruses that cause pneumonia and diarrhea and is responsible for a substantial proportion of measles-related morbidity and deaths. Delayed-type hypersensitivity responses to recall antigens, such as tuberculin, are suppressed, and cellular and humoral responses to new antigens are impaired. Reactivation of tuberculosis and remission of autoimmune diseases after measles have been described and are attributed to this state of immune suppression.

APPROACH TO THE PATIENT **Measles**

Clinicians should consider measles in persons presenting with fever and generalized rash, particularly when measles virus is known to be circulating or the patient has a history of travel to endemic areas. Appropriate precautions need to be taken to prevent nosocomial transmission. The diagnosis requires laboratory confirmation except during large outbreaks in which an epidemiologic link to a confirmed case can be established. Care is largely supportive and consists of the administration of vitamin A and antibiotics (see "Treatment," later in the chapter). Complications of measles, including secondary bacterial infections and encephalitis, may occur after acute illness and require careful monitoring, particularly in immunocompromised persons.

CLINICAL MANIFESTATIONS

In most persons, the signs and symptoms of measles are highly characteristic (Fig. 98-1B). Fever and malaise beginning ~10 days after exposure are followed by cough, coryza, and conjunctivitis. These signs and symptoms increase in severity over 4 days. Koplik's spots (see Fig. 11-2) develop on the buccal mucosa ~2 days before the rash appears. The characteristic rash of measles (see Fig. 11-3) begins 2 weeks after infection, when the clinical manifestations are most severe, and signal the host's immune response to the replicating virus. Headache, abdominal pain, vomiting, diarrhea, and myalgia may be present.

Koplik's spots (Fig. 11-2) are pathognomonic of measles and consist of bluish white dots ~1 mm in diameter surrounded by erythema. The lesions appear first on the buccal mucosa opposite the lower molars but rapidly increase in number to involve the entire buccal mucosa. They fade with the onset of rash.

The rash of measles begins as erythematous macules behind the ears and on the neck and hairline. The rash progresses to involve the face, trunk, and arms (Fig. 11-3), with involvement of the legs and feet by the end of the second day. Areas of confluent rash appear on the trunk and extremities, and petechiae may be present. The rash fades slowly in the same order of progression as it appeared, usually beginning on the third or fourth day after onset. Resolution of the rash may be followed by desquamation.

Because the characteristic rash of measles is a consequence of the cellular immune response, it may not develop in persons with impaired cellular immunity (e.g., those with AIDS; Chap. 93). These persons have a high case-fatality rate and frequently develop giant-cell pneumonitis caused by measles virus. T lymphocyte defects due to causes other than HIV-1 infection (e.g., cancer chemotherapy) also are associated with increased severity of measles.

A severe atypical measles syndrome was observed in recipients of a formalin-inactivated measles vaccine (used in the United States from 1963 to 1967 and in Canada until 1970) who were subsequently exposed to wild-type measles virus. The atypical rash began on the palms and soles and spread centripetally to the proximal extremities and trunk, sparing the face. The rash was initially erythematous and maculopapular but frequently progressed to vesicular, petechial, or purpuric lesions (see Fig. 11-22).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of measles includes other causes of fever, rash, and conjunctivitis, including rubella, Kawasaki disease, infectious mononucleosis, roseola, scarlet fever, Rocky Mountain spotted fever, enterovirus or adenovirus infection, and drug sensitivity. Rubella is a milder illness without cough and with distinctive lymphadenopathy. The rash of roseola (exanthem subitum) appears after fever has subsided. The atypical lymphocytosis in infectious mononucleosis contrasts with the leukopenia commonly observed in children with measles.

DIAGNOSIS

Measles is readily diagnosed on clinical grounds by clinicians familiar with the disease, particularly during outbreaks. Koplik's spots (Fig. 11-2) are especially helpful because they appear early and are pathognomonic. Clinical diagnosis is more difficult (1) during the prodromal illness; (2) when the rash is attenuated by passively acquired antibodies or prior immunization; (3) when the rash is absent or delayed in immunocompromised or severely malnourished children with impaired cellular immunity; and (4) in regions where the incidence of measles is low and other pathogens are responsible for the majority of illnesses with fever and rash. The Centers for Disease Control and Prevention case definition for measles requires (1) a generalized maculopapular rash of at least 3 days' duration; (2) fever of at least 38.3°C (101°F); and (3) cough, coryza, or conjunctivitis.

Serology is the most common method of laboratory diagnosis. The detection of measles virus–specific IgM in a single specimen of serum or oral fluid is considered diagnostic of acute infection, as is a fourfold or greater increase in measles virus–specific IgG antibody levels between acute- and convalescent-phase serum specimens. Primary infection in the immunocompetent host results in antibodies that are detectable within 1–3 days of rash onset and reach peak levels in 2–4 weeks. Measles virus–specific IgM antibodies may not be detectable until 4–5 days or more after rash onset and usually fall to undetectable levels within 4–8 weeks of rash onset.

Several methods for measurement of antibodies to measles virus are available. Neutralization tests are sensitive and specific, and the results are highly correlated with protective immunity; however, these tests require propagation of measles virus in cell culture and thus are expensive and laborious. Commercially available enzyme immunoassays are most frequently used. Measles also can be diagnosed by isolation of the virus in cell culture from respiratory secretions, nasopharyngeal or conjunctival swabs, blood, or urine. Direct detection of giant cells in respiratory secretions, urine, or tissue obtained by biopsy provides another method of diagnosis.

For detection of measles virus RNA by reverse-transcriptase polymerase chain reaction (RT-PCR) amplification of RNA extracted from clinical specimens, primers targeted to highly conserved regions of measles virus genes are used. Extremely sensitive and specific, RT-PCR assays may also permit identification and characterization of measles virus genotypes for molecular epidemiologic studies and can distinguish wild-type from vaccine virus strains.

TREATMENT Measles

There is no specific antiviral therapy for measles. Treatment consists of general supportive measures, such as hydration and administration of antipyretic agents. Because secondary bacterial infections are a major cause of morbidity and death following measles, effective case management involves prompt antibiotic treatment for patients who have clinical evidence of bacterial infection, including pneumonia and otitis media. *Streptococcus pneumoniae* and *Haemophilus influenzae* type b are common causes of bacterial pneumonia following measles; vaccines against these pathogens probably lower the incidence of secondary bacterial infections following measles.

Vitamin A is effective for the treatment of measles and can markedly reduce rates of morbidity and mortality. The World Health Organization recommends administration of once-daily doses of 200,000 IU of vitamin A

for 2 consecutive days to all children with measles who are ≥12 months of age. Lower doses are recommended for younger children: 100,000 IU per day for children 6–12 months of age and 50,000 IU per day for children <6 months old. A third dose is recommended 2–4 weeks later for children with evidence of vitamin A deficiency. While such deficiency is not a widely recognized problem in the United States, many American children with measles do, in fact, have low serum levels of vitamin A, and these children experience increased morbidity following measles. The Committee on Infectious Diseases of the American Academy of Pediatrics recommends that the administration of two consecutive daily doses of vitamin A be considered for children hospitalized with measles and its complications as well as for children with measles who are immunodeficient; who have ophthalmologic evidence of vitamin A deficiency, impaired intestinal absorption, or moderate to severe malnutrition; or who have recently immigrated from areas with high measles mortality rates. Parenteral and oral formulations of vitamin A are available.

Anecdotal reports have described the recovery of previously healthy pregnant and immunocompromised patients with measles pneumonia and of immunocompromised patients with measles encephalitis after treatment with aerosolized and IV ribavirin. However, the clinical benefits of ribavirin in persons with measles have not been conclusively demonstrated in clinical trials.

COMPLICATIONS

Most complications of measles involve the respiratory tract and include the effects of measles virus replication itself and secondary bacterial infections. Acute laryngotracheobronchitis (croup) can occur during measles and may result in airway obstruction, particularly in young children. Giant-cell pneumonitis due to replication of measles virus in the lungs can develop in immunocompromised children, including those with HIV-1 infection. Many children with measles develop diarrhea, which contributes to malnutrition.

Most complications of measles result from secondary bacterial infections of the respiratory tract that are attributable to a state of immune suppression lasting for several weeks to months after acute measles. Otitis media and bronchopneumonia are most common and may be caused by *S. pneumoniae*, *H. influenzae* type b, or staphylococci. Recurrence of fever or failure of fever to subside with the rash suggests secondary bacterial infection.

Rare but serious complications of measles involve the central nervous system (CNS). Postmeasles encephalomyelitis complicates ~1 in 1000 cases, affecting mainly older children and adults. Encephalomyelitis occurs within 2 weeks of rash onset and is characterized by fever, seizures, and a variety of neurologic abnormalities. The finding of periventricular demyelination, the induction of immune responses to myelin basic protein, and the absence of measles virus in the brain suggest that postmeasles encephalomyelitis is an autoimmune disorder triggered by measles virus infection. Other CNS complications that occur months to years after acute infection are measles inclusion body encephalitis (MIBE) and subacute sclerosing panencephalitis (SSPE). In contrast to postmeasles encephalomyelitis, MIBE and SSPE are caused by persistent measles virus infection. MIBE is a rare but fatal complication that affects individuals with defective cellular immunity and typically occurs months after infection. SSPE is a slowly progressive disease characterized by seizures and progressive deterioration of cognitive and motor functions, with death occurring 5–15 years after measles virus infection. SSPE most often develops in persons infected with measles virus at <2 years of age.

PROGNOSIS

Most persons with measles recover and develop long-term protective immunity to reinfection. Measles case-fatality proportions vary with the average age of infection, the nutritional and immunologic status of the population, measles vaccine coverage, and access to health care. Among previously vaccinated persons who do become infected, disease is less severe and mortality rates are significantly lower. In developed countries, <1 in 1000 children with measles die. In endemic areas of sub-Saharan Africa, the measles case-fatality proportion may be 5–10% or even higher. Measles is a major cause of childhood deaths in refugee camps and in internally displaced populations, where case-fatality proportions have been as high as 20–30%.

PREVENTION

Passive immunization

Human immunoglobulin given shortly after exposure can attenuate the clinical course of measles. In immunocompetent persons, administration of immunoglobulin within 72 h of exposure usually prevents measles virus infection and almost always prevents clinical measles. Administered up to 6 days after exposure, immunoglobulin will still prevent or modify the disease. Prophylaxis with immunoglobulin is recommended for susceptible household and nosocomial contacts who are at risk of developing severe measles, particularly children <1 year of age, immunocompromised persons (including HIV-infected persons previously immunized with live attenuated measles vaccine), and pregnant women. Except for premature infants, children <6 months of age usually will be partially or completely protected by passively acquired maternal antibody. If measles is diagnosed in a mother, all unimmunized children in the household should receive immunoglobulin. The recommended dose is 0.25 mL/kg given intramuscularly. Immunocompromised persons should receive 0.5 mL/kg. The maximum total dose is 15 mL. IV immunoglobulin contains antibodies to measles virus; the usual dose of 100–400 mg/kg generally provides adequate prophylaxis for measles exposures occurring as long as 3 weeks or more after IV immunoglobulin administration.

Active immunization

The first live attenuated measles vaccine was developed by passage of the Edmonston strain in chick embryo fibroblasts to produce the Edmonston B virus, which was licensed in 1963 in the United States. Further passage of Edmonston B virus produced the more attenuated Schwarz vaccine that currently serves as the standard in much of the world. The Moraten ("more attenuated") strain, which was licensed in 1968 and is used in the United States, is genetically closely related to the Schwarz strain.

Lyophilized measles vaccines are relatively stable, but reconstituted vaccine rapidly loses potency. Live attenuated measles vaccines are inactivated by light and heat and lose about half their potency at 20°C and almost all their potency at 37°C within 1 h after reconstitution. Therefore, a cold chain must be maintained before and after reconstitution. Antibodies first appear 12–15 days after vaccination and peak at 1–3 months. Measles vaccines are often combined with other live attenuated virus vaccines, such as those for mumps and rubella (MMR) and for mumps, rubella, and varicella (MMR-V).

The recommended age of first vaccination varies from 6 to 15 months and represents a balance between the optimal age for seroconversion and the probability of acquiring measles before that age. The proportions of children who develop protective levels of antibody after measles vaccination approximate 85% at 9 months of age and 95% at 12 months. Common childhood illnesses concomitant with vaccination may reduce the level of immune response, but such illness is not a valid reason to withhold vaccination. Measles vaccines have been well tolerated and immunogenic in HIV-1-infected children and adults, although antibody levels may wane. Because of the potential severity of wild-type measles virus infection in HIV-1-infected children, routine measles vaccination is recommended except for those who are severely immunocompromised. Measles vaccination is contraindicated in individuals with other severe deficiencies of cellular immunity because of the possibility of disease due to progressive pulmonary or CNS infection with the vaccine virus.

The duration of vaccine-induced immunity is at least several decades if not longer. Rates of secondary vaccine failure 10–15 years after immunization have been estimated at ~5% but are probably lower when the vaccination is given after 12 months of age. Decreasing antibody concentrations do not necessarily imply a complete loss of protective immunity: a secondary immune response usually develops after reexposure to measles virus, with a rapid rise in antibody titers in the absence of overt clinical disease.

Standard doses of currently licensed measles vaccines are safe for immunocompetent children and adults. Fever to 39.4°C (103°F) occurs in ~5% of seronegative vaccine recipients, and 2% of vaccine recipients develop a transient rash. Mild transient thrombocytopenia has been reported, with an incidence of ~1 case per 40,000 doses of MMR vaccine.

Since the publication of a report in 1998 hypothesizing that MMR vaccine may cause a syndrome of autism and intestinal inflammation, much public attention has focused on this purported association. The events that followed publication of this report led to diminished vaccine coverage in the United Kingdom and provide important lessons in the misinterpretation of epidemiologic evidence and the communication of scientific results to the public. The publication that incited the concern was a case series describing 12 children with a regressive developmental disorder and chronic enterocolitis; 9 of these children had autism. In 8 of the 12 cases, the parents associated onset of the developmental delay with MMR vaccination. This simple temporal association was misinterpreted and misrepresented as a possible causal relationship, first by the lead author of the study and then by elements of the media and the public. Subsequently, several comprehensive reviews and additional epidemiologic studies refuted evidence of a causal relationship between MMR vaccination and autism.

PROSPECTS FOR MEASLES ERADICATION

Progress in global measles control has renewed discussion of measles eradication. In contrast to poliovirus eradication, the eradication of measles virus will not entail challenges posed by prolonged shedding of potentially virulent vaccine viruses and environmental viral reservoirs. However, in comparison with smallpox eradication, higher levels of population immunity will be necessary to interrupt measles virus transmission, more highly skilled health care workers will be required to administer measles vaccines, and containment through case detection and ring vaccination will be more difficult for measles virus because of infectivity before rash onset. New tools, such as aerosol administration of measles vaccines, will facilitate mass vaccination campaigns. Despite enormous progress, measles remains a leading vaccine-preventable cause of childhood mortality worldwide and continues to cause outbreaks in communities with low vaccination coverage rates in industrialized nations.

CHAPTER 99

RUBELLA (GERMAN MEASLES)

Laura A. Zimmerman ■ Susan E. Reef

Rubella was historically viewed as a variant of measles or scarlet fever. Not until the mid-1900s was a separate viral agent for rubella isolated. After an epidemic of rubella in Australia in the early 1940s, the ophthalmologist Norman Gregg noticed the occurrence of congenital cataracts among infants whose mothers had reported rubella infection during early pregnancy, and congenital rubella syndrome (CRS) was first described.

ETIOLOGY

Rubella virus is a member of the Togaviridae family and the only member of the genus *Rubivirus*. This single-stranded RNA enveloped virus measures 50–70 nm in diameter. Its core protein is surrounded by a single-layer lipoprotein envelope with spike-like projections containing two glycoproteins, E1 and E2. There is only one antigenic type of rubella virus, and humans are its only known reservoir.

PATHOGENESIS AND PATHOLOGY

Although the pathogenesis of postnatal (acquired) rubella has been well documented, data on pathology are limited because of the mildness of the disease. Rubella virus is spread from person to person via respiratory droplets. Primary implantation and replication in the nasopharynx are followed by spread to the lymph nodes. Subsequent viremia occurs, which in pregnant women often results in infection of the placenta. Placental virus replication may lead to infection of fetal organs. The pathology of CRS in the infected fetus is well defined, with almost all organs found to be infected; however, the pathogenesis of CRS is only poorly delineated. In tissue, infections with rubella virus have diverse effects, ranging from no obvious impact to cell destruction. The hallmark of fetal infection is chronicity, with persistence throughout fetal development in utero and for up to 1 year after birth.

Individuals with acquired rubella may shed virus from 7 days before rash onset to ~5–7 days thereafter. Both clinical and subclinical infections are considered contagious. Infants with CRS may shed large quantities of virus from bodily secretions, particularly from the throat and in the urine, up to 1 year of age. Outbreaks of rubella, including some in nosocomial settings, have originated with index cases of CRS. Thus, only individuals immune to rubella should have contact with infants who have CRS or who are congenitally infected with rubella virus but are not showing signs of CRS.

EPIDEMIOLOGY

The largest recent rubella epidemic in the United States took place in 1964–1965, when an estimated 12.5 million cases occurred, resulting in ~20,000 cases of CRS. Since the introduction of the routine rubella vaccination program in the United States in 1969, the number of rubella cases reported each year has dropped by >99%; the rate of vaccination coverage with rubella-containing vaccine has been >90% among children 19–35 months old since 1995 and >95% for kindergarten and first-grade entrants since 1980. In 1989 a goal for the elimination of rubella and CRS in the United States was set, and in 2004 a panel of experts agreed unanimously that rubella was no longer an endemic disease in this country. The criteria used to document lack of endemic transmission included low disease incidence, high nationwide rubella antibody seroprevalence, outbreaks that were few and contained (i.e., small numbers of cases), and lack of endemic virus transmission (as assessed by genetic sequencing). In the United States, interruption of endemic transmission of rubella virus has been sustained since 2001.

Although rubella and CRS are no longer endemic in the United States, they remain important public health problems globally. The number of rubella cases reported worldwide in 1999 was ~900,000; this figure declined steadily to 165,000 in 2007. However, numbers of rubella cases are substantially underestimated because cases in many countries are identified through measles surveillance systems that are not specific for rubella. In developing countries, an estimated 110,000 cases of CRS occur during nonepidemic years.

CLINICAL FEATURES

Acquired rubella

Acquired rubella is characterized by a generalized maculopapular rash that usually lasts for up to 3 days **(Fig. 99-1)**. Up to 50% of rubella virus infections may be subclinical or inapparent. The rash is usually mild and may be difficult to detect in persons with darker skin. In children, rash is usually the first sign of illness. However, in older children and adults, a 1- to 5-day prodrome often precedes the rash and may include low-grade fever, malaise, and upper respiratory symptoms. The incubation period is 14 days (range, 12–23 days).

Lymphadenopathy, particularly occipital and postauricular, may be noted during the second week after exposure. Although acquired rubella is usually thought of as a benign disease, arthralgia and arthritis are common in infected adults, particularly women. Thrombocytopenia and encephalitis are less common complications.

Congenital rubella syndrome

The most serious consequence of rubella virus infection can develop when a woman becomes infected during pregnancy, particularly during the first trimester. The resulting complications may include miscarriage, fetal death, premature delivery, or live birth with congenital defects. Infants infected with rubella virus in utero may have a myriad of physical defects **(Table 99-1)**, which most commonly relate to the eyes, ears, and heart.

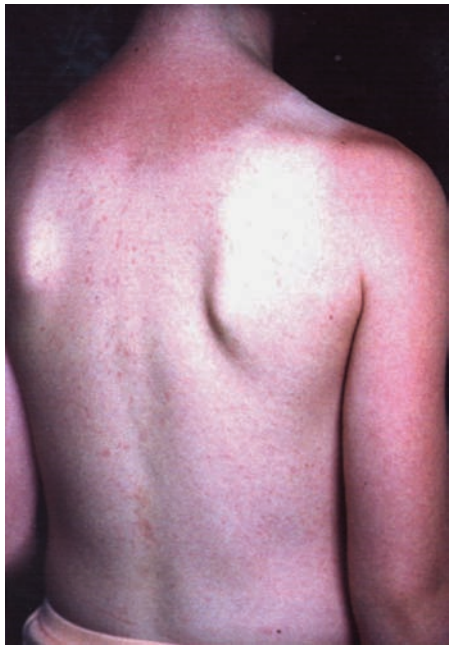


FIGURE 99-1
Mild maculopapular rash of rubella in a child.

TABLE 99-1
COMMON TRANSIENT AND PERMANENT MANIFESTATIONS IN INFANTS WITH CONGENITAL RUBELLA SYNDROME

TRANSIENT MANIFESTATIONS	PERMANENT MANIFESTATIONS
Hepatosplenomegaly	Hearing impairment/ deafness
Interstitial pneumonitis	Congenital heart defects (patent ductus arteriosus, pulmonary arterial stenosis)
Thrombocytopenia with purpura/petechiae (e.g., dermal erythropoiesis, or "blueberry muffin syndrome") Hemolytic anemia Bony radiolucencies	Eye defects (cataracts, cloudy cornea, microphthalmos, pigmentary retinopathy, congenital glaucoma)
Intrauterine growth retardation	Microcephaly
Adenopathy	
Meningoencephalitis	Central nervous system sequelae (mental and motor delay, autism)

This constellation of severe birth defects is known as *congenital rubella syndrome*. In addition to permanent manifestations, there are a host of transient physical manifestations, including thrombocytopenia with purpura/petechiae (e.g., dermal erythropoiesis, "blueberry muffin syndrome"). Some infants may be born with congenital rubella virus infection but have no apparent signs or symptoms of CRS and are referred to as infants with congenital rubella infection only.

DIAGNOSIS

Acquired rubella

Clinical diagnosis of acquired rubella is difficult because of the mimicry of many illnesses with rashes, the varied clinical presentations, and the high rates of subclinical and mild disease. Illnesses that may be similar to rubella in presentation include scarlet fever, roseola, toxoplasmosis, fifth disease, measles, and illnesses with suboccipital and postauricular lymphadenopathy. Thus laboratory documentation of rubella virus infection is considered the only reliable way to confirm acute disease.

Laboratory assessment of rubella infection is conducted by serologic and virologic methods. For acquired rubella, serologic diagnosis is most common and depends on the demonstration of IgM antibodies in an acute-phase serum specimen or a fourfold rise in IgG antibody titer between acute- and convalescent-phase specimens. The enzyme-linked immunosorbent assay IgM capture technique is considered most accurate for serologic

diagnosis, but the indirect IgM assay is also acceptable. After rubella virus infection, IgM antibody may be detectable for up to 6 weeks. In case of a negative result for IgM in specimens taken earlier than day 5 after rash onset, serologic testing should be repeated. Although uncommon, reinfection with rubella virus is possible, and IgM antibodies may be present. To detect a rise in IgG antibody titer indicative of acute disease, the acute-phase serum specimen should be collected within 7–10 days after onset of illness and the convalescent-phase specimen ~14–21 days after the first specimen.

IgG avidity testing is used in conjunction with IgG testing. Low-avidity antibodies indicate recent infection. Mature (high-avidity) IgG antibodies most likely indicate an infection occurring at least 2 months previously. This test helps distinguish primary infection from reinfection.

Rubella virus can be isolated from the blood and nasopharynx during the prodromal period and for as long as 2 weeks after rash onset. However, as the secretion of virus in individuals with acquired rubella is maximal just before or up to 4 days after rash onset, this is the optimal time frame for collecting specimens for viral cultures. Rubella RNA detection by reverse-transcriptase polymerase chain reaction (RT-PCR) is a more recently developed technique for rubella diagnosis.

Congenital rubella syndrome

A clinical diagnosis of CRS is reasonable when an infant presents with a combination of cataracts, hearing impairment, and heart defects; this pattern is seen in ~10% of infants with CRS. However, as with acquired rubella, laboratory diagnosis of congenital infection is highly recommended, particularly because most features of the clinical presentation are nonspecific and may be associated with other intrauterine infections. Early diagnosis of CRS facilitates appropriate medical intervention for specific disabilities and prompts implementation of infection control measures.

Diagnostic tests used to confirm CRS include serologic assays and virus isolation. In an infant with congenital infection, serum IgM antibodies may be present for up to 1 year after birth. In some instances, IgM may not be detectable until 1 month of age; thus infants who have symptoms consistent with CRS but who test negative shortly after birth should be retested at 1 month. A rubella serum IgG titer persisting beyond the time expected after passive transfer of maternal IgG antibody (i.e., a rubella titer that does not decline at the expected rate of a twofold dilution per month) is another serologic criterion used to confirm CRS.

In congenital infection, rubella virus is isolated most commonly from throat swabs and less commonly from urine and cerebrospinal fluid. Infants with congenital rubella may excrete virus for up to 1 year, but specimens for virus isolation are most likely to be positive if obtained within the first 6 months after birth. Rubella virus in infants with CRS can also be detected by RT-PCR.

Rubella diagnosis in pregnant women

In the United States, screening for rubella IgG antibodies is recommended as part of routine prenatal care. Pregnant women with a positive IgG antibody serologic test are considered immune. Susceptible pregnant women should be vaccinated postpartum.

A susceptible pregnant woman exposed to rubella virus should be tested for IgM antibodies and a fourfold rise in IgG antibody titer between acute- and convalescent-phase serum specimens to determine whether she was infected during pregnancy. Pregnant women with evidence of acute infection must be clinically monitored, and gestational age at the time of maternal infection must be determined to assess the possibility of risk to the fetus. Of women infected with rubella virus during the first 11 weeks of gestation, up to 90% deliver an infant with CRS; for maternal infection during the first 20 weeks of pregnancy, the CRS rate is 20%.

TREATMENT **Rubella**

No specific therapy is available for rubella virus infection. Symptom-based treatment for various manifestations, such as fever and arthralgia, is appropriate. Immunoglobulin does not prevent rubella virus infection after exposure and therefore is not recommended as routine postexposure prophylaxis. Although immunoglobulin may modify or suppress symptoms, it can create an unwarranted sense of security: infants with congenital rubella have been born to women who received immunoglobulin shortly after exposure. Administration of immunoglobulin should be considered only if a pregnant woman who has been exposed to rubella will not consider termination of pregnancy under any circumstances. In such cases, IM administration of 20 mL of immunoglobulin within 72 h of rubella exposure may reduce—but does not eliminate—the risk of rubella.

PREVENTION

After the isolation of rubella virus in the early 1960s and the occurrence of a devastating pandemic, a vaccine for rubella was developed and licensed in 1969. Currently, the majority of rubella-containing vaccines (RCVs) used worldwide are combined measles and rubella (MR) or measles, mumps, and rubella (MMR) formulations. A tetravalent measles, mumps, rubella, and varicella (MMRV) vaccine is available but is not widely used.

The public health burden of rubella infection is measured primarily through the resulting CRS cases. The 1964–1965 rubella epidemic in the United States encompassed >30,000 infections during pregnancy. CRS occurred in ~20,000 infants born alive, including >11,000 infants who were deaf, >3500 infants who were blind, and almost 2000 infants who were mentally retarded. The cost of the epidemic exceeded $1.5 billion.

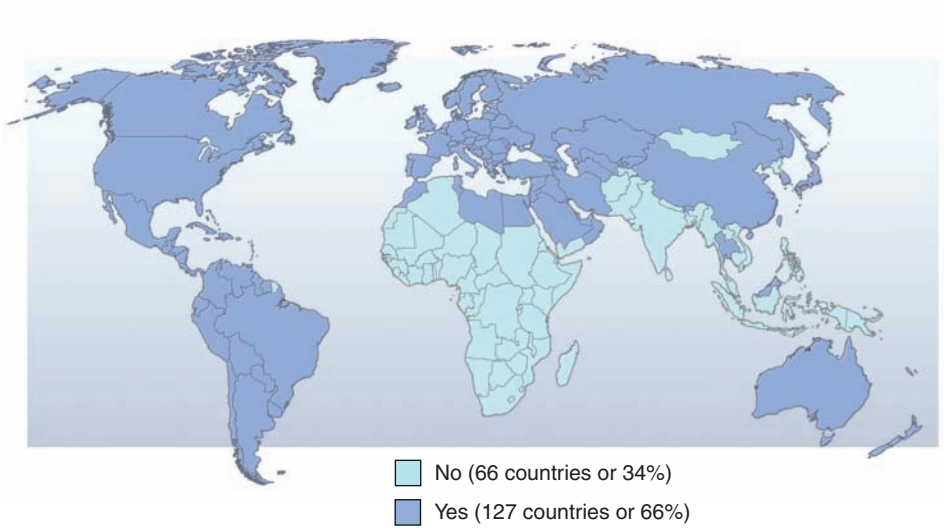


FIGURE 99-2

Countries using rubella vaccine in National Immunization Schedule, 2008. (*From the World Health Organization: Rubella, module 11, in The Immunological Basis for Immunization Series . Geneva, WHO, 2009 [http://www.who.int/immunization/documents/ISBN9789241596848/en/index.html*].)

In 1982, it was estimated that the cost per child with CRS exceeded $200,000.

In most countries, there is little documented evidence to illuminate the epidemiology of CRS. Clusters of CRS cases have been reported in developing countries, and modeling studies have shown that, before the introduction of an immunization program, the incidence of CRS is 0.1–0.2 per 1000 live births during endemic periods and 1–4 per 1000 live births during epidemic periods. Where rubella virus is circulating and women of childbearing age are susceptible, CRS cases will continue to occur.

The most effective method of preventing acquired rubella and CRS is through vaccination with an RCV. One dose induces seroconversion in ≥95% of persons >1 year of age. Immunity is considered long-term and is probably lifelong. The most commonly used vaccine globally is derived from the RA27/3 virus strain. The current recommendation for routine rubella vaccination in the United States is a first dose of MMR vaccine at 12–15 months of age and a second dose at 4–6 years. Target groups for rubella vaccine in all countries include children >1 year of age, adolescents and adults without documented evidence of immunity, individuals in congregate settings (e.g., college students, military personnel, child care and health care workers), and susceptible women before and after pregnancy.

Because of the theoretical risk of transmission of live attenuated rubella vaccine virus to the developing fetus, women known to be pregnant should not receive an RCV. In addition, pregnancy should be avoided for 28 days after receipt of an RCV. In follow-up studies of 680 unknowingly pregnant women who received rubella vaccine, no infant was born with CRS. Receipt of an RCV during pregnancy is not ordinarily a reason to consider termination of the pregnancy.

As of 2008, 127 (66%) of the 193 WHO member countries recommended inclusion of an RCV in the routine childhood vaccination schedule **(Fig. 99-2)**. Vaccination coverage varies widely among the member countries, with the European and American Regions reporting coverage of >90%. Goals for control or elimination of rubella and CRS have been established in the American Region, the European Region, and the Western Pacific Region. The other three regions (Eastern Mediterranean, South East Asian, and African) have not yet set such goals.

CHAPTER 100

MUMPS

Steven Rubin ■ Kathryn M. Carbone

DEFINITION

Mumps is an acute, systemic viral infection classically associated with swelling of one or both parotid glands.

ETIOLOGIC AGENT

Mumps is caused by a paramyxovirus with a negative-strand nonsegmented RNA genome of 15,384 bases encoding nine proteins. The nucleoprotein, phosphoprotein, and polymerase protein participate in viral replication and, together with genomic RNA, form the ribonucleocapsid. The ribonucleocapsid is surrounded by a host-derived lipid bilayer envelope containing the viral hemagglutinin-neuraminidase (HN) and fusion (F) proteins, which are responsible for cell binding by and entry of the virus and are major targets of virus-neutralizing antibodies. The functions of the other virus proteins (small-hydrophobic, matrix, V, and I) are less well understood. The small-hydrophobic gene sequence is highly variable and forms the basis for the 13 genotypes (A through M) used mainly for molecular epidemiologic purposes.

EPIDEMIOLOGY

Mumps is endemic worldwide, with epidemics occurring every 3–5 years in unvaccinated populations. The estimated annual global incidence is 100–1000 cases per 100,000 population in countries without national mumps vaccination programs, where virtually the entire population has been infected by adulthood. Following the 1967 introduction of mumps vaccine in the United States, the reported number of cases declined; by 2001, this number had decreased from >150,000 to <300—a 99.8% reduction from prevaccine levels. In 2006, the United States experienced its largest mumps outbreak in more than 20 years, with 6584 reported cases. This outbreak was preceded by outbreaks in the United Kingdom (2004–2005) and followed by outbreaks in Canada. Compelling epidemiologic evidence links the genotype G virus to the outbreaks in all three countries. The majority of cases occurred in college students 18–23 years of age, most of whom had been vaccinated in early childhood. These outbreaks are probably the result of several coincident circumstances, including (1) situations promoting the spread of respiratory viruses among young adults (e.g., residence in college dormitories), (2) waning of vaccine immunity with time, (3) lack of endemically circulating wild-type virus to periodically boost vaccine-induced immune responses, and (4) continuing global epidemics of mumps (due either to lack of mumps vaccination programs or to low rates of mumps vaccination where such programs do exist). Whereas in the pre- and early postvaccine era mumps was historically a disease of childhood, the majority of U.S. cases now occur in previously vaccinated young adults.

PATHOGENESIS

Humans are the only natural hosts for mumps virus infection. The incubation period of mumps is ~19 days (range, 7–23 days). The virus is transmitted by the respiratory route via droplets, saliva, and fomites. Mumps virus is typically shed from 1 week before to 1 week after symptom onset, although this window appears to be narrower in vaccinated individuals. Persons are most contagious 1–2 days before onset of clinical symptoms. Primary replication occurs in the nasal mucosa or upper respiratory mucosal epithelium. Mononuclear cells and cells within regional lymph nodes can become infected; such infection facilitates the development of viremia and poses a risk for a wide array of acute inflammatory reactions. Classic sites of mumps virus replication include the salivary glands, testes, pancreas, ovaries, mammary glands, and central nervous system (CNS).

Little is known of the pathology of mumps since the disease is rarely fatal. The virus replicates well in glandular epithelium, but classic parotitis is not a necessary component of mumps infection. Affected glands contain perivascular and interstitial mononuclear cell infiltrates and exhibit hemorrhage with prominent edema.

Necrosis of acinar and epithelial duct cells is evident in the salivary glands and in the germinal epithelium of the seminiferous tubules of the testes. The virus probably enters cerebrospinal fluid (CSF) through the choroid plexus or via transiting mononuclear cells during plasma viremia. Although relevant data are limited, typical mumps encephalitis appears to be secondary to respiratory spread and is probably a parainfectious process, as suggested by perivenous demyelination, perivascular mononuclear cell inflammation, and relative sparing of neurons. Although rare, presumed primary encephalitis has been associated with mumps virus isolation from brain tissue. Evidence of placental and intrauterine spread in pregnancy has been found in both early and late gestation.

CLINICAL MANIFESTATIONS

Up to half of mumps virus infections are asymptomatic or lead to nonspecific respiratory symptoms. Inapparent infections are more common in adults than in children. The prodrome of mumps consists of low-grade fever, malaise, myalgia, headache, and anorexia. Mumps parotitis—acute-onset unilateral or bilateral swelling of the parotid or other salivary glands lasting >2 days without another apparent cause—develops in 70–90% of symptomatic infections, usually within 24 h of prodromal symptoms but sometimes as long as 1 week thereafter. Parotitis is generally bilateral, although the two sides may not be involved synchronously. Unilateral involvement is documented in about one-third of cases. Swelling of the parotid is accompanied by tenderness and obliteration of the space between the earlobe and the angle of the mandible **(Figs. 100-1 and 100-2)**. The patient frequently reports an earache and finds it difficult to eat, swallow, or talk. The orifice of Stensen's duct is commonly red and swollen. The submaxillary and sublingual glands are involved less often than the parotid gland and are almost never involved alone. Glandular swelling increases for a few days and then gradually subsides, disappearing within 1 week. Recurrent sialadenitis is a rare sequela of mumps parotitis. In ~6% of mumps cases, obstruction of lymphatic drainage secondary to bilateral salivary gland swelling may lead to presternal pitting edema, associated often with submandibular adenitis and rarely with the more life-threatening supraglottic edema.

Epididymo-orchitis is the next most common manifestation of mumps, developing in 15–30% of cases in postpubertal males, with bilateral involvement in 10–30% of those cases. Orchitis, accompanied by fever, typically occurs during the first week of parotitis but can develop up to 6 weeks after parotitis or in its absence. The testis is painful and tender and can be enlarged to several times its normal size; this condition usually resolves within 1 week. Testicular atrophy develops in one-half of affected men. Sterility after mumps is rare, although subfertility is estimated to occur in 13% of cases of unilateral orchitis and in 30–87% of cases of bilateral orchitis. Oophoritis occurs in ~5% of women with mumps and may be associated with lower abdominal pain and vomiting but has only rarely been associated with sterility or premature menopause. Mumps infection in postpubertal women may also present with mastitis.

Documented CSF pleocytosis indicates that mumps virus invades the CNS in ~50% of cases; however, symptomatic CNS disease, typically in the form of aseptic meningitis, occurs in <10% of cases, with a male predominance. CNS symptoms of aseptic meningitis (e.g., stiff neck, headache, and drowsiness) appear ~5 days after parotitis and also occur often in the absence of parotid involvement. Within the first 24 h polymorphonuclear leukocytes may predominate in CSF (1000–2000 cells/μL), but by the second day

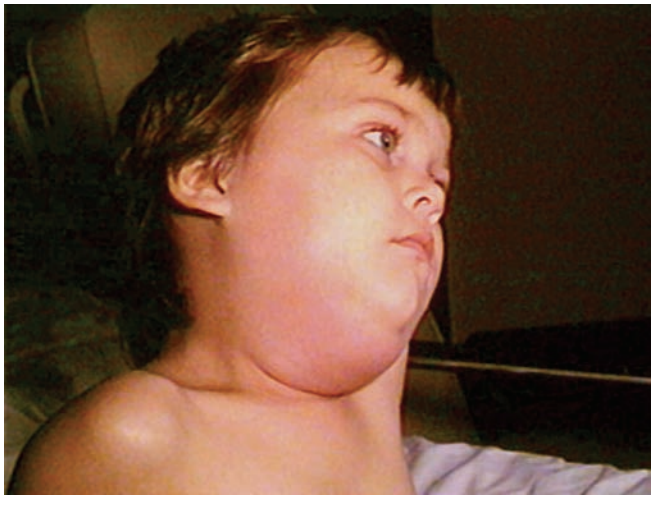


FIGURE 100-1
Child with mumps. Note the classic submandibular and preauricular enlargement of the parotid gland. (*From the Centers for Disease Control and Prevention.*)

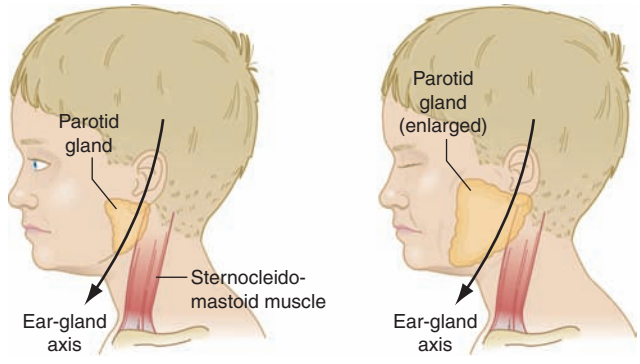


FIGURE 100-2
Schematic drawing of a parotid gland infected with mumps virus (*right*) compared with a normal gland (*left*). An enlarged cervical lymph node is usually posterior to the imaginary line. (*Reprinted with permission from A Gershon et al: Mumps, in* Krugman's Infectious Diseases of Children, *11th ed. Philadelphia, Elsevier, 2004, p 392.*)

nearly all the cells are lymphocytes. The glucose level in CSF may be low and the protein concentration high, a pattern reminiscent of bacterial meningitis. Mumps meningitis is a self-limited manifestation without significant risk of death or long-term sequelae. Cranial nerve palsies have occasionally led to permanent sequelae, particularly deafness. The reported incidence of mumps-associated hearing loss varies between 1 in 1000 and 1 in 100,000. In ~0.1% of infections, mumps virus may cause encephalitis, which presents as high fever with marked changes in the level of consciousness, seizures, and focal neurologic symptoms. Electroencephalographic abnormalities may be seen. Permanent sequelae are sometimes identified in survivors, and adult infections more commonly have poor outcomes than do pediatric infections. The mortality rate associated with mumps encephalitis is ~1.5%. Other CNS problems occasionally associated with mumps include cerebellar ataxia, facial palsy, transverse myelitis, hydrocephalus, Guillain-Barré syndrome, flaccid paralysis, and behavioral changes.

Mumps pancreatitis, which may present as abdominal pain, occurs in ~4% of infections but is difficult to diagnose because an elevated serum amylase level can be associated with either parotitis or pancreatitis. An etiologic association of mumps virus and juvenile diabetes mellitus remains controversial. Myocarditis and endocardial fibroelastosis are rare and self-limited but may represent severe complications of mumps infection; however, mumps-associated electrocardiographic abnormalities have been reported in up to 15% of cases. Other unusual complications include thyroiditis, nephritis, arthritis, hepatic disease, keratouveitis, and thrombocytopenic purpura. Abnormal renal function is common, but severe, life-threatening nephritis is rare. It remains at issue whether an excessive number of spontaneous abortions are associated with gestational mumps. Mumps in pregnancy does not appear to lead to premature birth, low birth weight, or fetal malformations.

DIFFERENTIAL DIAGNOSIS

During a mumps outbreak, the diagnosis is made easily in patients with parotitis and a history of recent exposure; however, when disease incidence is low, other causes of parotitis should be considered and laboratory testing is required for case confirmation. Infectious causes of parotitis include other viruses (e.g., HIV, coxsackievirus, parainfluenza virus type 3, influenza A virus, Epstein-Barr virus, adenovirus, parvovirus B19, lymphocytic choriomeningitis virus, human herpesvirus 6), gram-positive bacteria, atypical mycobacteria, and *Bartonella* species. Rarely, other gram-negative or anaerobic bacteria are associated with parotitis. Parotitis can also develop in the setting of sarcoidosis, Sjögren's syndrome, Mikulicz's syndrome, Parinaud's syndrome, uremia, diabetes mellitus, laundry starch ingestion, malnutrition, cirrhosis, and some drug treatments. Unilateral parotitis can be caused by ductal obstruction, cysts, and tumors. In the absence of parotitis or other salivary gland enlargement, symptoms of other visceral organ and/or CNS involvement may predominate, and a laboratory diagnosis is required. Other entities should be considered when manifestations consistent with mumps appear in organs other than the parotid. Testicular torsion may produce a painful scrotal mass resembling that seen in mumps orchitis. Other viruses (e.g., enteroviruses) may cause aseptic meningitis that is clinically indistinguishable from that due to mumps virus.

LABORATORY DIAGNOSIS

Laboratory diagnosis is based on detection of viral antigens or RNA or on serology. Viral antigens may be detected by mumps-specific immunofluorescent staining of clinical specimens either directly or, more commonly, after incubation of clinical samples with cell cultures. Most commonly, mumps virus is detected as viral RNA by reverse-transcription polymerase chain reaction (PCR), which is believed to be more rapid, sensitive, and specific than detection of live virus by immunofluorescence assays; however, false-negative results are not uncommon with either method. Virus is typically assayed in material obtained by throat swab, although it has been detected in CSF, urine, and seminal fluid. Despite the apparent frequency of viremia, mumps virus has only rarely been isolated from blood, possibly because of the presence of specific antibodies. In urine samples, presumed PCR inhibitors reduce the relative value of RNA testing methods.

Serologic diagnosis of mumps (i.e., a positive IgM response or a significant increase in IgG titer in paired acute- and convalescent-phase sera) is typically obtained by enzyme-linked immunosorbent assay (ELISA). Serologic diagnoses are now of limited value: IgM is detected in <20% of cases in immunized individuals, and IgG titers in convalescent-phase sera may be only nominally greater than those in acute-phase sera. Thus, at present, the capacity of RNA or viral antigen detection to confirm cases is much greater than that of serology. Traditional and labor-intensive serologic tests such as complement fixation, hemagglutination inhibition, and virus neutralization are now performed only rarely. The main downside to replacement of these functional serologic assays with the more rapid ELISA method is the latter's detection of all virus-specific antibodies, including those that are nonneutralizing (i.e., nonprotective). Thus, an individual may be seropositive by ELISA but may lack protective levels of antibody. While there is a strong association between the presence of mumps virus neutralizing antibody and protection from disease, an absolute antibody titer predictive of serologic protection is lacking; in this respect, mumps differs from other respiratory infections, such as measles.

PREVENTION

Vaccination is the only practical control measure; in the United States, the cost-benefit ratios for mumps vaccination alone are >13 for direct costs (e.g., medical expenses) and >24 for societal costs (including productivity losses for patients and caregivers). Several mumps

virus vaccines are used throughout the world; in the United States, only the live attenuated Jeryl Lynn strain is used. Current recommendations are that mumps vaccine be administered as part of the combined trivalent measles-mumps-rubella vaccine (MMR-II®) or the quadrivalent measles-mumps-rubella-varicella vaccine (ProQuad®). Monovalent vaccine (MumpsVax®) is not generally available.

Before administering mumps-containing vaccine, physicians should always consult the latest recommendations from the Advisory Committee on Immunization Practices (ACIP). Current recommendations for children specify two doses of mumps-containing vaccine: the first dose on or after the first birthday and the second dose administered no earlier than 1 month after the first. In the United States, children often receive the second dose between the ages of 4 and 6 years.

In 2009, the ACIP revised its recommendations for evidence of mumps immunity in health care personnel to include (1) documented administration of two doses of a preparation containing live mumps vaccine, (2) laboratory evidence of immunity or laboratory confirmation of disease, or (3) birth date before 1957. For unvaccinated health care personnel born before 1957 who lack laboratory evidence of mumps immunity or laboratory confirmation of mumps, health care facilities should consider two doses of MMR vaccine at the appropriate interval; during a mumps outbreak, vaccination of these individuals is recommended.

Mumps vaccine contains live attenuated virus. It is not recommended for pregnant women, for individuals who have had a life-threatening allergic reaction to components of the vaccine, or for people in settings of clinically significant primary or secondary immunosuppression. (For details, see the ACIP guidelines on the website of the Centers for Disease Control and Prevention.) Occasionally, febrile reactions and parotitis have been reported soon after mumps vaccination. Allergic reactions after vaccination (e.g., rash and pruritus) are uncommon and are usually mild and self-limited. More serious complications, such as aseptic meningitis, have been causally associated with certain vaccine strains but not with the Jeryl Lynn strain.

Immunity to mumps is associated with the development of neutralizing antibody, although a specific correlate of protection has not been established. Seroconversion occurs in ~95% of recipients of the Jeryl Lynn strain; however, vaccine efficacy is ~80% for one dose and 90% for two doses. Recent data indicate declining seropositivity rates with time since vaccination. Although it is generally accepted that mumps virus is serologically monotypic, antigenic differences between virus isolates have been detected. It is unclear whether such differences can lead to immune escape. The role of the cellular arm of the immune response is unclear, but there is evidence that it may help limit virus spread and complications.

TREATMENT **Mumps**

Mumps is generally a benign, self-resolving illness. Therapy for parotitis and other clinical manifestations is symptom based and supportive. The administration of analgesics and the application of warm or cold compresses to the parotid area may be helpful. Testicular pain may be minimized by the local application of cold compresses and gentle support for the scrotum. Anesthetic blocks may also be used. Neither the administration of glucocorticoids nor incision of the tunica albuginea is of proven value in severe orchitis. Anecdotal information on a small number of patients with orchitis suggests that subcutaneous administration of interferon α2b may help preserve the organ and fertility. Lumbar puncture is occasionally performed to relieve headache associated with meningitis. Mumps immune globulin has not been consistently shown to be effective in preventing mumps and is not recommended for treatment or postexposure prophylaxis.

ACKNOWLEDGMENT

The authors thank and acknowledge Dr. Anne Gershon, the author of this chapter in earlier editions of Harrison's Principles of Internal Medicine.

CHAPTER 101

RABIES AND OTHER RHABDOVIRUS INFECTIONS

Alan C. Jackson

RABIES

Rabies is a rapidly progressive, acute infectious disease of the central nervous system (CNS) in humans and animals that is caused by infection with rabies virus. The infection is normally transmitted from animal vectors. Rabies has encephalitic and paralytic forms that progress to death.

ETIOLOGIC AGENT

Rabies virus is a member of the family Rhabdoviridae. Two genera in this family, *Lyssavirus* and *Vesiculovirus*, contain species that cause human disease. Rabies virus is a lyssavirus that infects a broad range of animals and causes serious neurologic disease when transmitted to humans. This single-strand RNA virus has a nonsegmented, negative-sense (antisense) genome that consists of 11,932 nucleotides and encodes five proteins: nucleocapsid protein, phosphoprotein, matrix protein, glycoprotein, and a large polymerase protein. Rabies virus variants, which can be characterized by distinctive nucleotide sequences, are associated with specific animal reservoirs. Five other nonrabies virus species in the *Lyssavirus* genus have been reported to cause a clinical picture similar to rabies. Vesicular stomatitis virus, a vesiculovirus, causes vesiculation and ulceration in cattle, horses, and other animals and causes a self-limited, mild, systemic illness in humans (see "Other Rhabdoviruses," later in the chapter).

EPIDEMIOLOGY

Rabies is a zoonotic infection that occurs in a variety of mammals throughout the world except in Antarctica and on some islands. Rabies virus is usually transmitted to humans by the bite of an infected animal. Canine rabies is endemic in many resource-poor and resource-limited countries and continues to be a threat to humans, particularly in Asia and Africa (see "Global Considerations,"); endemic canine rabies has been eliminated from the United States and most other resource-rich countries. Rabies is endemic in wildlife species, and a variety of animal reservoirs have been identified in different countries. Surveillance data from 2008 identified 6841 confirmed animal cases of rabies in the United States (including Puerto Rico). Only 7% of these cases were in domestic animals, including 294 cases in cats, 75 in dogs, and 59 in cattle. North American wildlife reservoirs, including bats, raccoons, skunks, and foxes, have endemic infection, with involvement of one or more rabies virus variants in each species **(Fig. 101-1).** "Spillover" of rabies to other wildlife species and to domestic animals occurs. Bat rabies virus variants are present in every state except Hawaii and are responsible for most indigenously acquired human rabies cases in the United States. Raccoon rabies is endemic along the entire eastern coast of the United States. Skunk rabies is present in the midwestern states, with another focus in California. Rabies in foxes occurs in Texas, New Mexico, Arizona, and Alaska.

Rabies virus variants isolated from humans or other mammalian species can be identified by reverse-transcription polymerase chain reaction (RT-PCR) amplification and sequencing or by characterization with monoclonal antibodies. These techniques are helpful in human cases with no known history of an exposure. Worldwide, most human rabies is transmitted from dogs in countries with endemic canine rabies and dog-to-dog transmission, and human cases can be imported by travelers returning from these regions. In North America, human disease is usually associated with transmission from bats; there may be no known history of bat bite or other bat exposure in these cases. Most human cases are due to a bat rabies virus variant associated with silver-haired and eastern pipistrelle bats. These are small bats whose bite may not be recognized, and the virus has adapted for replication at skin temperature and in cell types that are present in the skin.

Transmission from nonbite exposures is relatively uncommon. Aerosols generated in the laboratory or in caves containing millions of Brazilian free-tail bats have

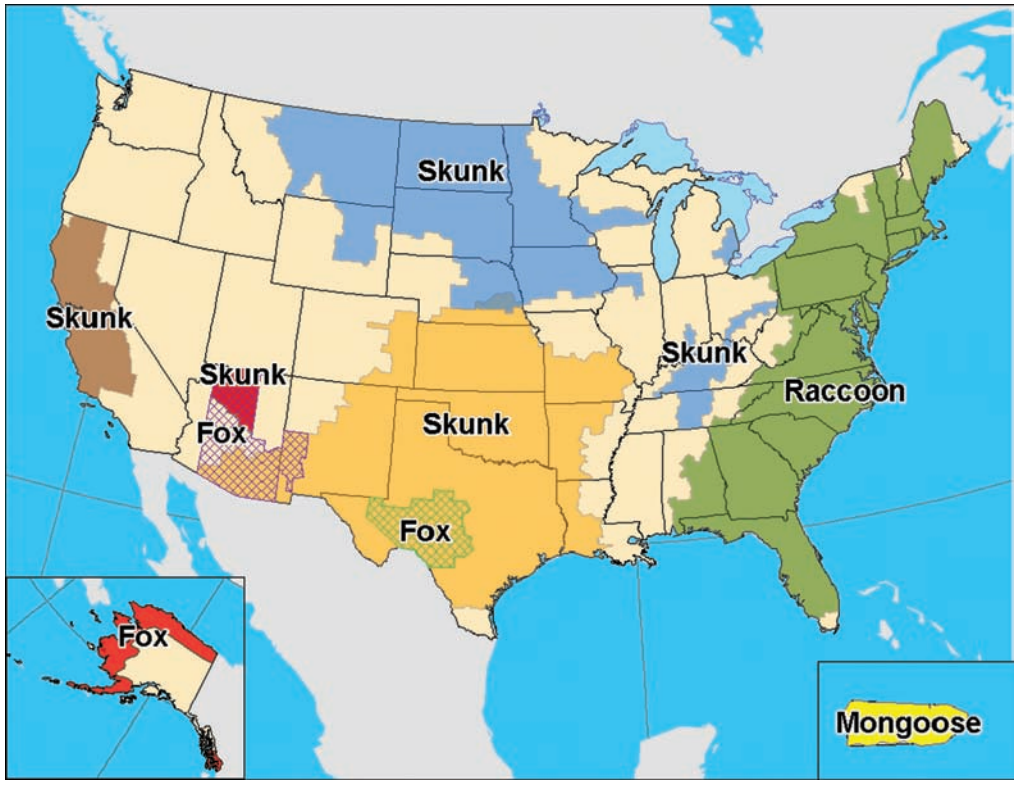


FIGURE 101-1
Distribution of the major rabies virus variants among wild terrestrial reservoirs in the United States and Puerto Rico, 2008. (*From JD Blanton et al: J Am Vet Med Assoc 235:676, 2009, Centers for Disease Control and Prevention.*)

rarely caused human rabies. Transmission has resulted from corneal transplantation and recently from solid organ transplantation and from a vascular conduit (for a liver transplant) from undiagnosed donors with rabies in Texas and Germany. Human-to-human transmission is extremely rare, although theoretical concern about transmission to health care workers has prompted the implementation of barrier techniques to prevent exposures.

PATHOGENESIS

The incubation period of rabies (defined as the interval between exposure and the onset of clinical disease) is usually 20–90 days but in rare cases is as short as a few days or is >1 year. During most of the incubation period, rabies virus is thought to be present at or close to the site of inoculation **(Fig. 101-2)**. In muscles, the virus is known to bind to nicotinic acetylcholine receptors on postsynaptic membranes at neuromuscular junctions, but the exact details of viral entry into the skin and subcutaneous tissues have not yet been clarified. Rabies virus spreads centripetally along peripheral nerves toward the CNS at a rate up to ~250 mm/d via retrograde fast axonal transport to the spinal cord or brainstem. There is no well-documented evidence for hematogenous spread of rabies virus. Once the virus enters the CNS, it rapidly disseminates to other regions of the CNS via fast axonal transport along neuroanatomic connections. Neurons are prominently infected in rabies; infection of astrocytes is unusual. After CNS infection becomes established, there is centrifugal spread along sensory and autonomic nerves to other tissues, including the salivary glands, heart, adrenal glands, and skin. Rabies virus replicates in acinar cells of the salivary glands and is secreted in the saliva of rabid animals that serve as vectors of the disease.

Pathologic studies show mild inflammatory changes in the CNS in rabies, with mononuclear inflammatory infiltration in the leptomeninges, perivascular regions, and parenchyma, including microglial nodules called *Babes nodules*. Degenerative neuronal changes usually are not prominent, and there is little evidence of neuronal death; neuronophagia is observed occasionally. The pathologic changes are surprisingly mild in light of the clinical severity and fatal outcome of the disease. The most characteristic pathologic finding in rabies is the *Negri body* **(Fig. 101-3)**. Negri bodies are eosinophilic cytoplasmic inclusions in brain neurons that are composed of rabies virus proteins and viral RNA. These inclusions occur in a minority of infected neurons, are commonly observed in Purkinje cells of the cerebellum and in pyramidal neurons of the hippocampus, and are less frequently seen in cortical and brainstem neurons. Negri bodies are not observed in all cases of rabies. The lack of prominent degenerative neuronal changes has led to the concept that neuronal dysfunction—rather than neuronal death—is responsible for clinical disease in rabies. The basis for behavioral changes, including the aggressive behavior of rabid animals, is not well understood.

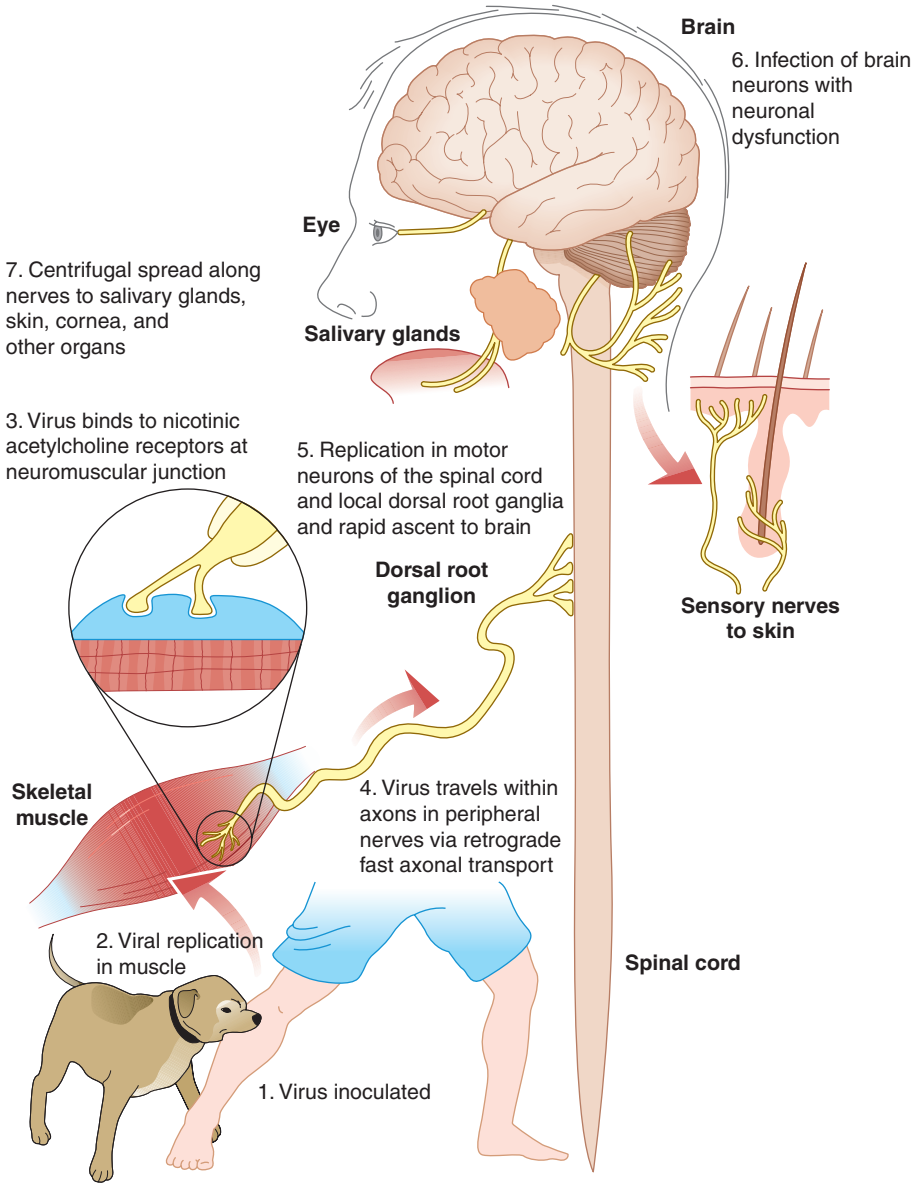


FIGURE 101-2
Schematic representation of the pathogenetic events following peripheral inoculation of rabies virus. (*Adapted from Jackson AC: Human disease, in Rabies, AC Jackson, WH Wunner [eds], San Diego, Academic Press, 2002, pp 219–244; with permission.*)

CLINICAL MANIFESTATIONS

In rabies, the emphasis must be on postexposure prophylaxis initiated before any symptoms or signs develop. Rabies should usually be suspected on the basis of the clinical presentation. The disease usually presents as an atypical encephalitis with relative preservation of consciousness. Rabies may be difficult to recognize late in the clinical course when progression to coma has occurred. A minority of patients present with acute flaccid paralysis. There are prodromal, acute neurologic, and comatose phases that usually progress to death despite aggressive therapy **(Table 101-1)**.

Prodromal features

The earliest clinical features of rabies begin with nonspecific prodromal manifestations, including fever, malaise, headache, nausea, and vomiting. Anxiety or agitation may also occur. The earliest specific neurologic symptoms of rabies include paresthesias, pain, or pruritus near the site of the exposure, which occurs in 50–80% of patients and strongly suggests rabies. The wound has usually healed by this point, and these symptoms probably reflect infection with associated inflammatory changes in local dorsal root or cranial sensory ganglia.

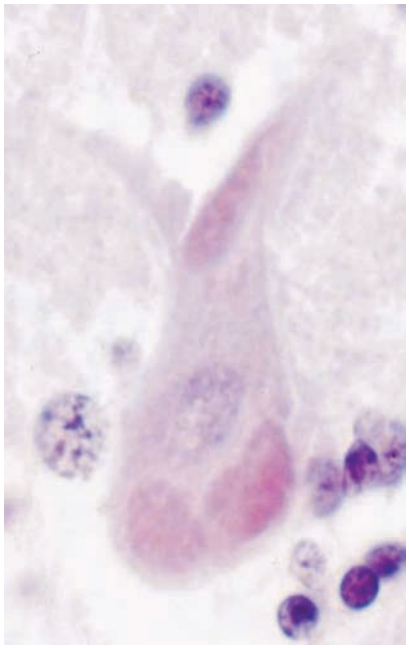


FIGURE 101-3
Three large Negri bodies in the cytoplasm of a cerebellar Purkinje cell from an 8-year-old boy who died of rabies after being bitten by a rabid dog in Mexico. (*From AC Jackson, E Lopez-Corella: N Engl J Med 335:568, 1996. © Massachusetts Medical Society.*)

Encephalitic rabies

Two acute neurologic forms of rabies are seen in humans: encephalitic (furious) in 80% and paralytic in 20%.

TABLE 101-1

CLINICAL STAGES OF RABIES

PHASE	TYPICAL DURATION	SYMPTOMS AND SIGNS
Incubation period	20–90 days	None
Prodrome	2–10 days	Fever, malaise, anorexia, nausea, vomiting, paresthesias, pain, or pruritus at the wound site
Acute neurologic disease Encephalitic (80%)	2–7 days	Anxiety, agitation, hyperactivity, bizarre behavior, hallucinations, autonomic dysfunction, hydrophobia
Paralytic (20%)	2–10 days	Flaccid paralysis in limb(s) progressing to quadriparesis with facial paralysis
Coma, death[a]	0–14 days	

[a]Recovery is rare.
Source: MAW Hattwick: Rabies virus, in *Principles and Practice of Infectious Diseases,* GL Mandell et al (eds). New York, Wiley, 1979, pp 1217–1228. Adapted with permission from Elsevier.

Some of the manifestations of encephalitic rabies may be seen in other viral encephalitides as well. These features include fever, confusion, hallucinations, combativeness, and seizures. Autonomic dysfunction is common and may result in hypersalivation, gooseflesh, cardiac arrhythmia, and priapism. In encephalitic rabies, episodes of hyperexcitability are typically followed by periods of complete lucidity that become shorter as the disease progresses. Rabies encephalitis is distinguished by early brainstem involvement, which results in the classic features of hydrophobia (involuntary, painful contraction of the diaphragm and accessory respiratory, laryngeal, and pharyngeal muscles in response to swallowing liquids) and aerophobia (the same features caused by stimulation from a draft of air). These symptoms are probably due to dysfunction of infected brainstem neurons that normally inhibit inspiratory neurons near the nucleus ambiguus, resulting in exaggerated defense reflexes that protect the respiratory tract. The combination of hypersalivation and pharyngeal dysfunction is also responsible for the classic appearance of "foaming at the mouth" **(Fig. 101-4)**. Brainstem dysfunction progresses rapidly, and coma followed within days by death is the rule unless the course is prolonged by supportive measures. With such measures, late complications can include cardiac and/or respiratory failure, disturbances of water balance (syndrome of inappropriate antidiuretic hormone secretion or diabetes insipidus), noncardiogenic pulmonary edema, and gastrointestinal hemorrhage. Cardiac arrhythmias may be due to dysfunction affecting vital centers in the brainstem or to

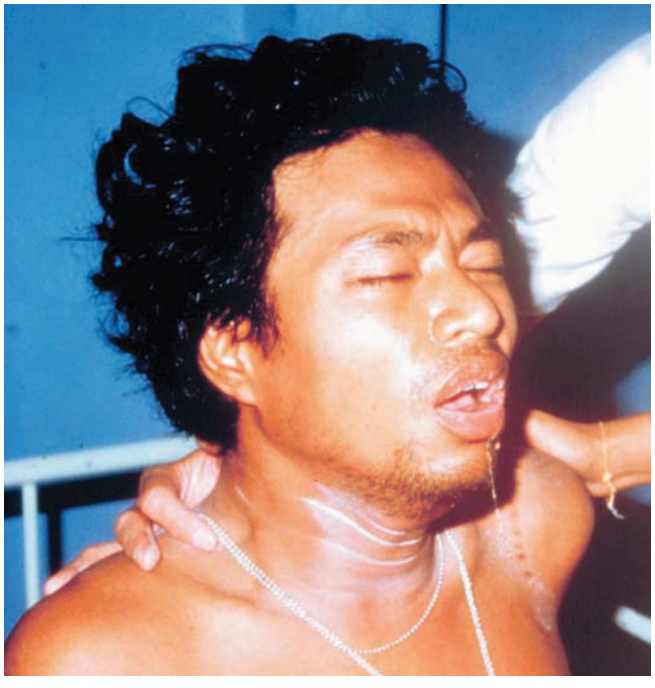


FIGURE 101-4
Hydrophobic spasm of inspiratory muscles associated with terror in a patient with encephalitic (furious) rabies who is attempting to swallow water. (*Copyright DA Warrell, Oxford, UK; with permission.*)

myocarditis. Multiple-organ failure is common in patients treated aggressively in critical care units.

Paralytic rabies

About 20% of patients have paralytic rabies in which muscle weakness predominates and cardinal features of encephalitic rabies (hyperexcitability, hydrophobia, and aerophobia) are lacking. There is early and prominent flaccid muscle weakness, often beginning in the bitten extremity and spreading to produce quadriparesis and facial weakness. Sphincter involvement is common, sensory involvement is usually mild, and these cases are commonly misdiagnosed as Guillain-Barré syndrome. Patients with paralytic rabies generally survive a few days longer than those with encephalitic rabies, but multiple-organ failure nevertheless ensues.

LABORATORY INVESTIGATIONS

Most routine laboratory tests in rabies yield normal results or show nonspecific abnormalities. Complete blood counts are usually normal. Examination of cerebrospinal fluid (CSF) often reveals mild mononuclear cell pleocytosis with a mildly elevated protein level. Severe pleocytosis (>1000 white cells/μL) is unusual and should prompt a search for an alternative diagnosis. CT head scans are usually normal in rabies. MRI brain scans may show signal abnormalities in the brainstem or other gray-matter areas, but these findings are variable and nonspecific. Electroencephalograms show only nonspecific abnormalities. Of course, important tests in suspected cases of rabies include those that may identify an alternative, potentially treatable diagnosis (see "Differential Diagnosis," later in the chapter).

DIAGNOSIS

In North America, a diagnosis of rabies often is not considered until relatively late in the clinical course, even with a typical clinical presentation. This diagnosis should be considered in patients presenting with acute atypical encephalitis or acute flaccid paralysis, including those in whom Guillain-Barré syndrome is suspected. The absence of an animal-bite history is common in North America. The lack of hydrophobia is not unusual in rabies. Once rabies is suspected, rabies-specific laboratory tests should be performed to confirm the diagnosis. Diagnostically useful specimens include serum, CSF, fresh saliva, skin biopsy samples from the neck, and brain tissue (rarely obtained before death). Because skin biopsy relies on the demonstration of rabies virus antigen in cutaneous nerves at the base of hair follicles, samples are usually taken from hairy skin at the nape of the neck. Corneal impression smears are of low diagnostic yield and are generally not performed. Negative antemortem rabies-specific laboratory tests never exclude a diagnosis of rabies, and tests may need to be repeated after an interval for diagnostic confirmation.

Rabies virus–specific antibodies

In a previously unimmunized patient, serum neutralizing antibodies to rabies virus are diagnostic. However, because rabies virus infects immunologically privileged neuronal tissues, serum antibodies may not develop until late in the disease. Antibodies may be detected within a few days after the onset of symptoms, but some patients die without detectable antibodies. The presence of rabies virus–specific antibodies in the CSF suggests rabies encephalitis, regardless of immunization status.

RT-PCR amplification

Detection of rabies virus RNA by RT-PCR is highly sensitive and specific. This technique can detect virus in fresh saliva samples, CSF, and skin and brain tissues. In addition, RT-PCR with genetic sequencing can distinguish among rabies virus variants, permitting identification of the probable source of an infection.

Direct fluorescent antibody testing

Direct fluorescent antibody (DFA) testing with rabies virus antibodies conjugated to fluorescent dyes is highly sensitive and specific and can be performed quickly and applied to skin biopsies and brain tissue. In skin biopsies, rabies virus antigen may be detected in cutaneous nerves at the base of hair follicles.

DIFFERENTIAL DIAGNOSIS

The diagnosis of rabies may be difficult without a history of animal exposure, and no exposure to an animal (e.g., a bat) may be recalled. The presentation of rabies is usually quite different from that of acute viral encephalitis due to most other causes, including herpes simplex encephalitis and arboviral (e.g., West Nile) encephalitis. Early neurologic symptoms may occur at the site of the bite, and there may be early features of brainstem involvement with preservation of consciousness. Postinfectious (immune-mediated) encephalomyelitis may follow influenza, measles, mumps, and other infections; it may also occur as a sequela of immunization with rabies vaccine derived from neural tissues, which are used only in resource-limited and resource-poor countries. Rabies may present with unusual neuropsychiatric symptoms and may be misdiagnosed as a psychiatric disorder. Rabies hysteria may occur as a psychological response to the fear of rabies and is often characterized by a shorter incubation period than rabies, aggressive behavior, inability to communicate, and a long course with recovery.

As previously mentioned, paralytic rabies may mimic Guillain-Barré syndrome. In these cases, fever, bladder dysfunction, a normal sensory examination, and CSF pleocytosis favor a diagnosis of rabies. Conversely, Guillain-Barré syndrome may occur as a complication of rabies vaccination with a neural tissue–derived product (e.g., suckling mouse brain vaccine) and may be mistaken for paralytic rabies (i.e., vaccine failure).

TREATMENT Rabies

There is no established treatment for rabies. There have been several recent treatment failures with the combination of antiviral drugs, ketamine, and therapeutic (induced) coma—measures that were used in a healthy survivor in whom antibodies to rabies virus were detected at presentation. Expert opinion should be sought before a course of experimental therapy is embarked upon. A palliative approach may be appropriate for some patients.

PROGNOSIS

Rabies is an almost uniformly fatal disease but is almost always preventable with appropriate postexposure therapy during the early incubation period (see later). There are seven well-documented cases of survival from rabies. All but one of these patients had received rabies vaccine before disease onset. The single survivor who had not received vaccine had neutralizing antibodies to rabies virus in serum and CSF at clinical presentation. Most patients with rabies die within several days of illness, despite aggressive care in a critical care unit.

PREVENTION

Postexposure prophylaxis

Since there is no effective therapy for rabies, it is extremely important to prevent the disease after an animal exposure. Figure 101-5 shows the steps involved in making decisions about rabies postexposure prophylaxis (PEP). On the basis of the history of the exposure and local epidemiologic information, the physician must decide whether initiation of PEP is warranted. Healthy dogs, cats, or ferrets may be confined and observed for 10 days. PEP is not necessary if the animal remains healthy. If the animal develops signs of rabies during the observation period, it should be euthanized immediately, and the head should be transported to the laboratory under refrigeration and examined for the presence of rabies virus by DFA testing and viral isolation using cell culture and/or mouse inoculation. Any animal other than a dog, cat, or ferret should be euthanized immediately and the head submitted for laboratory examination. In high-risk exposures and in areas where canine rabies is endemic, rabies prophylaxis should be initiated without waiting for laboratory results. If the laboratory results prove to be negative, it may safely be concluded that the animal's saliva did not contain rabies virus, and immunization should be discontinued. If an animal escapes after an exposure, it must be considered rabid, and PEP must be initiated unless information from public health officials indicates otherwise (i.e., there is no endemic rabies in the area). PEP may be warranted in situations where a person (e.g., a small child or a sleeping adult) is present in the same space as a bat and an unrecognized bite cannot be reliably excluded.

PEP includes local wound care and both active and passive immunization. Local wound care is essential and may greatly decrease the risk of rabies virus infection.

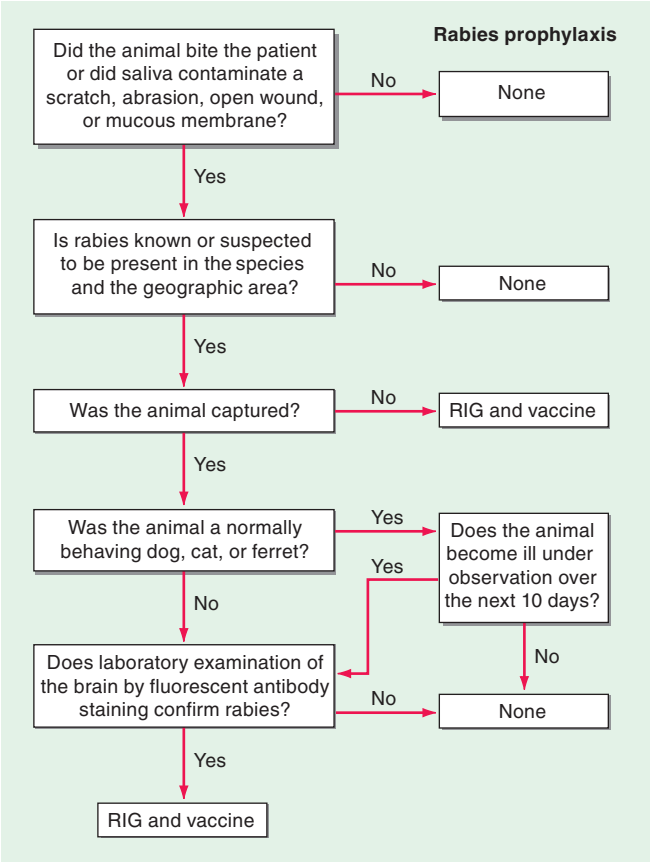


FIGURE 101-5
Algorithm for rabies postexposure prophylaxis. RIG, rabies immune globulin. (*From L Corey, in Harrison's Principles of Internal Medicine, 15th ed. E Braunwald et al [eds]: New York, McGraw-Hill, 2001; adapted with permission.*)

Wound care should not be delayed, even if the initiation of immunization is postponed pending the results of the 10-day observation period. All bite wounds and scratches should be washed thoroughly with soap and water. Devitalized tissues should be debrided, tetanus prophylaxis given, and antibiotic treatment initiated whenever indicated.

All previously unvaccinated persons (but not those who have previously been immunized) should be passively immunized with rabies immune globulin (RIG). If RIG is not immediately available, it should be administered no later than 7 days after the first vaccine dose. After day 7, endogenous antibodies are being produced, and passive immunization may actually be counterproductive. If anatomically feasible, the entire dose of RIG (20 IU/kg) should be infiltrated at the site of the bite; otherwise, any RIG remaining after infiltration of the bite site should be administered IM at a distant site. With multiple or large wounds, the RIG preparation may need to be diluted in order to obtain a sufficient volume for adequate infiltration of all wound sites. If the exposure involves a mucous membrane, the entire dose should be administered IM. Rabies vaccine and RIG should never be administered at the same site or with the same syringe. Commercially available RIG in

the United States is purified from the serum of hyperimmunized human donors. These human RIG preparations are much better tolerated than are the equine-derived preparations still in use in some countries (see "Global Considerations," next). Serious adverse effects of human RIG are uncommon. Local pain and low-grade fever may occur.

Two purified inactivated rabies vaccines are available for rabies PEP in the United States. They are highly immunogenic and remarkably safe compared with earlier vaccines. Four 1-mL doses of rabies vaccine should be given IM in the deltoid area. (The anterolateral aspect of the thigh is also acceptable in children.) Gluteal injections, which may not always reach muscle, should not be given and have been associated with rare vaccine failures. Ideally, the first dose should be given as soon as possible after exposure; failing that, it should be given without further delay. The three additional doses should be given on days 3, 7, and 14; a fifth dose on day 28 is no longer recommended. Pregnancy is not a contraindication for immunization. Glucocorticoids and other immunosuppressive medications may interfere with the development of active immunity and should not be administered during PEP unless they are essential. Routine measurement of serum neutralizing antibody titers is not required, but titers should be measured 2–4 weeks after immunization in immunocompromised persons. Local reactions (pain, erythema, edema, and pruritus) and mild systemic reactions (fever, myalgias, headache, and nausea) are common; anti-inflammatory and antipyretic medications may be used, but immunization should not be discontinued. Systemic allergic reactions are uncommon, but anaphylaxis does occur rarely and can be treated with epinephrine and antihistamines. The risk of rabies development should be carefully considered before the decision is made to discontinue vaccination because of an adverse reaction.

Preexposure rabies vaccination

Preexposure rabies prophylaxis should be considered for people with an occupational or recreational risk of rabies exposures, including certain travelers to rabies-endemic areas. This primary schedule consists of three doses of rabies vaccine given on days 0, 7, and 21 or 28. Serum neutralizing antibody tests help determine the need for subsequent booster doses. When a previously immunized individual is exposed to rabies, two booster doses of vaccine should be administered on days 0 and 3. Wound care remains essential. As stated earlier, RIG should not be administered to previously vaccinated persons.

GLOBAL CONSIDERATIONS

Worldwide, endemic canine rabies is estimated to cause 55,000 human deaths annually. Most of these deaths occur in Asia and Africa, with rural populations and children most frequently affected. Most of the burden of rabies PEP is borne by people with the least resources. In Latin America, rabies control efforts in dogs have been quite successful in recent years. In Canada and Europe, epizootics of rabies in red foxes have been well controlled with the use of baits containing rabies vaccine. A similar approach is used in Canada to control raccoon rabies.

In addition to the rabies vaccines discussed earlier, vaccines grown in either primary cell lines (hamster or dog kidney) or continuous cell lines (Vero cells) are satisfactory and are available in many countries outside the United States. Less expensive vaccines derived from neural tissues have been used in developing countries; however, these vaccines are associated with serious neuroparalytic complications, including postinfectious encephalomyelitis and Guillain-Barré syndrome. The use of these vaccines should be discontinued as soon as possible, and progress has been made in this regard. Worldwide, >10 million individuals receive postexposure vaccination against rabies each year.

If human RIG is unavailable, purified equine RIG can be used in the same manner at a dose of 40 IU/kg. Before the administration of equine RIG, hypersensitivity should be assessed by intradermal testing with a 1:10 dilution. The incidence of anaphylactic reactions and serum sickness has been low with recent equine RIG products.

OTHER RHABDOVIRUSES

OTHER LYSSAVIRUSES

A growing number of lyssaviruses other than rabies virus have been discovered to infect bat populations in Africa, Europe, and Australia. Four of these viruses have produced a very small number of cases of a human disease indistinguishable from rabies: European bat lyssaviruses 1 and 2, Australian bat lyssavirus, and the Duvenhage virus (in Africa). Mokola virus, a lyssavirus that has been isolated from shrews with an unknown reservoir species in Africa, may also produce human disease indistinguishable from rabies.

VESICULAR STOMATITIS VIRUS (VSV)

Vesicular stomatitis is a viral disease of cattle, horses, pigs, and some wild mammals. VSV is a member of the genus *Vesiculovirus* in the family Rhabdoviridae. Outbreaks of vesicular stomatitis in horses and cattle occur sporadically in the southwestern United States. The animal infection is associated with severe vesiculation and ulceration of oral tissues, teats, and feet and may be clinically indistinguishable from the more dangerous foot-and-mouth disease. Epidemics are usually seasonal, typically beginning in the late spring, and are probably due to arthropod vectors. Direct animal-to-animal spread can also occur, although the virus cannot

penetrate intact skin. Transmission to humans usually results from direct contact with infected animals (particularly cattle) and occasionally follows laboratory exposure. In human disease, early conjunctivitis is followed by an acute influenza-like illness with fever, chills, nausea, vomiting, headache, retrobulbar pain, myalgias, substernal pain, malaise, pharyngitis, and lymphadenitis. Small vesicular lesions may be present on the buccal mucosa or on the fingers. Encephalitis is very rare. The illness usually lasts 3–6 days, with complete recovery. Subclinical infections are common. A serologic diagnosis can be made on the basis of a rise in titer of complement-fixing or neutralizing antibodies. Therapy is symptom-based.

CHAPTER 102

INFECTIONS CAUSED BY ARTHROPOD- AND RODENT-BORNE VIRUSES

Clarence J. Peters

Some zoonotic viruses are transmitted in nature without regard to humans and only incidentally infect and produce disease in humans; in addition, a few agents are regularly spread among humans by arthropods. Most of these viruses either are maintained by arthropods or chronically infect rodents. Obviously, the mode of transmission is not a rational basis for taxonomic classification. Indeed, zoonotic viruses from at least seven families act as significant human pathogens **(Table 102-1)**. The virus families differ fundamentally from one another in terms of morphology, replication mechanisms, and genetics. Information on a virus's membership in a family or genus is enlightening with regard to maintenance strategies, sensitivity to antiviral agents, and some aspects of pathogenesis but does not necessarily predict which clinical syndromes (if any) the virus will cause in humans.

FAMILIES OF ARTHROPOD- AND RODENT-BORNE VIRUSES (TABLE 102-1)

The Arenaviridae

The Arenaviridae are spherical, 110- to 130-nm particles that bud from the cell's plasma membrane and utilize ambisense RNA genomes with two segments for replication. There are two main phylogenetic branches of Arenaviridae: the Old World viruses, such as Lassa fever and lymphocytic choriomeningitis (LCM) viruses, and the New World viruses, including those causing the South American hemorrhagic fevers (HFs). Arenaviruses persist in nature by chronically infecting rodents with a striking one-virus–one-rodent species relationship. These rodent infections result in long-term virus excretion and perhaps in lifelong viremia; vertical infection is common with some arenaviruses. Humans become infected through the inhalation of aerosols containing arenaviruses, which are then deposited in the terminal air passages, and probably also through close contact with rodents and their excreta, which results in the contamination of mucous membranes or breaks in the skin.

The Bunyaviridae

The family Bunyaviridae includes four medically significant genera. All of these spherical viruses have three negative-sense RNA segments maturing into 90- to 120-nm particles in the Golgi complex and exiting the cell by exocytosis. Viruses of the genus *Bunyavirus* are largely mosquito-borne and have a viremic vertebrate intermediate host; many are also transovarially transmitted in their specific mosquito host. One serologic group also uses biting midges as vectors. Sandflies or mosquitoes are the vectors for the genus *Phlebovirus* (named after phlebotomus fever or sandfly fever, the best-known disease associated with the genus), while ticks serve as vectors for the genus *Nairovirus*. Viruses of both of these genera are also associated with vertical transmission in the arthropod host and with horizontal spread through viremic vertebrate hosts. The genus *Hantavirus* is unique

TABLE 102-1

MAJOR ZOONOTIC VIRUS FAMILIES AND SOME CHARACTERISTICS OF TYPICAL MEMBERS

FAMILY	GENUS OR GROUP	SYNDROME(S): TYPICAL VIRUSES	MAINTENANCE STRATEGY
Arenaviridae	Old World complex	FM, E: Lymphocytic choriomeningitis virus HF: Lassa fever virus	Chronic infection of rodents, often with persistent viremia; vertical transmission common
	New World or Tacaribe complex	HF: South American HF viruses (Machupo, Junin, Guanarito, Sabia)	Chronic infection of rodents, sometimes with persistent viremia; vertical infection may occur
Bunyaviridae	*Bunyavirus*	E: California serogroup viruses (La Crosse, Jamestown Canyon, California encephalitis) FM: Bunyamwera, group C, Tahyna viruses	Mosquito-vertebrate cycle; transovarial transmission in mosquito common
		FM: Oropouche virus	Transmitted by *Culicoides*
	Phlebovirus	FM: Sandfly fever, Toscana viruses FM: Punta Toro virus	Sandfly transmission between vertebrates, with prominent transovarial component in sandfly
		HF, FM, E: Rift Valley fever virus	Mosquito-vertebrate transmission, with transovarial component in mosquito
	Nairovirus	HF: Crimean-Congo HF virus	Tick-vertebrate, with transovarial transmission in tick
	Hantavirus	HF: Hantaan, Dobrava, Puumala viruses	Rodent reservoir; chronic virus shedding, but chronic viremia unknown
		HF: Sin Nombre and related hantaviruses	Sigmodontine rodent reservoir
Filoviridae[a]	*Ebolavirus, Marburgvirus*	HF: Marburg viruses, Ebola viruses (4 species)	Unknown
Flaviviridae	*Flavivirus* (mosquito-borne)	HF: Yellow fever virus FM, HF: Dengue viruses (4 serotypes) E: St. Louis, Japanese, West Nile, and Murray Valley encephalitis viruses; Rocio viruses	Mosquito-vertebrate; transovarial rare
	Flavivirus (tick-borne)	E: Central European tick-borne encephalitis, Russian spring-summer encephalitis, Powassan viruses HF: Omsk HF, Kyasanur Forest; Alkhurma disease viruses	Tick-vertebrate
Reoviridae	*Coltivirus*	FM, E: Colorado tick fever virus	Tick-vertebrate
	Orbivirus	FM, E: Orungo, Kemerovo viruses	Arthropod-vertebrate
Rhabdoviridae[b]	*Vesiculovirus*	FM: Vesicular stomatitis virus (Indiana, New Jersey); Chandipura, Piry viruses	Sandfly-vertebrate, with prominent transovarial component in sandfly
Togaviridae	*Alphavirus*	AR: Sindbis, chikungunya, Mayaro, Ross River, Barmah Forest viruses E: Eastern, western, and Venezuelan equine encephalitis viruses	Mosquito-vertebrate

[a]The Filoviridae are discussed in Chap. 103.
[b]The Rhabdoviridae are discussed in Chap. 101.
Note: Abbreviations refer to the disease syndrome most commonly associated with the virus: AR, arthritis, rash; E, encephalitis; FM, fever, myalgia; HF, hemorrhagic fever.

among the Bunyaviridae in that it is not transmitted by arthropods but is maintained in nature by rodent hosts that chronically shed virus. Like the arenaviruses, the hantaviruses usually display striking virus–rodent species specificity. Hantaviruses do not cause chronic viremia in their rodent hosts and are transmitted only horizontally from rodent to rodent.

Other families

The Flaviviridae are positive-sense, single-strand RNA viruses that form particles of 40–50 nm in the endoplasmic reticulum. The flaviviruses discussed here are from the genus *Flavivirus* and make up two phylogenetically and antigenically distinct divisions transmitted among vertebrates by mosquitoes and ticks, respectively. The mosquito-borne viruses fall into phylogenetic groups that include yellow fever virus, the four dengue viruses, and encephalitis viruses, while the tick-borne group encompasses a geographically varied spectrum of species, some of which are responsible for encephalitis or for hemorrhagic disease with encephalitis. The Reoviridae are double-strand RNA viruses with multisegmented genomes. These 80-nm particles are the only viruses discussed in this chapter that do not have a lipid envelope and thus are insensitive to detergents. The Togaviridae have a single positive-strand RNA genome and bud particles of ~60–70 nm from the plasma membrane. The togaviruses discussed here are all members of the genus *Alphavirus* and are transmitted among vertebrates by mosquitoes in their natural cycle. The Filoviridae and the Rhabdoviridae are discussed in Chaps. 103 and 101, respectively.

PROMINENT FEATURES OF ARTHROPOD- AND RODENT-BORNE VIRUSES

Although this chapter discusses the major features of selected arthropod- and rodent-borne viruses, it does not deal with >500 other distinct recognized zoonotic viruses, about one-fourth of which infect humans. Zoonotic viruses are undergoing genetic evolution, "new" zoonotic viruses are being discovered, and the epidemiology of zoonotic viruses is continuing to evolve through environmental changes affecting vectors, reservoirs, and humans. These zoonotic viruses are most numerous in the tropics but are also found in temperate and frigid climates. Their distribution and seasonal activity may be variable and often depend largely on ecologic conditions such as rainfall and temperature, which in turn affect the density of vectors and reservoirs and the development of infection therein.

Maintenance and transmission

Arthropod-borne viruses infect their vectors after the ingestion of a blood meal from a viremic vertebrate. The vectors then develop chronic, systemic infection as the viruses penetrate the gut and spread throughout the body. The viruses eventually reach the salivary glands during a period that is referred to as *extrinsic incubation* and that typically lasts 1–3 weeks in mosquitoes. At this point, an arthropod is competent to continue the chain of transmission by infecting another vertebrate when a subsequent blood meal is taken. The arthropod generally is unharmed by the infection, and the natural vertebrate partner usually has only transient viremia with no overt disease. An alternative mechanism for virus maintenance in its arthropod host is transovarial transmission, which is common among members of the family Bunyaviridae.

Rodent-borne viruses such as the hantaviruses and arenaviruses are maintained in nature by chronic infection transmitted between rodents. As in arthropod-borne virus cycles, there is usually a high degree of rodent–virus specificity, and there is no overt disease in the reservoir/vector.

Epidemiology

The distribution of arthropod- and rodent-borne viruses is restricted by the areas inhabited by their reservoir/vectors and provides an important clue in the differential diagnosis. **Table 102-2** shows the approximate geographic distribution of the most important of these viruses. Members of each family, each genus, and even each serologically related group usually occur in each area but may not be pathogenic in all areas or may not be a commonly recognized cause of disease in all areas and so may not be included in the table.

Most of these diseases are acquired in a rural setting; a few have urban vectors. Seoul, sandfly fever, and Oropouche viruses are examples of urban viruses, but the most notable are yellow fever, dengue, and chikungunya viruses. A history of mosquito bite has little diagnostic significance in the individual; a history of tick bite is more diagnostically specific. Rodent exposure is often reported by persons infected with an arenavirus or a hantavirus but again has little specificity. Indeed, aerosols may infect persons who have no recollection of having even seen rodents.

Syndromes

Human disease caused by arthropod- and rodent-borne viruses is often subclinical. The spectrum of possible responses to infection is wide, and our knowledge of the outcome of most of these infections is limited. The usual disease syndromes associated with these viruses have been grouped into four categories: fever and myalgia, arthritis and rash, encephalitis, and hemorrhagic fever. Although for the purposes of this discussion most viruses have been placed in a single group, the categories often overlap. For example, West Nile and Venezuelan equine encephalitis viruses are discussed as encephalitis viruses, but during epidemics many cases of milder febrile syndromes are recognized relative to less common cases of encephalitis. Similarly, Rift Valley fever virus is best known as a cause of HF, but the attack rates for febrile disease are far

TABLE 102-2

GEOGRAPHIC DISTRIBUTION OF SOME IMPORTANT AND COMMONLY ENCOUNTERED HUMAN ZOONOTIC VIRAL DISEASES

AREA	ARENAVIRIDAE	BUNYAVIRIDAE	FLAVIVIRIDAE	RHABDOVIRIDAE	TOGAVIRIDAE
North America	Lymphocytic choriomeningitis	La Crosse, Jamestown Canyon, California encephalitis; hantavirus pulmonary syndrome	St. Louis, Powassan, West Nile encephalitis; dengue	Vesicular stomatitis	Eastern, western equine encephalitis
South America	Bolivian (Machupo, Chapare), Argentine, Venezuelan, and Brazilian HF; lymphocytic choriomeningitis	Oropouche, group C, Punta Toro infection; hantavirus pulmonary syndrome	Yellow fever, dengue, Rocio virus infection	Vesicular stomatitis, Piry virus infection	Mayaro virus infection, Venezuelan equine encephalitis
Europe	Lymphocytic choriomeningitis	Tahyna, Toscana, sandfly fever; HF with renal syndrome	West Nile, Central European tick-borne, Russian spring-summer encephalitis	—	Sindbis virus infection
Middle East	Alkhurma HF virus infection	Sandfly fever, Crimean-Congo HF	West Nile encephalitis, dengue	—	—
Eastern Asia	—	Sandfly fever; Hantaan, Seoul virus infection	Dengue; Japanese, Russian spring-summer encephalitis; Omsk HF	Chandipura virus infection	—
Southwestern Asia	—	Sandfly fever, Crimean-Congo HF	West Nile, Japanese encephalitis; dengue; Kyasanur Forest disease	—	Chikungunya virus infection
Southeast Asia	—	Seoul virus infection	Japanese encephalitis, dengue	—	Chikungunya virus infection
Africa	Lassa fever; Lujo virus infection	Bunyamwera virus infection, Rift Valley fever	Yellow fever, dengue	—	Sindbis, chikungunya virus infection
Australia	—	—	Murray Valley encephalitis, dengue	—	Ross River, Barmah Forest virus infection

Abbreviation: HF, hemorrhagic fever.

higher, and encephalitis is occasionally seen as well. LCM virus is classified as a cause of fever and myalgia because this syndrome is its most common disease manifestation and because, even when central nervous system (CNS) disease occurs, it is usually mild and is preceded by fever and myalgia. Dengue virus infection is considered as a cause of fever and myalgia (dengue fever) because this is by far the most common manifestation worldwide and is the syndrome most likely to be seen in the United States; however, dengue HF is also discussed in the HF section because of its complicated pathogenesis and importance in pediatric practice in certain areas of the world.

Diagnosis

Laboratory diagnosis is required in any given case, although epidemics occasionally provide clinical and epidemiologic clues on which an educated guess as to etiology can

be based. For most arthropod- and rodent-borne viruses, acute-phase serum samples (collected within 3 or 4 days of onset) have yielded isolates, and paired sera have been used to demonstrate rising antibody titers by a variety of tests. Intensive efforts to develop rapid tests for HF have resulted in an antigen-detection enzyme-linked immunosorbent assay (ELISA) and an IgM-capture ELISA that can provide a diagnosis based on a single serum sample within a few hours and are particularly useful in severe cases. More sensitive reverse-transcription polymerase chain reaction (RT-PCR) tests may yield diagnoses based on samples without detectable antigen and may also provide useful genetic information about the virus. Hantavirus infections differ from others discussed here in that severe acute disease is immunopathologic; patients present with serum IgM that serves as the basis for a sensitive and specific test.

At diagnosis, patients with encephalitis are generally no longer viremic or antigenemic and usually do not have virus in cerebrospinal fluid (CSF). In this situation, the value of serologic methods for IgM determination and RT-PCR is high. IgM capture is increasingly being used for the simultaneous testing of serum and CSF. IgG ELISA or classic serology is useful in the evaluation of past exposure to the viruses, many of which circulate in areas with a minimal medical infrastructure and sometimes cause mild or subclinical infection.

The remainder of this chapter offers general descriptions of the broad syndromes caused by arthropod- and rodent-borne viruses. Most of the diseases under consideration have not been studied in detail with modern medical approaches; thus available data may be incomplete or biased.

FEVER AND MYALGIA

Fever and myalgia constitute the syndrome most commonly associated with zoonotic virus infection. Many of the numerous viruses belonging to the families listed in Table 102-1 probably cause this syndrome, but several viruses have been selected for inclusion in the table because of their prominent associations with the syndrome and their biomedical importance.

The syndrome typically begins with the abrupt onset of fever, chills, intense myalgia, and malaise. Patients may also report joint or muscle pains, but no true arthritis is detectable. Anorexia is characteristic and may be accompanied by nausea or even vomiting. Headache is common and may be severe, with photophobia and retroorbital pain. Physical findings are minimal and are usually confined to conjunctival injection with pain on palpation of muscles or the epigastrium. The duration of symptoms is quite variable but generally is 2–5 days, with a biphasic course in some instances. The spectrum of disease varies from subclinical to temporarily incapacitating.

Less constant findings include a maculopapular rash. Epistaxis may occur but does not necessarily indicate a bleeding diathesis. A minority of the cases caused by some viruses are known or suspected to include aseptic meningitis, but this diagnosis is difficult to make in remote areas, given the patients' photophobia and myalgia as well as the lack of opportunity to examine the CSF. Although pharyngitis may be noted or radiographic evidence of pulmonary infiltrates found in some cases, these viruses are not primary respiratory pathogens. The differential diagnosis includes anicteric leptospirosis, rickettsial diseases, and the early stages of other syndromes discussed in this chapter. These diseases are often described as "flu-like," but the usual absence of cough and coryza makes influenza an unlikely confounder except at the earliest stages.

Complete recovery is generally the outcome in this syndrome, although prolonged asthenia and nonspecific symptoms have been described in some cases, particularly after infection with LCM or dengue virus. Treatment is supportive, with aspirin avoided because of the potential for exacerbated bleeding and Reye's syndrome. Efforts at prevention are best based on vector control, which, however, may be expensive or impossible. For mosquito control, destruction of breeding sites is generally the most economically and environmentally sound approach. Emerging technologies include mosquito genetic transformation and introduction of *Wolbachia* to limit multiplication rates. Measures taken by the individual to avoid the vector can be valuable. Avoiding the vector's habitat and times of peak activity, using screens or other barriers (e.g., permethrin-impregnated bed nets) to prevent the vector from entering dwellings, judiciously applying arthropod repellents such as diethyltoluamide (DEET) to the skin, and wearing permethrin-impregnated clothing are all possible approaches, depending on the vector and its habits.

LYMPHOCYTIC CHORIOMENINGITIS

LCM is transmitted from the common house mouse (*Mus musculus*) to humans by aerosols of excreta and secreta. LCM virus, an arenavirus, is maintained in the mouse mainly by vertical transmission from infected dams. The vertically infected mouse remains viremic for life, with high concentrations of virus in all tissues. Infected colonies of pet hamsters have also served as a link to humans. LCM virus is widely used in immunology laboratories as a model of T cell function and can silently infect cell cultures and passaged tumor lines, resulting in infections among scientists and animal caretakers. Patients with LCM may have a history of residence in rodent-infested housing or other exposure to rodents. An antibody prevalence of ~5–10% has been reported among adults from the United States, Argentina, and endemic areas of Germany.

LCM differs from the general syndrome of fever and myalgia in that its onset is gradual. Among the conditions occasionally associated with LCM are orchitis, transient alopecia, arthritis, pharyngitis, cough, and maculopapular rash. An estimated one-fourth of patients or fewer experience a febrile phase of 3–6 days and then, after a brief remission, develop renewed fever accompanied by severe headache, nausea and vomiting, and meningeal signs lasting for ~1 week. These patients

virtually always recover fully, as do the uncommon patients with clear-cut signs of encephalitis. Recovery may be delayed by transient hydrocephalus.

During the initial febrile phase, leukopenia and thrombocytopenia are common and virus can usually be isolated from blood. During the CNS phase, virus may be found in the CSF, but antibodies are present in blood. The pathogenesis of LCM is thought to resemble that following direct intracranial inoculation of the virus into adult mice; the onset of the immune response leads to T cell–mediated immunopathologic meningitis. During the meningeal phase, CSF mononuclear-cell counts range from the hundreds to the low thousands per microliter, and hypoglycorrhachia is found in one-third of cases. The IgM-capture ELISA of serum and CSF is usually positive; RT-PCR assays have been developed for application to CSF. Recent infections transmitted by organ transplantation did not include evidence of an immune response, followed a fulminant course (not unlike that of Lassa fever), and required immunohistochemistry or RT-PCR for diagnosis.

Infection with LCM virus should be suspected in acutely ill febrile patients with marked leukopenia and thrombocytopenia. In cases of aseptic meningitis, any of the following should suggest LCM: well-marked febrile prodrome, adult age, autumn seasonality, low CSF glucose levels, or CSF mononuclear cell counts of >1000/μL.

In pregnant women, LCM virus infection may lead to fetal invasion with consequent congenital hydrocephalus and chorioretinitis. Since the maternal infection may be mild, consisting of only a short febrile illness, antibodies to the virus should be sought in both the mother and the fetus in suspicious circumstances, particularly TORCH-negative neonatal hydrocephalus. (TORCH is a battery of tests encompassing *t*oxoplasmosis, *o*ther conditions [congenital syphilis and viral infection], *r*ubella, *c*ytomegalovirus infection, and *h*erpes simplex virus infection.)

BUNYAMWERA VIRUS INFECTION

The mosquito-transmitted Bunyamwera serogroup viruses are found on every continent except Australia and Antarctica. Bunyamwera virus and its close relative Ilesha virus commonly cause febrile disease in Africa. Ngari virus, a reassortant of Bunyamwera virus, has recently been identified as an important human pathogen in Africa. Other related viruses are implicated in such disease in Southeast Asia (Batai virus), Europe (Calovo virus), and South America (Wyeomyia virus). In North America, Cache Valley virus has been implicated in febrile human disease and in rare instances of more serious systemic illness; the presence of serum antibodies to this virus may be associated with congenital malformations. In Central America, the closely related Fort Sherman virus causes the fever-myalgia syndrome.

GROUP C VIRUS INFECTION

The group C viruses include at least 11 agents transmitted by mosquitoes in neotropical forests. These agents are among the most common causes of arboviral infection in humans entering American jungles and cause acute febrile disease.

TAHYNA VIRUS INFECTION

This California serogroup virus (see discussion of California encephalitis, later in the chapter) occurs in central and western Europe, and related viruses are emerging in Russia. The significance of Tahyna virus in human health has been well studied only in the Czech and Slovak Republics; there, the virus was found to be a prominent cause of febrile disease, in some cases causing pharyngitis, pulmonary syndromes, and aseptic meningitis. The potential for arboviruses to be unexpectedly involved in such cases in areas of high mosquito prevalence needs to be kept in mind.

OROPOUCHE FEVER

Oropouche virus is transmitted in Central and South America by a biting midge, *Culicoides paraensis*, which often breeds to high density in cacao husks and other vegetable detritus found in towns and cities. Explosive epidemics involving thousands of cases have been reported from several towns in Brazil and Peru. Rash and aseptic meningitis have been detected in a number of cases.

SANDFLY FEVER

The sandfly *Phlebotomus papatasi* transmits sandfly fever. Female sandflies may be infected by the oral route as they take a blood meal and may transmit the virus to offspring when they lay their eggs after a second blood meal. This prominent transovarial pattern was the first to be recognized among dipterans and complicates virus control. A previous designation for sandfly fever, "3-day fever," instructively describes the brief, debilitating course associated with this essentially benign infection. There is neither a rash nor CNS involvement, and complete recovery is the rule.

Sandfly fever is found in the circum-Mediterranean area, extending to the east through the Balkans into parts of China as well as into the Middle East and southwestern Asia. The vector is found in both rural and urban settings and is known for its small size, which enables it to penetrate standard mosquito screens and netting, and for its short flight range. Epidemics have been described in the wake of natural disasters and wars. In parts of Europe, sandfly populations and virus transmission were greatly reduced by the extensive residual spraying conducted after World War II to control malaria, and the incidence continues to be low. A common pattern of disease in endemic areas consists of high attack rates among travelers and military personnel and little or no disease in the local population, who are protected after childhood infection. More than 30 related phleboviruses are transmitted by sandflies and mosquitoes, but most are of unknown significance in terms of human health.

TOSCANA VIRUS DISEASE

Toscana virus is a *Phlebovirus* (family Bunyaviridae) transmitted primarily by the circum-Mediterranean sandfly *P. perniciosus*. The vertebrate amplifying host, if one exists, is unknown. Toscana virus infection is common during the summer among rural residents and vacationers, particularly in Italy, Spain, and Portugal; a number of cases have been identified in travelers returning to Germany and Scandinavia. The disease may manifest as an uncomplicated febrile illness but is often associated with aseptic meningitis, with virus isolated from the CSF.

PUNTA TORO VIRUS DISEASE

Of the several phleboviruses that are associated with New World sandflies and infect humans, Punta Toro virus is the best known. The disease caused by this virus is clinically similar to but epidemiologically different from that caused by the Naples or Sicilian sandfly fever viruses. Punta Toro virus infections are sporadic and are acquired in the tropical forest, where the vectors rest on tree buttresses. Epidemics have not been reported, but antibody prevalences among inhabitants of villages in the endemic areas indicate a cumulative lifetime exposure rate of >50%.

DENGUE FEVER

All four distinct dengue viruses (dengue 1–4) have *Aedes aegypti* as their principal vector, and all cause a similar clinical syndrome. In rare cases, second infection with a serotype of dengue virus different from that involved in the primary infection leads to dengue HF with severe shock (see later). Sporadic cases are seen in the settings of endemic transmission and epidemic disease. Year-round transmission between latitudes 25°N and 25°S has been established, and seasonal forays of the viruses to points as far north as Philadelphia are thought to have taken place in the United States. Dengue fever is seen in the Caribbean region, including Puerto Rico. With increasing spread of the vector mosquito throughout the tropics and subtropics, large areas of the world have become vulnerable to the introduction of dengue viruses, particularly through air travel by infected humans, and both dengue fever and the related dengue HF are becoming increasingly common. Conditions favorable to dengue transmission exist in Hawaii and the southern United States, and bursts of dengue fever activity are to be expected in this region, particularly along the Mexican border, where water may be stored in containers and *A. aegypti* numbers may therefore be greatest. This mosquito, which is also an efficient vector of the yellow fever and chikungunya viruses, typically breeds near human habitation, using relatively fresh water from sources such as water jars, vases, discarded containers, coconut husks, and old tires. *A. aegypti* usually inhabits dwellings and bites during the day. Closed habitations with air-conditioning inhibit transmission of many arboviruses, as has been particularly well illustrated by studies along the Texas-Mexico border. *Aedes albopictus* has now extended its range from Asia to the United States, the Indian Ocean, and parts of Europe. For example, *A. albopictus* has transmitted dengue virus in Hawaii, chikungunya virus in Italy, and chikungunya virus in the Indian Ocean (see later in the chapter).

After an incubation period of 2–7 days, the typical patient experiences the sudden onset of fever, headache, retroorbital pain, and back pain along with the severe myalgia that gave rise to the colloquial designation "break-bone fever." There is often a macular rash on the first day as well as adenopathy, palatal vesicles, and scleral injection. The illness may last a week, with additional symptoms usually including anorexia, nausea or vomiting, marked cutaneous hypersensitivity, and—near the time of defervescence—a maculopapular rash beginning on the trunk and spreading to the extremities and the face. Epistaxis and scattered petechiae are often noted in uncomplicated dengue, and preexisting gastrointestinal lesions may bleed during the acute illness.

Laboratory findings include leukopenia, thrombocytopenia, and, in many cases, serum aminotransferase elevations. The diagnosis is made by IgM ELISA or paired serology during recovery or by antigen-detection ELISA or RT-PCR during the acute phase. Virus is readily isolated from blood in the acute phase if mosquito inoculation or mosquito cell culture is used.

COLORADO TICK FEVER

Several hundred cases of Colorado tick fever are reported annually in the United States. The infection is acquired between March and November through the bite of an infected *Dermacentor andersoni* tick in mountainous western regions at altitudes of 1200–3000 m (4000–10,000 ft). Small mammals serve as the amplifying host. The most common presentation consists of fever and myalgia; meningoencephalitis is not uncommon, and hemorrhagic disease, pericarditis, myocarditis, orchitis, and pulmonary presentations are also reported. Rash develops in a substantial minority of cases. The disease usually lasts 7–10 days and is often biphasic. The most important differential diagnostic considerations since the beginning of the twentieth century have been Rocky Mountain spotted fever and tularemia. In Colorado, Colorado tick fever is much more common than Rocky Mountain spotted fever.

Infection of erythroblasts and other marrow cells by Colorado tick fever virus results in the appearance and persistence (for several weeks) of erythrocytes containing the virus. This feature, detected in smears stained by immunofluorescence, can be diagnostically helpful. The clinical laboratory detects leukopenia and thrombocytopenia.

ORBIVIRUS INFECTION

The orbiviruses encompass many human and veterinary pathogens. For example, Orungo virus is widely transmitted by mosquitoes in tropical Africa and causes febrile disease in humans. The Kemerovo complex includes the Kemerovo, Lipovnik, and Tribec viruses of

Russia and central Europe; these viruses are transmitted by ticks and are associated with febrile and neurologic disease.

ENCEPHALITIS

Arboviral encephalitis is a seasonal disease, commonly occurring in the warmer months. Its incidence varies markedly with time and place, depending on ecologic factors. The causative viruses differ substantially in terms of case-infection ratio (i.e., the ratio of clinical to subclinical infections), mortality rate, and residua **(Table 102-3)**. Humans are not an important amplifier of these viruses.

All the viral encephalitides discussed in this section have a similar pathogenesis as far as is known. An infected arthropod ingests a blood meal from a human and infects the host. The initial period of viremia is thought to originate most commonly from the lymphoid system. Viremia leads to CNS invasion, presumably through infection of olfactory neuroepithelium with passage through the cribriform plate or through infection of brain capillaries and multifocal entry into the CNS. During the viremic phase, there may be little or no recognized disease except in the case of tick-borne flaviviral encephalitis, in which there may be a clearly delineated phase of fever and systemic illness. The disease process in the CNS arises partly from direct neuronal infection and subsequent damage and partly from edema, inflammation, and other indirect effects. The usual pathologic picture is one of focal necrosis of neurons, inflammatory glial nodules, and perivascular lymphoid cuffing; the severity and distribution of these abnormalities vary with the infecting virus. Involved areas display the "luxury perfusion" phenomenon, with normal or increased total blood flow and low oxygen extraction.

The typical patient presents with a prodrome of nonspecific constitutional symptoms, including fever, abdominal pain, vertigo, sore throat, and respiratory symptoms. Headache, meningeal signs, photophobia, and vomiting follow quickly. Involvement of deeper structures may be signaled by lethargy, somnolence, and intellectual deficit (as disclosed by the mental status examination or failure at serial 7 subtraction); more severely affected patients are obviously disoriented and may be comatose. Tremors, loss of abdominal reflexes, cranial nerve palsies, hemiparesis, monoparesis, difficulty in swallowing, and frontal lobe signs are all common. Spinal and motor neuron diseases are documented with West Nile and Japanese encephalitis viruses. Convulsions and focal signs may be evident early or may appear during the course of the disease. Some patients present with an abrupt onset of fever, convulsions, and other signs of CNS involvement. The results of human infection range from no significant symptoms through febrile headache to aseptic meningitis and finally to full-blown encephalitis; the proportions and severity of these manifestations vary with the infecting virus.

The acute encephalitis usually lasts from a few days to as long as 2–3 weeks, but recovery may be slow, with weeks or months required for the return of maximal recoupable function. Difficulty concentrating, fatigability, tremors, and personality changes are common during recovery. The acute illness requires management of a comatose patient who may have intracranial pressure elevations, inappropriate secretion of antidiuretic hormone, respiratory failure, and convulsions. There is no specific therapy for these viral encephalitides. The only practical preventive measures are vector management and personal protection against the arthropod transmitting the virus; for Japanese encephalitis or tick-borne encephalitis, vaccination should be considered in certain circumstances (see relevant sections that follow).

The diagnosis of arboviral encephalitis depends on the careful evaluation of a febrile patient with CNS disease, with rapid identification of treatable herpes simplex encephalitis, ruling out of brain abscess, exclusion of bacterial meningitis by serial CSF examination, and performance of laboratory studies to define the viral etiology. Leptospirosis, neurosyphilis, Lyme disease, cat-scratch fever, and newer viral encephalitides such as Nipah virus infection from Malaysia and southwestern Asia should be considered. The CSF examination usually shows a modest cell count—in the tens or hundreds or perhaps a few thousand. Early in the process, a significant proportion of these cells may be polymorphonuclear leukocytes, but usually there is a mononuclear cell predominance. CSF glucose levels are generally normal. There are exceptions to this pattern of findings. In eastern equine encephalitis, for example, polymorphonuclear leukocytes may predominate during the first 72 h of disease and hypoglycorrhachia may be detected. In LCM, lymphocyte counts may be in the thousands, and the glucose concentration may be diminished. Experience with imaging studies is still evolving; clearly, however, both CT and MRI may be normal, except for evidence of preexisting conditions, or sometimes may suggest diffuse edema. Several patients with eastern equine encephalitis have had focal abnormalities, and individuals with severe Japanese encephalitis have presented with bilateral thalamic lesions that have often been hemorrhagic. Electroencephalography usually shows diffuse abnormalities and is not directly helpful.

A humoral immune response is usually detectable at or near the onset of disease. Both serum and CSF should be examined for IgM antibodies. Virus generally cannot be isolated from blood or CSF, although Japanese encephalitis virus has been recovered from CSF in severe cases. RT-PCR analysis of CSF may yield positive results. Virus can be obtained from and viral antigen is present in brain tissue, although its distribution may be focal.

CALIFORNIA, LA CROSSE, AND JAMESTOWN CANYON VIRUS ENCEPHALITIS

The isolation of California encephalitis virus established the California serogroup of viruses as a cause of encephalitis, and its use as a diagnostic antigen led to the description of many cases of "California encephalitis."

TABLE 102-3

PROMINENT FEATURES OF ARBOVIRAL ENCEPHALITIS

VIRUS	NATURAL CYCLE	INCUBATION PERIOD, DAYS	ANNUAL NO. OF CASES	CASE-TO-INFECTION RATIO	AGE OF CASES	CASE-FATALITY RATE, %	RESIDUA
La Crosse	*Aedes triseriatus*–chipmunk (transovarial component in mosquito also important)	~3–7	70 (U.S.)	<1:1000	<15 years	<0.5	Recurrent seizures in ~10%; severe deficits in rare cases; decreased school performance and behavioral change suspected in small proportion
St. Louis	*Culex tarsalis*, *C. pipiens*, *C. quinquefasciatus*–birds	4–21	85, with hundreds to thousands in epidemic years (U.S.)	<1:200	Milder cases in the young; more severe cases in adults >40 years old, particularly the elderly	7	Common in the elderly
Japanese	*Culex tritaeniorhynchus*–birds	5–15	>25,000	1:200–300	All ages; children in highly endemic areas	20–50	Common (approximately half of cases); may be severe
West Nile	*Culex* mosquitoes–birds	3–6	?	Very low	Mainly the elderly	5–10	Uncommon
Central European	*Ixodes ricinus*–rodents, insectivores	7–14	Thousands	1:12	All ages; milder in children	1–5	20%
Russian spring-summer	*I. persulcatus*–rodents, insectivores	7–14	Hundreds	—	All ages; milder in children	20	Approximately half of cases; often severe; limb-girdle paralysis
Powassan	*I. cookei*–wild mammals	~10	~1 (U.S.)	—	All ages; some predilection for children	~10	Common (approximately half of cases)
Eastern equine	*Culiseta melanura*–birds	~5–10	5 (U.S.)	1:40 (adult) 1:17 (child)	All ages; predilection for children	50–75	Common
Western equine	*Culex tarsalis*–birds	~5–10	~20 (U.S.)	1:1000 (adult) 1:50 (child) 1:1 (infant)	All ages; predilection for children <2 years old (increased mortality among elderly)	3–7	Common only among infants <1 year old
Venezuelan equine (epidemic)	Unknown (multiple mosquito species and horses in epidemics)	1–5	?	1:250 (adult) ~1:25 (child)	All ages; predilection for children	~10	—

In fact, however, this virus has been implicated in only a few cases of encephalitis, and the serologically related La Crosse virus is the major cause of encephalitis among viruses in the California serogroup. "California encephalitis" due to La Crosse virus infection is most commonly reported from the upper Midwest but is also found in other areas of the central and eastern United States, most often in West Virginia, Tennessee, North Carolina, and Georgia. The serogroup includes 13 other viruses, some of which may also be involved in human disease that is misattributed because of the complexity of the group's serology; these viruses include the Jamestown Canyon, snowshoe hare, Inkoo, and Trivittatus viruses, all of which have *Aedes* mosquitoes as their vector and all of which have a strong element of transovarial transmission in their natural cycles.

The mosquito vector of La Crosse virus is *A. triseriatus*. In addition to a prominent transovarial component of transmission, a mosquito can become infected through feeding on viremic chipmunks and other mammals as well as through venereal transmission from another mosquito. The mosquito breeds in sites such as tree holes and abandoned tires and bites during daylight hours. These habits correlate with the risk factors for human cases: recreation in forested areas, residence at the forest's edge, and the presence of abandoned tires around the home. Intensive environmental modification based on these findings has reduced the incidence of disease in a highly endemic area in the Midwest. Most cases occur from July through September. The Asian tiger mosquito, *A. albopictus*, efficiently transmits the virus to mice and also transmits the agent transovarially in the laboratory; this aggressive anthropophilic mosquito has the capacity to urbanize, and its possible impact on transmission to humans is of concern.

An antibody prevalence of ≥20% in endemic areas indicates that infection is common, but CNS disease has been recognized primarily in children <15 years of age. The illness varies from a picture of aseptic meningitis accompanied by confusion to severe and occasionally fatal encephalitis. Although there may be prodromal symptoms, the onset of CNS disease is sudden, with fever, headache, and lethargy often joined by nausea and vomiting, convulsions (in one-half of patients), and coma (in one-third of patients). Focal seizures, hemiparesis, tremor, aphasia, chorea, Babinski signs, and other evidence of significant neurologic dysfunction are common, but residua are not. Perhaps 10% of patients have recurrent seizures in the succeeding months. Other serious sequelae are rare, although a decrease in scholastic standing has been reported and mild personality change has occasionally been suggested. Treatment is supportive over a 1- to 2-week acute phase during which status epilepticus, cerebral edema, and inappropriate secretion of antidiuretic hormone are important concerns. Ribavirin has been used in severe cases, and a clinical trial of this drug is under way.

The blood leukocyte count is commonly elevated, sometimes reaching levels of 20,000/μL, and there is usually a left shift. CSF cell counts are typically 30–500/μL with a mononuclear cell predominance (although 25–90% of cells are polymorphonuclear in some cases). The protein level is normal or slightly increased, and the glucose level is normal. Specific virologic diagnosis based on IgM-capture assays of serum and CSF is efficient. The only human anatomic site from which virus has been isolated is the brain.

Jamestown Canyon virus has been implicated in several cases of encephalitis in adults; in these cases, the disease was usually associated with a significant respiratory illness at onset. Human infection with this virus has been documented in New York, Wisconsin, Ohio, Michigan, Ontario, and other areas of North America where the vector mosquito, *A. stimulans*, feeds on its main host, the white-tailed deer.

ST. LOUIS ENCEPHALITIS

St. Louis encephalitis virus is transmitted between *Culex* mosquitoes and birds. This virus causes low-level endemic infection among rural residents of the western and central United States, where *C. tarsalis* is the vector (see "Western Equine Encephalitis"), but the more urbanized mosquito species *C. pipiens* and *C. quinquefasciatus* have been responsible for epidemics resulting in hundreds or even thousands of cases in cities of the central and eastern United States. Most cases occur in June through October. The urban mosquitoes breed in accumulations of stagnant water and sewage with high organic content and readily bite humans in and around houses at dusk. The elimination of open sewers and trash-filled drainage systems is expensive and may not be possible, but screening of houses and implementation of personal protective measures may be an effective approach for individuals. The rural vector is most active at dusk and outdoors; its bites can be avoided by modification of activities and use of repellents.

Disease severity increases with age: infections that result in aseptic meningitis or mild encephalitis are concentrated in children and young adults, while severe and fatal cases primarily affect the elderly. Infection rates are similar in all age groups; thus the greater susceptibility of older persons to disease is a biologic consequence of aging. The disease has an abrupt onset, sometimes following a prodrome, and begins with fever, lethargy, confusion, and headache. In addition, nuchal rigidity, hypotonia, hyperreflexia, myoclonus, and tremor are common. Severe cases can include cranial nerve palsies, hemiparesis, and convulsions. Patients often report dysuria and may have viral antigen in urine as well as pyuria. The overall mortality rate is generally ~7%, but may reach 20% among patients over the age of 60. Recovery is slow. Emotional lability, difficulties in concentration and memory, asthenia, and tremor are commonly prolonged in older patients.

The CSF of patients with St. Louis encephalitis usually contains tens to hundreds of cells, with a lymphocytic predominance and a normal glucose level. Leukocytosis with a left shift is often documented.

JAPANESE ENCEPHALITIS

Japanese encephalitis virus is found throughout Asia, including far eastern Russia, Japan, China, India, Pakistan, and Southeast Asia, and causes occasional epidemics on western Pacific islands. The virus has been detected in the Torres Strait islands, and a human encephalitis case has been identified on the nearby Australian mainland. This flavivirus is particularly common in areas where irrigated rice fields attract the natural avian vertebrate hosts and provide abundant breeding sites for mosquitoes such as *C. tritaeniorhynchus*, which transmit the virus to humans. Additional amplification by pigs, which suffer abortion, and horses, which develop encephalitis, may be significant as well. Vaccination of these additional amplifying hosts may reduce the transmission of the virus. An effective, formalin-inactivated vaccine purified from mouse brain is produced in Japan and licensed for human use in the United States. It is given on days 0, 7, and 30 or—with some sacrifice in serum neutralizing titer—on days 0, 7, and 14. Vaccination is indicated for summer travelers to rural Asia, where the risk of clinical disease may be 0.05–2.1/10,000 per week. The severe and often fatal disease reported in expatriates must be balanced against the 0.1–1% chance of a late systemic or cutaneous allergic reaction. These reactions are rarely fatal but may be severe and have been known to begin 1–9 days after vaccination, with associated pruritus, urticaria, and angioedema. Live attenuated vaccines are being used in China, but are not recommended in the United States at this time.

WEST NILE VIRUS INFECTION

West Nile virus was initially described as being transmitted among wild birds by *Culex* mosquitoes in Africa, the Middle East, southern Europe, and Asia. It is a common cause of febrile disease without CNS involvement, but it occasionally causes aseptic meningitis and severe encephalitis; these serious infections are particularly common among the elderly. The febrile-myalgic syndrome caused by West Nile virus differs from many others by the frequent appearance of a maculopapular rash concentrated on the trunk and lymphadenopathy. Headache, ocular pain, sore throat, nausea and vomiting, and arthralgia (but not arthritis) are common accompaniments. In addition, the virus has been implicated in severe and fatal hepatic necrosis in Africa.

West Nile virus was introduced into New York City in 1999 and subsequently spread to other areas of the northeastern United States, causing >60 cases of aseptic meningitis or encephalitis among humans as well as die-offs among crows, exotic zoo birds, and other birds. The virus has continued to spread and is now found in almost all states as well as in Canada, Mexico, South America, and the Caribbean. *C. pipiens* remains the major vector in the northeastern United States, but several other *Culex* species are also involved, and blue jays compete with crows as amplifiers and lethal targets in other areas of the country. Annually, ~1000–3000 cases of encephalitis with ~100–300 deaths are reported in the United States. The ratio of CNS involvement to infection is thought to be ~1:100; the remainder of patients have subclinical infection or West Nile fever. Encephalitis, sequelae, and death are all more common among elderly, diabetic, and hypertensive patients and among patients with previous CNS insults. In addition to the more severe motor and cognitive sequelae, milder findings may include tremor, slight abnormalities in motor skills, and loss of executive functions. Intense clinical interest and the availability of laboratory diagnostic methods have made it possible to define a number of unusual clinical features, including chorioretinitis, flaccid paralysis with histologic lesions resembling poliomyelitis, and initial presentation with fever and focal neurologic deficits in the absence of diffuse encephalitis. Immunosuppressed patients may have fulminant courses or develop persistent CNS infection. Virus transmission through both transplantation and blood transfusion has necessitated screening of blood and organ donors by nucleic acid–based tests. Pregnant women may occasionally infect the fetus. All these "new" findings, particularly transfusion-transmitted disease and severe disease associated with transplantation, show what could be expected in the United States should other arboviruses be transmitted in North America with a high frequency or should surveillance in other areas of the world be more efficient and deeper.

West Nile virus falls into the same phylogenetic group of flaviviruses as St. Louis and Japanese encephalitis viruses, as do Murray Valley and Rocio viruses. The latter two viruses are both maintained in mosquitoes and birds and produce a clinical picture resembling that of Japanese encephalitis. Murray Valley virus has caused occasional epidemics and sporadic cases in Australia. Rocio virus caused recurrent epidemics in a focal area of Brazil in 1975–1977 and then virtually disappeared.

CENTRAL EUROPEAN TICK-BORNE ENCEPHALITIS AND RUSSIAN SPRING-SUMMER ENCEPHALITIS

A spectrum of tick-borne flaviviruses has been identified across the Eurasian land mass. Many are known mainly as agricultural pathogens (e.g., louping ill virus in the United Kingdom). From Scandinavia to the Urals, central European tick-borne encephalitis is transmitted by *Ixodes ricinus*. Human cases occur between April and October, with a peak in June and July. A related and more virulent virus is that of Russian spring-summer encephalitis, which is associated with *I. persulcatus* and is distributed from Europe across the Urals to the Pacific Ocean. The ticks transmit the disease primarily in the spring and early summer, with a lower rate of transmission later in summer. Small mammals are the vertebrate amplifiers for both viruses. The risk varies by geographic area and can be highly localized within a given area; human cases usually follow outdoor activities or consumption of raw milk from infected goats or other infected animals.

After an incubation period of 7–14 days or perhaps longer, the central European viruses classically result in a febrile-myalgic phase that lasts for 2–4 days and is thought to correlate with viremia. A subsequent remission for several days is followed by the recurrence of fever and the onset of meningeal signs. The CNS phase varies from mild aseptic meningitis, which is more common among younger patients, to severe encephalitis with coma, convulsions, tremors, and motor signs lasting for 7–10 days before improvement begins. Spinal and medullary involvement can lead to typical limb-girdle paralysis and to respiratory paralysis. Most patients recover, only a minority with significant deficits. Infections with the Far Eastern viruses generally run a more abrupt course. The encephalitic syndrome caused by these viruses sometimes begins without a remission and has more severe manifestations than the European syndrome. The mortality rate is high, and major sequelae—most notably, lower motor neuron paralyses of the proximal muscles of the extremities, trunk, and neck—are common.

In the early stage of the illness, virus may be isolated from the blood. In the CNS phase, IgM antibodies are detectable in serum and/or CSF. Thrombocytopenia sometimes develops during the initial febrile illness, which resembles the early hemorrhagic phase of some other tick-borne flaviviral infections, such as Kyasanur Forest disease. Other tick-borne flaviviruses are less common causes of encephalitis, including louping ill virus in the United Kingdom and Powassan virus.

There is no specific therapy for infection with these viruses. However, effective alum-adjuvanted, formalin-inactivated vaccines are produced in Austria, Germany, and Russia. Two doses of the Austrian vaccine separated by an interval of 1–3 months appear to be effective in the field, and antibody responses are similar when vaccine is given on days 0 and 14. Other vaccines have elicited similar neutralizing antibody titers. Since rare cases of postvaccination Guillain-Barré syndrome have been reported, vaccination should be reserved for persons likely to experience rural exposure in an endemic area during the season of transmission. Cross-neutralization for the central European and Far Eastern strains has been established, but there are no published field studies on cross-protection of formalin-inactivated vaccines. Because 0.2–4% of ticks in endemic areas may be infected, tick bites raise the issue of immunoglobulin prophylaxis. Prompt administration of high-titered specific preparations should probably be undertaken, although no controlled data are available to prove the efficacy of this measure. Immunoglobulin should not be administered late because of the risk of antibody-mediated enhancement.

POWASSAN ENCEPHALITIS

Powassan virus is a member of the tick-borne encephalitis virus complex and is transmitted by *I. cookei* among small mammals in eastern Canada and the United States, where it has been responsible for 20 recognized cases of human disease. Other ticks may transmit the virus in a wider geographic area, and there is some concern that *I. scapularis* (also called *I. dammini*), a competent vector in the laboratory, may become involved as it becomes more prominent in the United States. Patients with Powassan encephalitis (many of whom are children) present in May through December after outdoor exposure and an incubation period thought to be ~1 week. Powassan encephalitis is severe, and sequelae are common.

EASTERN EQUINE ENCEPHALITIS

Eastern equine encephalitis is found primarily within endemic swampy foci along the eastern coast of the United States, with a few inland foci as far removed as Michigan. Human cases present from June through October, when the bird–*Culiseta* mosquito cycle spills over into other mosquito species such as *A. sollicitans* or *A. vexans*, which are more likely to bite mammals. There is concern over the potential role of the introduced anthropophilic mosquito species *A. albopictus*, which has been found to be naturally infected and is an effective vector in the laboratory. Horses are a common target for the virus; contact with unvaccinated horses may be associated with human disease, but horses probably do not play a significant role in amplification of the virus.

Eastern equine encephalitis is one of the most destructive of the arboviral conditions, with a brusque onset, rapid progression, high mortality rate, and frequent residua. This severity is reflected in the extensive necrotic lesions and polymorphonuclear infiltrates found at postmortem examination of the brain and the acute polymorphonuclear CSF pleocytosis often occurring during the first 1–3 days of disease. In addition, leukocytosis with a left shift is a common feature. A formalin-inactivated vaccine has been used to protect laboratory workers but is not generally available or applicable.

WESTERN EQUINE ENCEPHALITIS

The primary maintenance cycle for western equine encephalitis virus in the United States is between *C. tarsalis* and birds, principally sparrows and finches. Equines and humans become infected, and both species suffer encephalitis without amplifying the virus in nature. St. Louis encephalitis is transmitted in a similar cycle in the same region but causes human disease about a month earlier than the period (July through October) in which western equine encephalitis virus is active. Large epidemics of western equine encephalitis took place in the western and central United States and Canada during the 1930s to 1950s, but in recent years the disease has been uncommon. There were 41 reported cases in the United States in 1987 but only 5 reported cases from 1988 to 2001. This decline in incidence may reflect in part the integrated approach to mosquito management that has been employed in irrigation projects and the

increasing use of agricultural pesticides; it almost certainly reflects the increased tendency for humans to be indoors behind closed windows at dusk—the peak period of biting by the major vector.

Western equine encephalitis virus causes a typical diffuse viral encephalitis with an increased attack rate and increased morbidity rate among the young, particularly children <2 years old. In addition, mortality rates are high among the young and the very elderly. One-third of individuals who have convulsions during the acute illness have subsequent seizure activity. Infants <1 year old—particularly those in the first months of life—are at serious risk of motor and intellectual damage. Twice as many males as females develop clinical encephalitis after 5–9 years of age; this difference may be related to greater outdoor exposure of boys to the vector but is also likely to be due in part to biologic differences. A formalin-inactivated vaccine has been used to protect laboratory workers but is not generally available or applicable.

VENEZUELAN EQUINE ENCEPHALITIS

There are six known types of virus in the Venezuelan equine encephalitis complex. An important distinction is between the *epizootic* viruses (subtypes IAB and IC) and the *enzootic* viruses (subtypes ID to IF and types II to VI). The epizootic viruses have an unknown natural cycle but periodically cause extensive epidemics in equines and humans in the Americas. These epidemics rely on the high-level viremia in horses and mules that results in the infection of several species of mosquitoes, which in turn infect humans and perpetuate virus transmission. Humans also have high-level viremia but probably are not important in virus transmission. Enzootic viruses are found primarily in humid tropical forest habitats and are maintained between *Culex* mosquitoes and rodents; these viruses cause human disease but are not pathogenic for horses and do not cause epizootics.

Epizootics of Venezuelan equine encephalitis occurred repeatedly in Venezuela, Colombia, Ecuador, Peru, and other South American countries at intervals of ≤10 years from the 1930s until 1969, when a massive epizootic spread throughout Central America and Mexico, reaching southern Texas in 1972. Genetic sequencing of the virus from the 1969–1972 outbreak suggested that it originated from residual "un-inactivated" virus in veterinary vaccines. The outbreak was terminated in Texas with the use of a live attenuated vaccine (TC-83) originally developed for human use by the U.S. Army; the epizootic virus was then used for further production of inactivated veterinary vaccines. No further epizootic disease was identified until 1995 and subsequently, when additional epizootics took place in Colombia, Venezuela, and Mexico. The viruses involved in these epizootics as well as previously epizootic subtype IC viruses have been shown to be close phylogenetic relatives of known enzootic subtype ID viruses. This finding suggests that active evolution and selection of epizootic viruses are under way in northern South America.

During epizootics, extensive human infection is the rule, with clinical disease in 10–60% of infected individuals. Most infections result in notable acute febrile disease, while relatively few result in encephalitis. A low rate of CNS invasion is supported by the absence of encephalitis among the many infections resulting from exposure to aerosols in the laboratory or from vaccine accidents. The most recent large epizootic of Venezuelan equine encephalitis occurred in Colombia and Venezuela in 1995; of the >85,000 clinical cases, 4% (with a higher proportion among children than adults) included neurologic symptoms and 300 ended in death.

Enzootic strains of Venezuelan equine encephalitis virus are common causes of acute febrile disease, particularly in areas such as the Florida Everglades and the humid Atlantic coast of Central America. Encephalitis has been documented only in the Florida infections; the three cases were caused by type II enzootic virus, also called *Everglades virus*. All three patients had preexisting cerebral disease. Extrapolation from the rate of genetic change suggests that Everglades virus may have been introduced into Florida <200 years ago and that it is most closely related to the ID subtypes that appear to have given evolutionary rise to the epizootic strains active in South America.

The prevention of epizootic Venezuelan equine encephalitis depends on vaccination of horses with the attenuated TC-83 vaccine or with an inactivated vaccine prepared from that strain. Humans can be protected with similar vaccines, but the use of such products is restricted to laboratory personnel because of reactogenicity and limited availability. In addition, wild-type virus and perhaps TC-83 vaccine may have some degree of fetal pathogenicity. Enzootic viruses are genetically and antigenically different from epizootic viruses, and protection against the former with vaccines prepared from the latter is relatively ineffective.

ARTHRITIS AND RASH

True arthritis is a common accompaniment of several viral diseases, such as rubella (caused by a non-alphavirus togavirus), parvovirus B19 infection, and hepatitis B; it is an occasional accompaniment of infection due to mumps virus, enteroviruses, herpesviruses, and adenoviruses. It is not generally appreciated that the alphaviruses are also common causes of arthritis. In fact, the lphaviruses discussed next all cause acute febrile diseases accompanied by the development of true arthritis and a maculopapular rash. Rheumatic involvement includes arthralgia alone, periarticular swelling, and (less commonly) joint effusions. Most of these diseases are less severe and have fewer articular manifestations in children than in adults. In temperate climates, these are summer diseases. No specific therapy or licensed vaccines exist.

SINDBIS VIRUS INFECTION

Sindbis virus is transmitted among birds by mosquitoes. Infections with the northern European strains of

this virus (which cause, for example, Pogosta disease in Finland, Karelian fever in the independent states of the former Soviet Union, and Ockelbo disease in Sweden) and with the genetically related southern African strains are particularly likely to result in the arthritis-rash syndrome. Exposure to a rural environment is commonly associated with this infection, which has an incubation period of <1 week.

The disease begins with rash and arthralgia. Constitutional symptoms are not marked, and fever is modest or lacking altogether. The rash, which lasts ~1 week, begins on the trunk, spreads to the extremities, and evolves from macules to papules that often vesiculate. The arthritis of this condition is multiarticular, migratory, and incapacitating, with resolution of the acute phase in a few days. Wrists, ankles, phalangeal joints, knees, elbows, and—to a much lesser extent—proximal and axial joints are involved. Persistence of joint pains and occasionally of arthritis is a major problem and may go on for months or even years despite a lack of deformity.

CHIKUNGUNYA VIRUS INFECTION

It is likely that chikungunya virus ("that which bends up") is of African origin and is maintained among nonhuman primates on that continent by *Aedes* mosquitoes of the subgenus *Stegomyia* in a fashion similar to yellow fever virus. Like yellow fever virus, chikungunya virus is readily transmitted among humans in urban areas by *A. aegypti*. The *A. aegypti*–chikungunya virus transmission cycle has also been introduced into Asia, where it poses a prominent health problem. The disease is endemic in rural areas of Africa, and intermittent epidemics take place in towns and cities of Africa and Asia. In 2004, a massive epidemic in the Indian Ocean region began; it now appears to have been spread by travelers. *A. albopictus* was identified as the major vector, and there were multiple exportations to temperate zones and to areas where *A. aegypti* is present. Chikungunya is one more reason (in addition to dengue and yellow fever) that *A. aegypti* and *A. albopictus* must be controlled.

Full-blown disease is most common among adults, in whom the clinical picture may be dramatic. The abrupt onset follows an incubation period of 2–3 days. Fever and severe arthralgia are accompanied by chills and constitutional symptoms such as headache, photophobia, conjunctival injection, anorexia, nausea, and abdominal pain. Migratory polyarthritis mainly affects the small joints of the hands, wrists, ankles, and feet, with lesser involvement of the larger joints. Rash may appear at the outset or several days into the illness; its development often coincides with defervescence, which takes place around day 2 or 3 of disease. The rash is most intense on the trunk and limbs and may desquamate. Petechiae are occasionally seen, and epistaxis is not uncommon, but this virus is not a regular cause of the HF syndrome, even in children. A few patients develop leukopenia. Elevated levels of aspartate aminotransferase (AST) and C-reactive protein have been described, as have mildly decreased platelet counts. Recovery may require weeks. Some older patients continue to experience stiffness, joint pain, and recurrent effusions for several years; this persistence may be especially common in HLA-B27 patients. An investigational live attenuated vaccine has been developed but requires additional testing. It appears to be headed for further development and commercial manufacture stimulated by the Indian Ocean outbreak.

A related virus, O'nyong-nyong, caused a major epidemic of arthritis and rash involving at least 2 million people as it moved across eastern and central Africa in the 1960s. After its mysterious emergence, the virus virtually disappeared, leaving only occasional evidence of its persistence in Kenya until a transient resurgence of epidemic activity in 1997.

MAYARO FEVER

Mayaro virus is maintained in the forests of the Americas by *Haemagogus* mosquitoes and nonhuman primates. It causes a frequently endemic and sometimes epidemic infection of humans and appears to produce a syndrome resembling chikungunya virus infection.

EPIDEMIC POLYARTHRITIS (ROSS RIVER VIRUS INFECTION)

Ross River virus has caused epidemics of distinctive clinical disease in Australia since the beginning of the twentieth century and continues to be responsible for thousands of cases in rural and suburban areas annually. The virus is transmitted by *A. vigilax* and other mosquitoes, and its persistence is thought to involve transovarial transmission. No definitive vertebrate host has been identified, but several mammalian species, including wallabies, have been suggested. Endemic transmission has also been documented in New Guinea, and in 1979 the virus swept through the eastern Pacific Islands, causing hundreds of thousands of illnesses. The virus was carried from island to island by infected humans and was believed to have been transmitted among humans by *A. polynesiensis* and *A. aegypti*.

The incubation period is 7–11 days long, and the onset of illness is sudden, with joint pain usually ushering in the disease. The rash generally develops coincidentally or follows shortly but in some cases precedes joint pains by several days. Constitutional symptoms such as low-grade fever, asthenia, myalgia, headache, and nausea are not prominent and indeed are absent in many cases. Most patients are incapacitated for considerable periods by joint involvement, which interferes with sleeping, walking, and grasping. Wrist, ankle, metacarpophalangeal, interphalangeal, and knee joints are the most commonly involved, although toes, shoulders, and elbows may be affected with some frequency. Periarticular swelling and tenosynovitis are common, and one-third of patients have true arthritis. Only half of all arthritis patients can resume normal activities within 4 weeks, and 10% still must limit their activity at 3 months. Occasional patients are symptomatic for 1–3 years but without progressive arthropathy. Aspirin and nonsteroidal anti-inflammatory drugs are effective for the treatment of symptoms.

Clinical laboratory values are normal or variable in Ross River virus infection. Tests for rheumatoid factor and antinuclear antibodies are negative, and the erythrocyte sedimentation rate is acutely elevated. Joint fluid contains 1000–60,000 mononuclear cells/μL, and Ross River virus antigen is demonstrable in macrophages. IgM antibodies are valuable in the diagnosis of this infection, although they occasionally persist for years. The isolation of the virus from blood by mosquito inoculation or mosquito cell culture is possible early in the illness. Because of the great economic impact of annual epidemics in Australia, an inactivated vaccine is being developed and has been found to be protective in mice.

Perhaps because of the local interest in arboviruses in general and in Ross River virus in particular, other arthritogenic arboviruses have been identified in Australia, including Gan Gan virus, a member of the family Bunyaviridae; Kokobera virus, a flavivirus; and Barmah Forest virus, an alphavirus. The last virus is a common cause of infection and must be differentiated from Ross River virus by specific testing.

HEMORRHAGIC FEVERS

The viral HF syndrome is a constellation of findings based on vascular instability and decreased vascular integrity. An assault, direct or indirect, on the microvasculature leads to increased permeability and (particularly when platelet function is decreased) to actual disruption and local hemorrhage. Blood pressure is decreased, and in severe cases shock supervenes. Cutaneous flushing and conjunctival suffusion are examples of common, observable abnormalities in the control of local circulation. The hemorrhage is inconstant and is in most cases an indication of widespread vascular damage rather than a life-threatening loss of blood volume. Disseminated intravascular coagulation (DIC) is occasionally found in any severely ill patient with HF but is thought to occur regularly only in the early phases of HF with renal syndrome, Crimean-Congo HF, and perhaps some cases of filovirus HF. In some viral HF syndromes, specific organs may be particularly impaired, such as the kidney in HF with renal syndrome, the lung in hantavirus pulmonary syndrome, or the liver in yellow fever, but in all these diseases the generalized circulatory disturbance is critically important.

The pathogenesis of HF is poorly understood and varies among the viruses regularly implicated in the syndrome, which number more than a dozen. In some cases direct damage to the vascular system or even to parenchymal cells of target organs is important, whereas in others soluble mediators are thought to play the major role. The acute phase in most cases of HF is associated with ongoing virus replication and viremia. Exceptions are the hantavirus diseases and dengue HF/dengue shock syndrome (DHF/DSS), in which the immune response plays a major pathogenic role.

The HF syndromes all begin with fever and myalgia, usually of abrupt onset. Within a few days the patient presents for medical attention because of increasing prostration that is often accompanied by severe headache, dizziness, photophobia, hyperesthesia, abdominal or chest pain, anorexia, nausea or vomiting, and other gastrointestinal disturbances. Initial examination often reveals only an acutely ill patient with conjunctival suffusion, tenderness to palpation of muscles or abdomen, and borderline hypotension or postural hypotension, perhaps with tachycardia. Petechiae (often best visualized in the axillae), flushing of the head and thorax, periorbital edema, and proteinuria are common. Levels of AST are usually elevated at presentation or within a day or two thereafter. Hemoconcentration from vascular leakage, which is usually evident, is most marked in hantavirus diseases and in DHF/DSS. The seriously ill patient progresses to more severe symptoms and develops shock and other findings typical of the causative virus. Shock, multifocal bleeding, and CNS involvement (encephalopathy, coma, convulsions) are all poor prognostic signs.

One of the major diagnostic clues is travel to an endemic area within the incubation period for a given syndrome **(Table 102-4)**. Except for Seoul, dengue, and yellow fever virus infections, which have urban vectors, travel to a rural setting is especially suggestive of a diagnosis of HF.

Early recognition is important because of the need for virus-specific therapy and supportive measures, including prompt, atraumatic hospitalization; judicious fluid therapy that takes into account the patient's increased capillary permeability; administration of cardiotonic drugs; use of pressors to maintain blood pressure at levels that will support renal perfusion; treatment of the relatively common secondary bacterial infections; replacement of clotting factors and platelets as indicated; and the usual precautionary measures used in the treatment of patients with hemorrhagic diatheses. DIC should be treated only if clear laboratory evidence of its existence is found and if laboratory monitoring of therapy is feasible; there is no proven benefit of such therapy. The available evidence suggests that HF patients have a decreased cardiac output and will respond poorly to fluid loading as it is often practiced in the treatment of shock associated with bacterial sepsis. Specific therapy is available for several of the HF syndromes. In addition, several diseases considered in the differential diagnosis—malaria, shigellosis, typhoid fever, leptospirosis, relapsing fever, and rickettsial diseases—are treatable and potentially lethal. Strict barrier nursing and other precautions against infection of medical staff and visitors are indicated in HF except that due to hantaviruses, yellow fever, Rift Valley fever, and dengue.

LASSA FEVER

Lassa virus is known to cause endemic and epidemic disease in Nigeria, Sierra Leone, Guinea, and Liberia, although it is probably more widely distributed in West Africa. This virus and its relatives exist elsewhere in Africa, but their health significance is unknown. Like other arenaviruses, Lassa virus is spread to humans by small-particle aerosols from chronically infected rodents and may also be

TABLE 102-4

VIRAL HEMORRHAGIC FEVER (HF) SYNDROMES AND THEIR DISTRIBUTION

DISEASE	INCUBATION PERIOD, DAYS	CASE-INFECTION RATIO	CASE-FATALITY RATE, %	GEOGRAPHIC RANGE	TARGET POPULATION
Lassa fever	5–16	Mild infections probably common	15	West Africa	All ages, both sexes
South American HF	7–14	Most infections (more than half) result in disease	15–30	Selected rural areas of Bolivia, Argentina, Venezuela, and Brazil	Bolivia: Men in countryside; all ages, both sexes in villages Argentina: All ages, both sexes; excess exposure and disease in men Venezuela: All ages, both sexes
Rift Valley fever	2–5	~1:100[a]	~50	Sub-Saharan Africa, Madagascar, Egypt	All ages, both sexes; more often diagnosed in men; preexisting liver disease may predispose
Crimean-Congo HF	3–12	≥1:5	15–30	Africa, Middle East, Turkey, Balkans, southern region of former Soviet Union, western China	All ages, both sexes; men more exposed in some settings
HF with renal syndrome	9–35	Hantaan, >1:1.25; Puumala, 1:20	Hantaan, 5–15; Puumala, <1	Worldwide, depending on rodent reservoir	Excess of male patients (partially due to greater exposure); mainly adults
Hantavirus pulmonary syndrome	~7–28	Very high	40–50	Americas	Excess of male patients due to some occupational exposure; mainly adults
Marburg or Ebola HF	3–16	High	25–90	Sub-Saharan Africa	All ages, both sexes; children less exposed
Yellow fever	3–6	1:2–1:20	20	Africa, South America	All ages, both sexes; adults more exposed in jungle setting; preexisting flavivirus immunity may cross-protect
Dengue HF/dengue shock syndrome	2–7	Nonimmune, 1:10,000; heterologous immune, 1:100	<1 with supportive treatment	Tropics and subtropics worldwide	Predominantly children; previous heterologous dengue infection predisposes to HF
Kyasanur Forest/Omsk HF	3–8	Variable	0.5–10	Mysore State, India/western Siberia	Variable

[a]Figure is for HF cases only. Most infections with Rift Valley fever virus result in fever and myalgia rather than HF.

acquired during the capture or eating of these animals. It can be transmitted by close person-to-person contact. The virus is often present in urine during convalescence and is suspected to be present in seminal fluid early in recovery. Nosocomial spread has occurred but is uncommon if proper sterile parenteral techniques are used. Individuals of all ages and both sexes are affected; the incidence of disease is highest in the dry season, but transmission takes place year-round. In countries where Lassa virus is endemic, Lassa fever can be a prominent cause of febrile disease. For example, in one hospital in Sierra Leone, laboratory-confirmed Lassa fever is consistently responsible

for one-fifth of admissions to the medical wards. There are probably tens of thousands of Lassa fever cases annually in West Africa alone. New arenaviruses continue to be discovered, often without being thoroughly characterized. These arenaviruses include Chapare virus in Bolivia (distinct from Machupo virus) and Lujo virus in Zambia.

Among the HF agents, only the arenaviruses are typically associated with a gradual onset of illness. The average case of Lassa fever has a gradual onset that gives way to more severe constitutional symptoms and prostration. Bleeding is seen in only ~15–30% of cases. A maculopapular rash is often noted in light-skinned Lassa patients. Effusions are common, and male-dominant pericarditis may develop late. The fetal death rate is 92% in the last trimester, when the maternal mortality rate is also increased from the usual 15–30%; these figures suggest that interruption of the pregnancy of infected women should be considered. White blood cell counts are normal or slightly elevated, and platelet counts are normal or somewhat low. Deafness coincides with clinical improvement in ~20% of cases and is permanent and bilateral in some. Reinfection may occur but has not been associated with severe disease.

High-level viremia or a high serum concentration of AST statistically predicts a fatal outcome. Thus patients with an AST level of >150 IU/mL should be treated with IV ribavirin. This antiviral nucleoside analogue appears to be effective in reducing mortality rates from the levels documented among retrospective controls, and its only major side effect is reversible anemia that usually does not require transfusion. The drug should be given by slow IV infusion in a dose of 32 mg/kg; this dose should be followed by 16 mg/kg every 6 h for 4 days and then by 8 mg/kg every 8 h for 6 days.

SOUTH AMERICAN HF SYNDROMES (ARGENTINE, BOLIVIAN, VENEZUELAN, AND BRAZILIAN)

These diseases are similar to one another clinically, but their epidemiology differs with the habits of their rodent reservoirs and the interactions of these animals with humans. Person-to-person or nosocomial transmission is rare but has occurred.

The basic disease resembles Lassa fever, with two marked differences. First, thrombocytopenia—often marked—is the rule, and bleeding is quite common. Second, CNS dysfunction is much more common than in Lassa fever and is often manifested by marked confusion, tremors of the upper extremities and tongue, and cerebellar signs. Some cases follow a predominantly neurologic course, with a poor prognosis. The clinical laboratory is helpful in diagnosis since thrombocytopenia, leukopenia, and proteinuria are typical findings.

Argentine HF is readily treated with convalescent-phase plasma given within the first 8 days of illness. In the absence of passive antibody therapy, IV ribavirin in the dose recommended for Lassa fever is likely to be effective in all the South American HF syndromes. The transmission of the disease from men convalescing from Argentine HF to their wives suggests the need for counseling of arenavirus HF patients concerning the avoidance of intimate contacts for several weeks after recovery. A safe, effective, live attenuated vaccine exists for Argentine HF; after vaccination of >250,000 high-risk persons in the endemic area, incidence decreased markedly. In experimental animals, this vaccine is cross-protective against the Bolivian HF virus.

RIFT VALLEY FEVER

The mosquito-borne Rift Valley fever virus is also a pathogen of domestic animals such as sheep, cattle, and goats. It is maintained in nature by transovarial transmission in floodwater *Aedes* mosquitoes and presumably also has a vertebrate amplifier. Epizootics and epidemics occur when sheep or cattle become infected during particularly heavy rains; developing high-level viremia, these animals infect many species of mosquitoes. Remote sensing via satellite can detect the ecologic changes associated with high rainfall that predict the likelihood of Rift Valley fever transmission; it can also detect the special depressions from which the floodwater *Aedes* mosquito vectors emerge. In addition, the virus is infectious when transmitted by contact with blood or aerosols from domestic animals or their abortuses. The slaughtered meat is not infectious; anaerobic glycolysis in postmortem tissues results in an acidic environment that rapidly inactivates Bunyaviridae such as Rift Valley fever virus and Crimean-Congo HF virus. The natural range of Rift Valley fever virus is confined to sub-Saharan Africa, where its circulation is markedly enhanced by substantial rainfall such as that which occurred during the El Niño phenomenon of 1997; subsequent spread to the Arabian Peninsula caused epidemic disease in 2000. The virus has also been found in Madagascar and has been introduced into Egypt, where it caused major epidemics in 1977–1979, 1993, and subsequently. Neither person-to-person nor nosocomial transmission has been documented.

Rift Valley fever virus is unusual in that it causes several clinical syndromes. Most infections are manifested as the febrile-myalgic syndrome. A small proportion of infections result in HF with especially prominent liver involvement. Renal failure and probably DIC are also common features. Perhaps 10% of otherwise mild infections lead to retinal vasculitis; funduscopic examination reveals edema, hemorrhages, and infarction, and some patients have permanently impaired vision. A small proportion of cases (<1 in 200) are followed by typical viral encephalitis. One of the complicated syndromes does not appear to predispose to another.

There is no proven therapy for any of the syndromes described above. Both retinal disease and encephalitis occur after the acute febrile syndrome has ended and serum neutralizing antibody has developed—events suggesting that only supportive care need be given. Epidemic disease is best prevented by vaccination of livestock. The established ability of this virus to propagate after an introduction into Egypt suggests that other potentially receptive areas, including the United States,

should have a response ready for such an eventuality. It seems likely that this disease, like Venezuelan equine encephalitis, can be controlled only with adequate stocks of an effective live attenuated vaccine, and there are no such global stocks. A formalin-inactivated vaccine confers immunity to humans, but quantities are limited and three injections are required; this vaccine is recommended for exposed laboratory workers and for veterinarians working in sub-Saharan Africa. A new live attenuated vaccine, MP-12, is being tested in humans and may soon become available for general use.

CRIMEAN-CONGO HF

This severe HF syndrome has a wide geographic distribution, potentially being found wherever ticks of the genus *Hyalomma* occur. The propensity of these ticks to feed on domestic livestock and certain wild mammals means that veterinary serosurveys are the most effective mechanism for the surveillance of virus circulation in a region. Human infection is acquired via a tick bite or during the crushing of infected ticks. Domestic animals do not become ill but do develop viremia; thus, there is danger of infection at the time of slaughter and for a brief interval thereafter (through contact with hides or carcasses). Cases have followed sheep shearing. An epidemic in South Africa was associated with slaughter of tick-infested ostriches. Nosocomial epidemics are common and are usually related to extensive blood exposure or needle sticks.

Although generally similar to other HF syndromes, Crimean-Congo HF causes extensive liver damage, resulting in jaundice in some cases. Clinical laboratory values indicate DIC and show elevations in AST, creatine phosphokinase, and bilirubin. Patients with fatal cases generally have more marked changes, even in the early days of illness, and also develop leukocytosis rather than leukopenia. In addition, thrombocytopenia is more marked and develops earlier in cases with a fatal outcome.

No controlled trials have been performed with IV ribavirin, but clinical experience and retrospective comparison of patients with ominous clinical laboratory values suggest that ribavirin is efficacious and should be given. No human or veterinary vaccines are recommended.

HF WITH RENAL SYNDROME

This disease, the first to be identified as an HF, is widely distributed over Europe and Asia; the major causative viruses and their rodent reservoirs on these two continents are Puumala virus (bank vole, *Clethrionomys glareolus*) and Hantaan virus (striped field mouse, *Apodemus agrarius*), respectively. Other potential causative viruses exist, including Dobrava virus (yellow-necked field mouse, *A. flavicollis*), which causes severe HF with renal syndrome in the Balkans. Seoul virus is associated with the Norway or sewer rat, *Rattus norvegicus*, and has a worldwide distribution through the migration of the rodent; it is associated with mild or moderate HF with renal syndrome in Asia, but in many areas of the world the human disease has been difficult to identify. Most cases occur in rural residents or vacationers; the exception is Seoul virus disease, which may be acquired in an urban or rural setting or from contaminated laboratory rat colonies. Classic Hantaan disease in Korea (Korean HF) and in rural China (epidemic HF) is most common in spring and fall and is related to rodent density and agricultural practices. Human infection is acquired primarily through aerosols of rodent urine, although virus is also present in saliva and feces. Patients with hantavirus diseases are not infectious. HF with renal syndrome is the most important form of HF today, with >100,000 cases of severe disease in Asia annually and milder Puumala infections numbering in the thousands as well.

Severe cases of HF with renal syndrome caused by Hantaan virus evolve in identifiable stages: the febrile stage with myalgia, lasting 3 or 4 days; the hypotensive stage, often associated with shock and lasting from a few hours to 48 h; the oliguric stage with renal failure, lasting 3–10 days; and the polyuric stage with diuresis and hyposthenuria.

The *febrile stage* is initiated by the abrupt onset of fever, headache, severe myalgia, thirst, anorexia, and often nausea and vomiting. Photophobia, retroorbital pain, and pain on ocular movement are common, and the vision may become blurred with ciliary body inflammation. Flushing over the face, the V area of the neck, and the back is characteristic, as are pharyngeal injection, periorbital edema, and conjunctival suffusion. Petechiae often develop in areas of pressure, the conjunctivae, and the axillae. Back pain and tenderness to percussion at the costovertebral angle reflect massive retroperitoneal edema. Laboratory evidence of mild to moderate DIC is present. Other laboratory findings include proteinuria and an active urinary sediment.

The *hypotensive stage* is ushered in by falling blood pressure and sometimes by shock. The relative bradycardia typical of the febrile phase is replaced by tachycardia. Kinin activation is marked. The rising hematocrit reflects increasing vascular leakage. Leukocytosis with a left shift develops, and thrombocytopenia continues. Atypical lymphocytes—which in fact are activated CD8+ (and, to a lesser extent, CD4+) T cells—circulate. Proteinuria is marked, and the urine's specific gravity falls to 1.010. The renal circulation is congested and compromised from local and systemic circulatory changes resulting in necrosis of tubules, particularly at the corticomedullary junction, and oliguria.

During the *oliguric stage*, hemorrhagic tendencies continue, probably in large part because of uremic bleeding defects. The oliguria persists for 3–10 days before the return of renal function marks the onset of the *polyuric stage*, which carries the danger of dehydration and electrolyte abnormalities.

Mild cases of HF with renal syndrome may be much less stereotypical. The presentation may include only fever, gastrointestinal abnormalities, and transient oliguria followed by hyposthenuria.

HF with renal syndrome should be suspected in patients with rural exposure in an endemic area. Prompt recognition of the disease permits rapid hospitalization and expectant management of shock and renal failure. Useful clinical laboratory parameters include leukocytosis, which may be leukemoid and is associated with a left shift; thrombocytopenia; and proteinuria. Mainstays of therapy are the management of shock, reliance on pressors, modest crystalloid infusion, IV use of human serum albumin, and treatment of renal failure with prompt dialysis for the usual indications. Hydration may result in pulmonary edema, and hypertension should be avoided because of the possibility of intracranial hemorrhage. Use of IV ribavirin has reduced mortality and morbidity rates in severe cases provided treatment is begun within the first 4 days of illness. The case-fatality ratio may be as high as 15% but with proper therapy should be <5%. Sequelae have not been definitively established, but there is a correlation in the United States between chronic hypertensive renal failure and the presence of antibodies to Seoul virus.

Infections with Puumala virus, the most common cause of HF with renal syndrome in Europe, result in a much attenuated picture but the same general presentation. The syndrome may be referred to by its former name, *nephropathia epidemica*. Bleeding manifestations are found in only 10% of cases, hypotension rather than shock is usually seen, and oliguria is present in only about half of patients. The dominant features may be fever, abdominal pain, proteinuria, mild oliguria, and sometimes blurred vision or glaucoma followed by polyuria and hyposthenuria in recovery. The mortality rate is <1%.

The diagnosis is readily made by IgM-capture ELISA, which should be positive at admission or within 24–48 h thereafter. The isolation of virus is difficult, but RT-PCR of a blood clot collected early in the clinical course or of tissues obtained postmortem will give positive results. Such testing is usually undertaken only if definitive identification of the infecting viral species is required or if molecular epidemiologic questions exist.

HANTAVIRUS PULMONARY SYNDROME

Hantavirus pulmonary syndrome was discovered in 1993, but retrospective identification of cases by immunohistochemistry (1978) and serology (1959) support the idea that it is a recently discovered rather than a truly new disease. The causative agents are hantaviruses of a distinct phylogenetic lineage that is associated with the rodent subfamily Sigmodontinae. Sin Nombre virus, which chronically infects the deer mouse (*Peromyscus maniculatus*), is the most important agent of hantavirus pulmonary syndrome in the United States. The disease is also caused by a Sin Nombre virus variant from the white-footed mouse (*P. leucopus*), by Black Creek Canal virus (*Sigmodon hispidus*, the cotton rat), and by Bayou virus (*Oryzomys palustris*, the rice rat). Several other related viruses cause the disease in South America, but Andes virus is unusual in that it, alone among hantaviruses, has been implicated in human-to-human transmission. The disease is linked to rodent exposure and particularly affects rural residents living in dwellings permeable to rodent entry or working at occupations that pose a risk of rodent exposure. Each rodent species has its own particular habits; in the case of the deer mouse, these behaviors include living in and around human habitation.

The disease begins with a prodrome of ~3–4 days (range, 1–11 days) comprising fever, myalgia, malaise, and often gastrointestinal disturbances such as nausea, vomiting, and abdominal pain. Dizziness is common and vertigo occasional. Severe prodromal symptoms bring some individuals to medical attention, but patients are usually recognized as the cardiopulmonary phase begins. Typically, there is slightly lowered blood pressure, tachycardia, tachypnea, mild hypoxemia, and early radiographic signs of pulmonary edema. Physical findings in the chest are often surprisingly scant. The conjunctival and cutaneous signs of vascular involvement seen in other types of HF are absent. During the next few hours, decompensation may progress rapidly to severe hypoxemia and respiratory failure. Most patients surviving the first 48 h of hospitalization are extubated and discharged within a few days, with no apparent residua.

Management during the first few hours after presentation is critical. The goal is to prevent severe hypoxemia by oxygen therapy, with intubation and intensive respiratory management if needed. During this period, hypotension and shock with increasing hematocrit invite aggressive fluid administration, but this intervention should be undertaken with great caution. Because of low cardiac output with myocardial depression and increased pulmonary vascular permeability, shock should be managed expectantly with pressors and modest infusion of fluid guided by the pulmonary capillary wedge pressure. Mild cases can be managed by frequent monitoring and oxygen administration without intubation. Many patients require intubation to manage hypoxemia and also develop shock. Mortality rates remain at ~30–40% even with good management. The antiviral drug ribavirin inhibits the virus in vitro but did not have a marked effect on patients treated in an open-label study.

During the prodrome, the differential diagnosis of hantavirus pulmonary syndrome is difficult, but by the time of presentation or within 24 h thereafter, a number of diagnostically helpful clinical features become apparent. Cough is not usually present at the outset but may develop later. Interstitial edema is evident on the chest x-ray. Later, bilateral alveolar edema with a central distribution develops in the setting of a normal-sized heart; occasionally, the edema is initially unilateral. Pleural effusions are often seen. Thrombocytopenia, circulating atypical lymphocytes, and a left shift (often with leukocytosis) are almost always evident; thrombocytopenia is a particularly important early clue. Hemoconcentration, proteinuria, and hypoalbuminemia should also be sought. Although thrombocytopenia virtually always

develops and prolongation of the partial thromboplastin time is the rule, clinical evidence for coagulopathy or laboratory indications of DIC are found in only a minority of cases, usually in severely ill patients. Patients with severe illness also have acidosis and elevated serum levels of lactate. Mildly increased values in renal function tests are common, but patients with severe cases often have markedly elevated concentrations of serum creatinine; some of the viruses other than Sin Nombre virus have been associated with more kidney involvement, but few such cases have been studied. The differential diagnosis includes abdominal surgical conditions and pyelonephritis as well as rickettsial disease, sepsis, meningococcemia, plague, tularemia, influenza, and relapsing fever.

A specific diagnosis is best made by IgM testing of acute-phase serum, which has yielded positive results even in the prodrome. Tests using a Sin Nombre virus antigen detect the related hantaviruses causing the pulmonary syndrome in the Americas. Occasionally, heterologous viruses will react only in the IgG ELISA, but this finding is highly suspicious given the very low seroprevalence of these viruses in normal populations. RT-PCR is usually positive when used to test blood clots obtained in the first 7–9 days of illness as well as tissues; this test is useful in identifying the infecting virus in areas outside the home range of the deer mouse and in atypical cases.

YELLOW FEVER

Yellow fever virus caused major epidemics in the Americas, Africa, and Europe before the discovery of mosquito transmission in 1900 led to its control through attacks on its urban vector, *A. aegypti*. Only then was it found that a jungle cycle also existed in Africa, involving other *Aedes* mosquitoes and monkeys, and that colonization of the New World with *A. aegypti*, originally an African species, had established urban yellow fever as well as an independent sylvatic yellow fever cycle involving *Haemagogus* mosquitoes and New World monkeys in American jungles. Today, urban yellow fever transmission occurs only in some African cities, but the threat exists in the great cities of South America, where reinfestation by *A. aegypti* has taken place and dengue transmission by the same mosquito is common. As late as 1905, New Orleans suffered >3000 cases with 452 deaths from "yellow jack." Despite the existence of a highly effective and safe vaccine, several hundred jungle yellow fever cases occur annually in South America, and thousands of jungle and urban cases occur each year in Africa.

Yellow fever is a typical HF accompanied by prominent hepatic necrosis. A period of viremia, typically lasting 3 or 4 days, is followed by a period of "intoxication." During the latter phase in severe cases, the characteristic jaundice, hemorrhages, black vomit, anuria, and terminal delirium occur, perhaps related in part to extensive hepatic involvement. Blood leukocyte counts may be normal or reduced and are often high in terminal stages. Albuminuria is usually noted and may be marked; as renal function fails in terminal or severe cases, the level of blood urea nitrogen rises proportionately. Abnormalities detected in liver function tests range from modest elevations of AST levels in mild cases to severe derangement.

Urban yellow fever can be prevented by the control of *A. aegypti*. The continuing sylvatic cycle requires vaccination of all visitors to areas of potential transmission. With few exceptions, reactions to vaccine are minimal; immunity is provided within 10 days and lasts for at least 10 years. An egg allergy dictates caution in vaccine administration. Although there are no documented harmful effects of the vaccine on the fetus, pregnant women should be immunized only if they are definitely at risk of yellow fever exposure. Since vaccination has been associated with several cases of encephalitis in children <6 months of age, it should be delayed until after 12 months of age unless the risk of exposure is very high. Rare, serious, multisystemic adverse reactions (occasionally fatal) have been reported, particularly affecting the elderly; nevertheless, the number of deaths of unvaccinated travelers with yellow fever exceeds the number of deaths from vaccination, and a liberal vaccination policy for travelers to involved areas should be pursued. Timely information on changes in yellow fever distribution and yellow fever vaccine requirements can be obtained from the Centers for Disease Control and Prevention (*wwwnc.cdc.gov/travel*).

DENGUE HEMORRHAGIC FEVER/DENGUE SHOCK SYNDROME

A syndrome of HF noted in the 1950s among children in the Philippines and Southeast Asia was soon associated with dengue virus infections, particularly those occurring against a background of previous exposure to another dengue-virus serotype. The transient heterotypic protection after dengue virus infection is replaced within several weeks by the potential for heterotypic infection resulting in typical dengue fever (see earlier) or—uncommonly—in enhanced disease (secondary DHF/DSS). In rare instances, primary dengue infections lead to an HF syndrome, but much less is known about pathogenesis in this situation. In the past 20 years, *A. aegypti* has progressively reinvaded Latin America and other areas, and frequent travel by infected individuals has introduced multiple strains of dengue virus from many geographic areas. Thus the pattern of hyperendemic transmission of multiple dengue serotypes has now been established in the Americas and the Caribbean and has led to the emergence of DHF/DSS as a major problem there as well. Millions of dengue infections, including many thousands of cases of DHF/DSS, occur annually. The severe syndrome is unlikely to be seen in U.S. citizens since few children have the dengue antibodies that can trigger the pathogenetic cascade when a second infection is acquired.

Macrophage/monocyte infection is central to the pathogenesis of dengue fever and to the origin of DHF/DSS. Previous infection with a heterologous dengue-virus serotype may result in the production of

nonprotective antiviral antibodies that nevertheless bind to the virion's surface and through interaction with the Fc receptor focus secondary dengue viruses on the target cell, the result being enhanced infection. The host is also primed for a secondary antibody response when viral antigens are released and immune complexes lead to activation of the classic complement pathway, with consequent phlogistic effects. Cross-reactivity at the T cell level results in the release of physiologically active cytokines, including interferon γ and tumor necrosis factor α. The induction of vascular permeability and shock depends on multiple factors, including the following:

1. *Presence of enhancing and nonneutralizing antibodies*—Transplacental maternal antibody may be present in infants <9 months old, or antibody elicited by previous heterologous dengue infection may be present in older individuals. T cell reactivity is also intimately involved.
2. *Age*—Susceptibility to DHF/DSS drops considerably after 12 years of age.
3. *Sex*—Females are more often affected than males.
4. *Race*—Whites are more often affected than blacks.
5. *Nutritional status*—Malnutrition is protective.
6. *Sequence of infection*—For example, serotype 1 followed by serotype 2 seems to be more dangerous than serotype 4 followed by serotype 2.
7. *Infecting serotype*—Type 2 is apparently more dangerous than other serotypes.

In addition, there is considerable variation among strains of a given serotype, with Southeast Asian serotype 2 strains having more potential to cause DHF/DSS than others.

Dengue HF is identified by the detection of bleeding tendencies (tourniquet test, petechiae) or overt bleeding in the absence of underlying causes such as preexisting gastrointestinal lesions. Dengue shock syndrome, usually accompanied by hemorrhagic signs, is much more serious and results from increased vascular permeability leading to shock. In mild DHF/DSS, restlessness, lethargy, thrombocytopenia (<100,000/μL), and hemoconcentration are detected 2–5 days after the onset of typical dengue fever, usually at the time of defervescence. The maculopapular rash that often develops in dengue fever may also appear in DHF/DSS. In more severe cases, frank shock is apparent, with low pulse pressure, cyanosis, hepatomegaly, pleural effusions, ascites, and in some cases severe ecchymoses and gastrointestinal bleeding. The period of shock lasts only 1 or 2 days, and most patients respond promptly to close monitoring, oxygen administration, and infusion of crystalloid or—in severe cases—colloid. The case-fatality rates reported vary greatly with case ascertainment and the quality of treatment; however, most DHF/DSS patients respond well to supportive therapy, and the overall mortality rate at an experienced center in the tropics is probably as low as 1%.

A virologic diagnosis can be made by the usual means, although multiple flavivirus infections lead to a broad immune response to several members of the group, and this situation may result in a lack of virus specificity of the IgM and IgG immune responses. A secondary antibody response can be sought with tests against several flavivirus antigens to demonstrate the characteristic wide spectrum of reactivity.

The key to control of both dengue fever and DHF/DSS is the control of *A. aegypti*, which also reduces the risk of urban yellow fever and chikungunya virus circulation. Control efforts have been handicapped by the presence of nondegradable tires and long-lived plastic containers in trash repositories, insecticide resistance, urban poverty, and an inability of the public health community to mobilize the populace to respond to the need to eliminate mosquito breeding sites. Live attenuated dengue vaccines are in the late stages of development and have produced promising results in early tests. Whether vaccines can provide safe, durable immunity to an immunopathologic disease such as DHF/DSS in endemic areas is an issue that will have to be tested, but it is hoped that vaccination will reduce transmission to negligible levels.

KYASANUR FOREST DISEASE AND OMSK HEMORRHAGIC FEVER

Kyasanur Forest virus and Omsk HF virus are geographically restricted, tick-borne flaviviruses that cause a syndrome of viral HF during a wave of viremia and that may also enter the CNS to cause subsequent viral encephalitis (see discussion of tick-borne encephalitis, earlier). There is no therapy for these infections, but an inactivated vaccine has been used in India against Kyasanur Forest disease. A new and related virus isolate has been obtained from butchers with HF in the Middle East; the implication is that there are more agents in this group.

FILOVIRUS HEMORRHAGIC FEVER

See Chap. 103.

CHAPTER 103

EBOLA AND MARBURG VIRUSES

Clarence J. Peters

DEFINITION

Both Marburg virus and Ebola virus cause an acute febrile illness associated with a high mortality rate. This illness is characterized by multisystem involvement that begins with the abrupt onset of headache, myalgias, and fever and proceeds to prostration, rash, and shock and often to bleeding manifestations. Epidemics usually begin with a single case acquired from an unknown reservoir in nature (bats are suspected; see "Epidemiology") and spread mainly through close contact with sick persons or their body fluids, either at home or in the hospital.

ETIOLOGY

The family Filoviridae **(Fig. 103-1)** comprises two antigenically and genetically distinct genera: *Marburgvirus* and

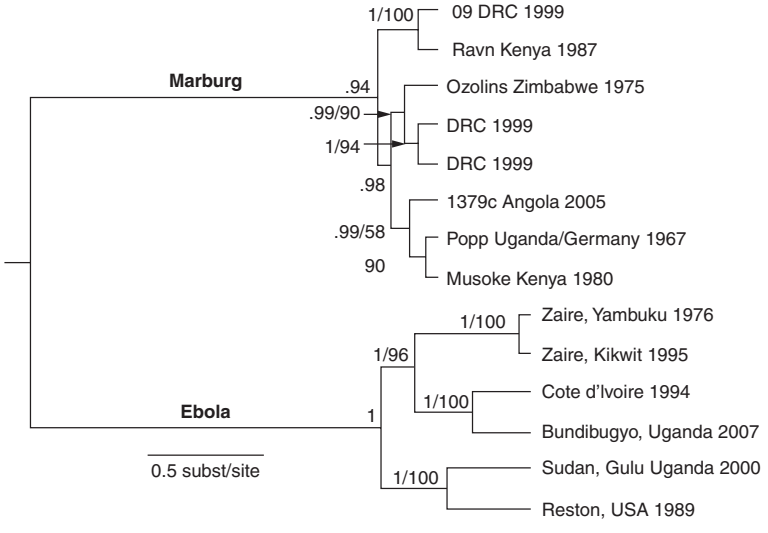


FIGURE 103-1

Phylogenetic tree of filoviruses. *Marburgvirus* and *Ebolavirus* are seen to be two different genera. The genus *Ebolavirus* includes five distinct species. Note that the Yambuku and Kikwit Zaire viruses are virtually identical even though the epidemics for which they were responsible are separated by two decades and hundreds of kilometers. Virtually every virus sequenced from each of those two epidemics is identical over the part of the genome examined. This pattern is typical of that seen with single introductions followed by human-to-human passage via needle or close contact in an African hospital. In the *Marburgvirus* branch of the tree, there is one major clade with a slightly divergent group characterized by the Ravn 1987 Kenya isolate. All the viruses from the major Angola 2005 outbreak are represented by a single virus because the sequences in this human-to-human epidemic are virtually identical. However, in the outbreak occurring in the Democratic Republic of the Congo (DRC) in 1999 and resulting from multiple independent infections after cave entry, two viruses with slightly different phylogenies are represented within the major group, and there is even another virus within the Ravn subgroup. These sequences were selected from hundreds determined at the U.S. Centers for Disease Control and Prevention and elsewhere. (*Adapted from CJ Peters: Filoviridae: Marburg and Ebola virus hemorrhagic fevers, in GL Mandell et al [eds]: Principles and Practice of Infectious Diseases, 7th ed. Philadelphia, Churchill Livingstone, 2010, pp 2259-2262.*)

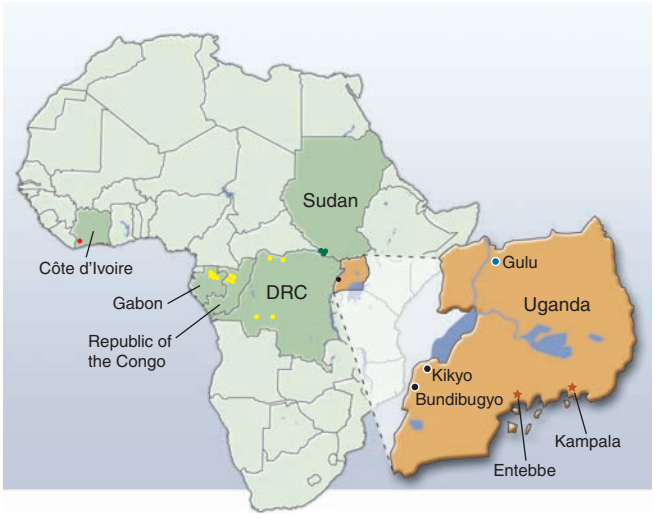


FIGURE 103-2

Left: **Geographic sites of *Ebolavirus* species identification,** as represented by dots (yellow, Zaire; green, Sudan; red, Côte d'Ivoire; black, Bundibugyo), in or adjacent to the Central African primary or secondary forest. Even *Ebolavirus* Côte d'Ivoire was isolated in the Tai forest reserve. ***Right:*** **Amplified map of Uganda** shows the zone along the border of the Democratic Republic of the Congo (DRC, formerly Zaire) where the newest *Ebolavirus* species, Bundibugyo, was identified. Bundibugyo and the nearby town of Kikyo, which was also affected by this epidemic, are tourist destinations close to the Ugandan capital of Kampala. (*Adapted from CJ Peters: Filoviridae: Marburg and Ebola virus hemorrhagic fevers, in GL Mandell et al [eds]: Principles and Practice of Infectious Diseases , 7th ed. Philadelphia, Churchill Livingstone, 2010 , pp 2259-2262.*)

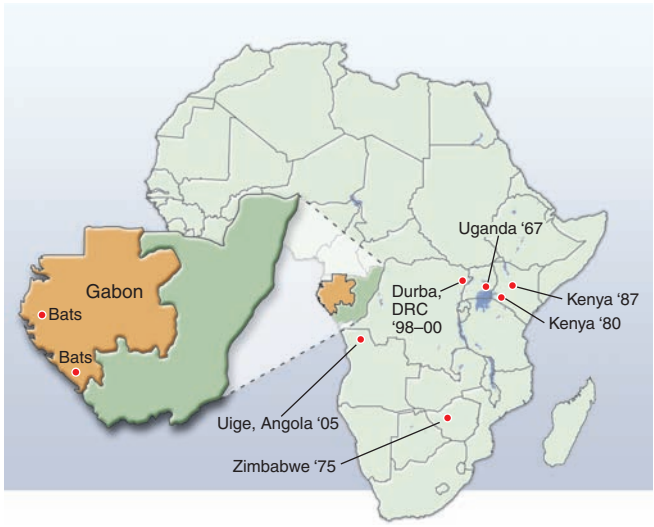


FIGURE 103-3

Maps of the African continent and the country of Gabon (with adjacent Republic of the Congo) show the geographic distribution of *Marburgvirus* identification. Red dots indicate a case or an epidemic. Uige, Angola, is the site of the largest Marburg epidemic (252 cases, 90% mortality rate). The Angolan strains differ by only 0–0.07% at the nucleotide level (Fig. 103-1). The Durba outbreak lasted 3 years and was characterized by multiple introductions of virus into men entering a subterranean mine. Nine distinct lineages were detected, of which one was in the rather distant (21%) Ravn lineage. Red dots on the Gabon map indicate detection of virus in bats by PCR. (*Adapted from CJ Peters: Filoviridae: Marburg and Ebola virus hemorrhagic fevers, in GL Mandell et al [eds]: Principles and Practice of Infectious Diseases, 7th ed. Philadelphia, Churchill Livingstone, 2010, pp 2259-2262.*)

Ebolavirus. *Ebolavirus* has five readily distinguishable species named for their original sites of recognition: Zaire, Sudan, Côte d'Ivoire, Bundibugyo, and Reston. Except for the Reston virus, all the Filoviridae are African viruses that cause severe and often fatal disease in humans **(Figs. 103-2 and 103-3)**. The Reston virus, which has been exported from the Philippines on several occasions, has caused fatal infections in monkeys but only subclinical infections in humans. Different strains of the five Ebola species, isolated over time and space, exhibit remarkable sequence conservation, indicating marked genetic stability in their selective niche.

Typical filovirus particles contain a single linear, negative-sense, single-stranded RNA arranged in a helical nucleocapsid. The virions are 790–970 nm in length; they may also appear in elongated, contorted forms **(Fig. 103-4)**. The lipid envelope confers sensitivity to lipid solvents and common detergents. The viruses are largely destroyed by heat (60°C, 30 min) and by acidity but may persist for weeks in blood at room temperature. The glycoprotein self-associates to form the virion surface spikes, which presumably mediate attachment to cells and fusion. The glycoprotein's high sugar content may contribute to its low capacity to elicit effective neutralizing antibodies. A smaller form of the glycoprotein,

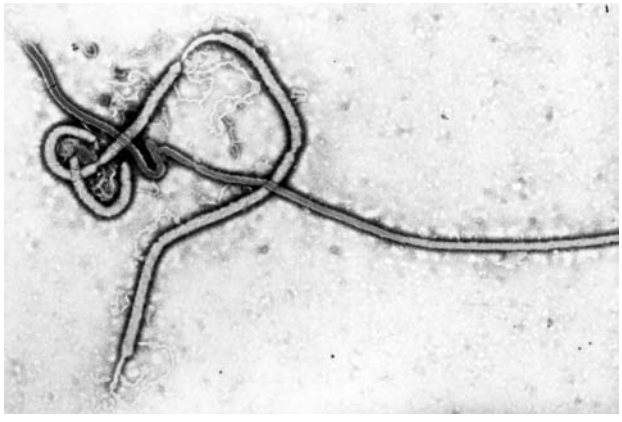


FIGURE 103-4

Ebola virions: diagnostic specimen from the first passage in Vero cells of a blood sample from a patient. Some of the filamentous (negatively stained) virions were fused together, end-to-end, giving the appearance of a "bowl of spaghetti." This image was from the first isolation and visualization of Ebola virus in 1970. (*Courtesy of Fredrick A. Murphy, MD, University of Texas Medical Branch, Galveston, Texas; with permission.*)

bearing many of its antigenic determinants, is produced by in vitro–infected cells and is found in the circulation in human disease; it has been speculated that this circulating soluble protein may suppress the immune response to the virion surface protein or block antiviral effector mechanisms. Both Marburg virus and Ebola virus are biosafety level 4 pathogens because of their high associated mortality rate and aerosol infectivity.

EPIDEMIOLOGY

Marburg virus was first identified in Germany in 1967, when infected African green monkeys (*Cercopithecus aethiops*) imported from Uganda transmitted the agent to workers in a vaccine laboratory. Of the 25 human cases acquired from monkeys, seven ended in death. The six secondary cases were associated with close contact or parenteral exposure. Secondary spread to the wife of one patient was documented, and virus was isolated from the husband's semen despite the presence of circulating serum antibodies. Isolated cases of Marburg virus infection were reported from eastern and southern Africa, with limited spread. Then, in 1999, repeated transmission of Marburg virus to workers in a gold mine in eastern Democratic Republic of the Congo (DRC; formerly Zaire) was studied. The secondary spread of the virus among patients' families was more extensive than previously noted, resembling that of Ebola virus and suggesting the importance of hygiene and proper barrier nursing in the epidemiology of these viruses in Africa. Finally, in 2004–2005, an alarming, massive Marburg virus epidemic, with >250 cases, occurred in Angola. The epidemiologic features resembled those of the Ebola virus epidemics described next, and the case-fatality rate was 90%. This high figure may have been due in part to poor conditions in African hospitals; however, the virus isolated in this epidemic was slightly different phylogenetically from other known strains and exhibited increased virulence in nonhuman primates.

Ebola virus first appeared in 1976, causing simultaneous epidemics of severe hemorrhagic fever (550 human cases) in Zaire and Sudan. Later, it was shown that different species of virus (with associated mortality rates of 90% and 50%, respectively) had caused the two epidemics. Both epidemics were associated with interhuman spread (particularly in the hospital setting) and the use of unsterilized needles and syringes—a common practice in developing-country hospitals. The epidemics dwindled as the clinics were closed and as persons in the endemic area increasingly shunned affected persons and avoided traditional burial practices.

After an interval of apparent inactivity of almost 20 years, the Zaire Ebola virus recurred in a major epidemic (317 cases) in the DRC in 1995 and in smaller epidemics in Gabon in 1994–1996. Mortality rates were high (88% in the DRC), transmission to caregivers and others who had direct contact with body fluids was common, and poor hygiene in hospitals exacerbated spread. In the DRC epidemic, an index case was infected in Kikwit in January 1995. The epidemic smoldered until April, when intense nosocomial transmission forced closure of the hospitals; samples were finally sent to the laboratory for Ebola testing, which yielded positive results within a few hours. International assistance, with barrier nursing instruction and materials, was provided; nosocomial transmission ceased, hospitals reopened, and patients were segregated to prevent intrafamilial spread. The last case was reported in June 1995.

Separate emergences of Ebola virus (Zaire) were detected in Gabon in 1994–2003, usually in association with deep-forest exposure and subsequent familial and nosocomial transmission. Die-offs of nonhuman primates were sometimes documented, and Ebola infection was confirmed in at least some animals. In a 1996 episode, a physician exposed to Ebola-infected patients traveled to South Africa with a fever; a nurse who assisted in a cutdown on the physician developed Ebola hemorrhagic fever and died despite intensive care. The index patient was identified retrospectively on the basis of serum antibodies and virus isolation from semen. No additional cases arising from care of the primary or secondary case were detected, nor did any secondary cases follow care of an unsuspected Côte d'Ivoire Ebola case in Switzerland. Thus, distant transport of Ebola virus is an established risk, but limited nosocomial spread occurs under proper hygienic conditions.

After its first documented activity in 1976, the Sudan Ebola species returned in epidemic form to cause an indolent outbreak in Uganda in 2000–2001. This outbreak claimed the lives of 224 (53%) of 425 patients.

Reston Ebola virus was first seen in the United States in 1989, when it caused a fatal, highly transmissible disease among cynomolgus macaques imported from the Philippines and quarantined in Reston, Virginia, pending distribution to biomedical researchers. This and other appearances of the Reston virus have been traced to a single export facility in the Philippines, but no source in nature had been established until the discovery of this viral species in Philippine pigs. Occasional serologic evidence of human infection was found, but no cases of human disease were identified.

Epidemiologic studies (including a specific search in the Kikwit epidemic) have failed to yield evidence for an important role of airborne particles in human disease. This lack of epidemiologic evidence is surprising and seems to conflict with the viruses' classification as biosafety level 4 pathogens (which is based in large part on aerosol infectivity) and with formal laboratory assessments showing a high degree of aerosol infectivity for monkeys. Sick humans apparently do not usually generate sufficient amounts of infectious aerosols to pose a significant hazard to those around them.

Although numerous die-offs have been reported among chimpanzees and gorillas (some even threatening the viability of these endangered species), these animals (like humans) appear to be sentinels for virus activity. Speculation about the true reservoirs has centered on bats, and preliminary evidence indicates that bats may indeed be the reservoirs of filoviruses. This evidence includes the detection of antibodies and reverse-transcriptase polymerase

chain reaction (RT-PCR) products in bats, the epidemiologic findings in subterranean gold mines in Durba (DRC) where Marburg transmission has occurred, and reported associations of human antibody production with the handling of bats. Recent isolation of Marburg virus from Egyptian fruit bats (*Rousettus aegyptiacus*) captured in Uganda in proximity to cases of human disease further supports bats as reservoirs, but the exact biologic relation and the natural cycle remain to be elucidated.

PATHOLOGY AND PATHOGENESIS

In humans and in animal models, Ebola and Marburg viruses replicate well in virtually all cell types, including endothelial cells, macrophages, and parenchymal cells of multiple organs. In macaques, the earliest involvement—that of the mononuclear phagocyte system—is responsible for initiation of the disease process. In human disease and macaque models, upregulation of tissue factor and disseminated intravascular coagulation (DIC) are the inciting mechanisms. Viral replication is associated with cellular necrosis both in vivo and in vitro. Significant findings at the light-microscopic level include liver necrosis with Councilman bodies, intracellular inclusions that correlate with extensive collections of viral nucleocapsids, interstitial pneumonitis, cerebral glial nodules, and small infarcts. Antigen and virions are abundant in fibroblasts, interstitium, and (to a lesser extent) the appendages of the subcutaneous tissues in fatal cases; escape through small breaks in the skin or possibly through sweat glands may occur and, if so, may be correlated with the established epidemiologic risk of close contact with patients and the touching of the deceased. Inflammatory cells are not prominent, even in necrotic areas.

In addition to sustaining direct damage from viral infection, patients infected with Ebola virus (Zaire) have high circulating levels of proinflammatory cytokines, which presumably contribute to the severity of the illness. In fact, the virus interacts intimately with the cellular cytokine system. It is resistant to the antiviral effects of interferon α, although this mediator is amply induced. Viral infection of endothelial cells selectively inhibits the expression of major histocompatibility complex class I molecules and blocks the induction of several genes by the interferons. In addition, glycoprotein expression inhibits αV integrin expression, an effect that leads to detachment and subsequent death of endothelial cells in vitro and that correlates with the limited inflammatory response evident in lesions.

Acute infection is associated with high levels of circulating virus and viral antigen. Clinical improvement takes place when viral titers decrease concomitant with the onset of a virus-specific immune response, as detected by enzyme-linked immunosorbent assay (ELISA) or fluorescent antibody testing. In fatal cases, there is usually little evidence of an antibody response, and there is extensive depletion of spleen and lymph nodes. Ebola Sudan virus amplification by PCR shows a correlation between serum viral RNA concentration and the likelihood of death. Recovery is apparently mediated by the cellular immune response: convalescent-phase plasma has little in vitro virus-neutralizing capacity and is not protective in humans or in passive transfer experiments in monkey and guinea pig models.

CLINICAL MANIFESTATIONS

After an incubation period of ~7–10 days (range, 3–16 days), the patient abruptly develops fever, severe headache, malaise, myalgia, nausea, and vomiting. Continued fever is joined by diarrhea (often severe), chest pain (accompanied by cough), prostration, and depressed mentation. In light-skinned patients (and less often in dark-skinned individuals), a maculopapular rash appears around day 5–7 and is followed by desquamation. Bleeding may begin about this time and is apparent from any mucosal site and into the skin. In some epidemics, fewer than half of patients have had overt bleeding, and this manifestation has been absent even in some fatal cases. Additional findings include edema of the face, neck, and/or scrotum; hepatomegaly; flushing; conjunctival injection; and pharyngitis. Around 10–12 days after the onset of disease, the sustained fever may break, with improvement and eventual recovery of the patient. Recrudescence of fever may be associated with secondary bacterial infections or possibly with localized virus persistence. Late hepatitis, uveitis, and orchitis have been reported, with isolation of virus from semen or detection of PCR products in vaginal secretions for several weeks.

LABORATORY FINDINGS

Leukopenia is common early on; neutrophilia has its onset later. Platelet counts fall below (sometimes much below) 50,000/μL. Laboratory evidence of DIC is found, but its clinical significance and the need for therapy are controversial. Serum levels of alanine and aspartate aminotransferases (particularly the latter) rise progressively, and jaundice develops in some cases. The serum amylase level may be elevated, and this elevation may be associated with abdominal pain, suggesting pancreatitis. Proteinuria is usual; decreased kidney function is proportional to shock.

DIAGNOSIS

Most patients acutely ill as a result of infection with Ebola or Marburg virus have high concentrations of virus in blood. Antigen-detection ELISA is a sensitive, robust diagnostic modality. Virus isolation and reverse-transcription PCR are also effective and provide additional sensitivity needed in some cases. Recovering patients develop IgM and IgG antibodies that are readily detected by ELISA. The indirect fluorescent antibody test with paired sera is an effective diagnostic tool in most acute cases but is extremely misleading in population-based serologic surveys for Ebola virus activity.

Real-time PCR is extremely useful in detecting the need for quarantine or geographic spread. Skin biopsies are an extremely useful adjunct in postmortem diagnosis of infection with Ebola virus (and, to a lesser extent, Marburg virus) because of the presence of large amounts of viral antigen, the relatively low risk posed by sample collection, and the lack of cold-chain requirements for formalin-fixed tissues.

TREATMENT Marburg and Ebola Virus Infections

No virus-specific therapy is available, and—given the extensive viral involvement in fatal cases—supportive treatment may not be as useful as was once hoped. However, studies in rhesus monkeys have shown improved survival among animals treated with an inhibitor of factor VIIa/tissue factor or with activated protein C; this effect demonstrates the importance of DIC in pathogenesis. In addition, direct intervention against viral replication with small interfering RNA (siRNA) is effective in postexposure prophylaxis against the highly virulent Zaire species in macaques. Vigorous treatment of shock should take into account the likelihood of vascular leak in the pulmonary and systemic circulation and of myocardial functional compromise. The membrane fusion mechanism of Ebola virus resembles that of retroviruses, and the identification of "fusogenic" sequences suggests that inhibitors of cell entry may be developed. Despite the poor neutralizing capacity of polyclonal convalescent-phase sera, phage display of immunoglobulin mRNA from convalescent-phase bone marrow has yielded monoclonal antibodies that have in vitro neutralizing capacity and mediate protection in guinea pig models (but, unfortunately, not in the more sensitive monkey models).

PREVENTION

No vaccine or antiviral drug is currently available, but barrier nursing precautions in African hospitals can greatly decrease the spread of filoviruses beyond the index case and thus prevent epidemics of infection with these viruses and other agents as well. An adenovirus-vectored Ebola glycoprotein gene has proved protective in nonhuman primates and is undergoing phase 1 trials in humans. An experimental vesicular stomatitis virus–based vaccine has protected macaques when given both before and after infection with the Zaire Ebola virus.

This page intentionally left blank

SECTION VI

PRION DISEASES

CHAPTER 104

PRION DISEASES

Stanley B. Prusiner ■ Bruce L. Miller

Prions are infectious proteins that cause degeneration of the central nervous system (CNS). Prion diseases are disorders of protein conformation, the most common of which in humans is called Creutzfeldt-Jakob disease (CJD). CJD typically presents with dementia and myoclonus, is relentlessly progressive, and generally causes death within a year of onset. Most CJD patients are between 50 and 75 years of age; however, patients as young as 17 and as old as 83 have been recorded.

In mammals, prions reproduce by binding to the normal, *c*ellular isoform of the *pr*ion *p*rotein (PrP^C) and stimulating conversion of PrP^C into the disease-*c*ausing isoform (PrP^{Sc}). PrP^C is rich in α-helix and has little β-structure, while PrP^{Sc} has less α-helix and a high amount of β-structure **(Fig. 104-1)**. This α-to-β structural transition in the prion protein (PrP) is the fundamental event underlying prion diseases **(Table 104-1)**.

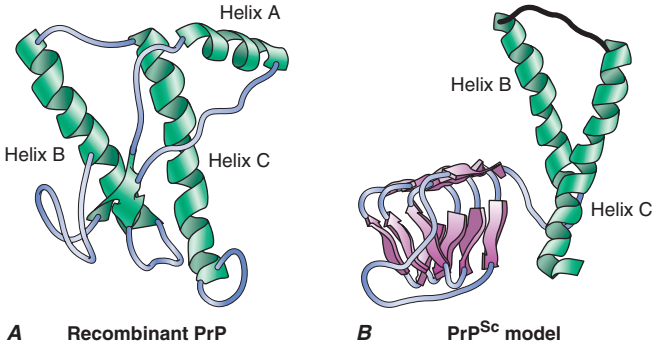


FIGURE 104-1

Structures of prion proteins. *A.* NMR structure of Syrian hamster recombinant (rec) PrP(90–231). Presumably, the structure of the α-helical form of recPrP(90–231) resembles that of PrP^C. recPrP(90–231) is viewed from the interface where PrP^{Sc} is thought to bind to PrP^C. Shown are: α-helices A (residues 144–157), B (172–193), and C (200–227). Flat ribbons depict β-strands S1 (129–131) and S2 (161–163). (*From SB Prusiner: N Engl J Med 344:1516, 2001; with permission.*) ***B.*** Structural model of PrP^{Sc}. The 90–160 region has been modeled onto a β-helical architecture, while the COOH terminal helices B and C are preserved as in PrP^C. (*Image prepared by C. Govaerts.*)

Four new concepts have emerged from studies of prions: (1) Prions are the only known infectious pathogens that are devoid of nucleic acid; all other infectious agents possess genomes composed of either RNA or DNA that direct the synthesis of their progeny. (2) Prion diseases may be manifest as infectious, genetic, and sporadic disorders; no other group of illnesses with a single etiology presents with such a wide spectrum of

TABLE 104-1

GLOSSARY OF PRION TERMINOLOGY	
Prion	*Pro*teinaceous *in*fectious particle that lacks nucleic acid. Prions are composed entirely of PrP^{Sc} molecules. They can cause scrapie in sheep and goats and related neurodegenerative diseases of humans, such as Creutzfeldt-Jakob disease (CJD).
PrP^{Sc}	Disease-causing isoform of the prion protein. This protein is the only identifiable macromolecule in purified preparations of scrapie prions.
PrP^C	Cellular isoform of the prion protein. PrP^C is the precursor of PrP^{Sc}.
PrP 27-30	A fragment of PrP^{Sc}, generated by truncation of the NH_2-terminus by limited digestion with proteinase K. PrP 27-30 retains prion infectivity and polymerizes into amyloid.
PRNP	PrP gene located on human chromosome 20.
Prion rod	An aggregate of prions composed largely of PrP 27-30 molecules. Created by detergent extraction and limited proteolysis of PrP^{Sc}. Morphologically and histochemically indistinguishable from many amyloids.
PrP amyloid	Amyloid containing PrP in the brains of animals or humans with prion disease; often accumulates as plaques.

clinical manifestations. (3) Prion diseases result from the accumulation of PrP^{Sc}, the conformation of which differs substantially from that of its precursor, PrP^{C}. (4) PrP^{Sc} can exist in a variety of different conformations, each of which seems to specify a particular disease phenotype. How a specific conformation of a PrP^{Sc} molecule is imparted to PrP^{C} during prion replication to produce nascent PrP^{Sc} with the same conformation is unknown. Additionally, it is unclear what factors determine where in the CNS a particular PrP^{Sc} molecule will be deposited.

SPECTRUM OF PRION DISEASES

The sporadic form of CJD is the most common prion disorder in humans. Sporadic CJD (sCJD) accounts for ~85% of all cases of human prion disease, while inherited prion diseases account for 10–15% of all cases **(Table 104-2)**. Familial CJD (fCJD), Gerstmann-Sträussler-Scheinker (GSS) disease, and fatal familial insomnia (FFI) are all dominantly inherited prion diseases that are caused by mutations in the PrP gene.

Although infectious prion diseases account for <1% of all cases and infection does not seem to play an important role in the natural history of these illnesses, the transmissibility of prions is an important biologic feature. *Kuru* of the Fore people of New Guinea is thought to have resulted from the consumption of brains from dead relatives during ritualistic cannibalism. With the cessation of ritualistic cannibalism in the late 1950s, kuru has nearly disappeared, with the exception of a few recent patients exhibiting incubation periods of >40 years. Iatrogenic CJD (iCJD) seems to be the result of the accidental inoculation of patients with prions. Variant CJD (vCJD) in teenagers and young adults in Europe is the result of exposure to tainted beef from cattle with bovine spongiform encephalopathy (BSE).

Six diseases of animals are caused by prions (Table 104-2). Scrapie of sheep and goats is the prototypic prion disease. Mink encephalopathy, BSE, feline spongiform encephalopathy, and exotic ungulate encephalopathy are all thought to occur after the consumption of prion-infected foodstuffs. The BSE epidemic emerged in Britain in the late 1980s and was shown to be due to industrial cannibalism. Whether BSE began as a sporadic case of BSE in a cow or started with scrapie in sheep is unknown. The origin of chronic wasting disease (CWD), a prion disease endemic in deer and elk in regions of North America, is uncertain. In contrast to other prion diseases, CWD is highly communicable. Feces from asymptomatic, infected cervids contain prions that are likely to be responsible for the spread of CWD.

TABLE 104-2

THE PRION DISEASES

DISEASE	HOST	MECHANISM OF PATHOGENESIS
Human		
Kuru	Fore people	Infection through ritualistic cannibalism
iCJD	Humans	Infection from prion-contaminated hGH, duramater grafts, etc.
vCJD	Humans	Infection from bovine prions
fCJD	Humans	Germ-line mutations in *PRNP*
GSS	Humans	Germ-line mutations in *PRNP*
FFI	Humans	Germ-line mutation in *PRNP* (D178N, M129)
sCJD	Humans	Somatic mutation or spontaneous conversion of PrP^{C} into PrP^{Sc}?
sFI	Humans	Somatic mutation or spontaneous conversion of PrP^{C} into PrP^{Sc}?
Animal		
Scrapie	Sheep, goats	Infection in genetically susceptible sheep
BSE	Cattle	Infection with prion-contaminated MBM
TME	Mink	Infection with prions from sheep or cattle
CWD	Mule deer, elk	Unknown
FSE	Cats	Infection with prion-contaminated beef
Exotic ungulate encephalopathy	Greater kudu, nyala, or oryx	Infection with prion-contaminated MBM

Abbreviations: BSE, bovine spongiform encephalopathy; CJD, Creutzfeldt-Jakob disease; CWD, chronic wasting disease; fCJD, familial Creutzfeldt-Jakob disease; FFI, fatal familial insomnia; FSE, feline spongiform encephalopathy; GSS, Gerstmann-Sträussler-Scheinker disease; hGH, human growth hormone; iCJD, iatrogenic Creutzfeldt-Jakob disease; MBM, meat and bone meal; sCJD, sporadic Creutzfeldt-Jakob disease; sFI, sporadic fatal insomnia; TME, transmissible mink encephalopathy; vCJD, variant Creutzfeldt-Jakob disease.

EPIDEMIOLOGY

CJD is found throughout the world. The incidence of sCJD is approximately one case per million population, and thus it accounts for about 1 in every 10,000 deaths. Because sCJD is an age-dependent neurodegenerative disease, its incidence is expected to increase steadily as older segments of populations in developed and developing countries continue to expand. Although many geographic clusters of CJD have been reported, each has been shown to segregate with a PrP gene mutation. Attempts to identify common exposure to some etiologic agent have been unsuccessful for both the sporadic and familial cases. Ingestion of scrapie-infected sheep or goat meat as a cause of CJD in humans has not been demonstrated by epidemiologic studies, although speculation about this potential route of inoculation continues. Of particular interest are deer hunters who develop CJD, because up to 90% of culled deer in some game herds have been shown to harbor CWD prions. Whether prion disease in deer or elk has passed to cows, sheep, or directly to humans remains unknown. Studies with rodents demonstrate that oral infection with prions can occur, but the process is inefficient compared to intracerebral inoculation.

PATHOGENESIS

The human prion diseases were initially classified as neurodegenerative disorders of unknown etiology on the basis of pathologic changes being confined to the CNS. With the transmission of kuru and CJD to apes, investigators began to view these diseases as infectious CNS illnesses caused by slow viruses. Even though the familial nature of a subset of CJD cases was well described, the significance of this observation became more obscure with the transmission of CJD to animals. Eventually the meaning of heritable CJD became clear with the discovery of mutations in the *PRNP* gene of these patients. The prion concept explains how a disease can manifest as a heritable as well as an infectious illness. Moreover, the hallmark of all prion diseases, whether sporadic, dominantly inherited, or acquired by infection, is that they involve the aberrant metabolism of PrP.

A major feature that distinguishes prions from viruses is the finding that both PrP isoforms are encoded by a chromosomal gene. In humans, the PrP gene is designated *PRNP* and is located on the short arm of chromosome 20. Limited proteolysis of PrP^{Sc} produces a smaller, protease-resistant molecule of ~142 amino acids designated PrP 27-30; PrP^{C} is completely hydrolyzed under the same conditions **(Fig. 104-2)**. In the presence of detergent, PrP 27-30 polymerizes into amyloid. Prion rods formed by limited proteolysis and detergent extraction are indistinguishable from the filaments that aggregate to form PrP amyloid plaques in the CNS. Both the rods and the PrP amyloid filaments found in brain tissue exhibit similar ultrastructural morphology and green-gold birefringence after staining with Congo red dye.

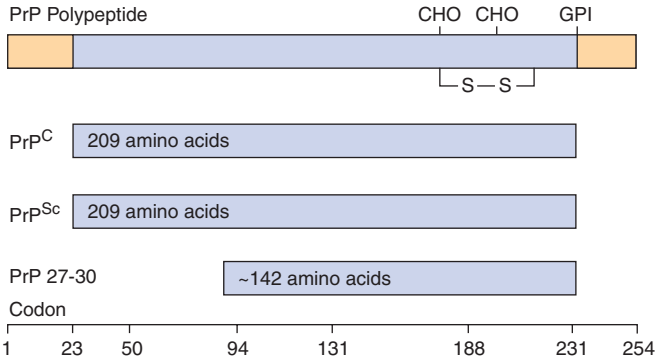


FIGURE 104-2
Prion protein isoforms. Bar diagram of Syrian hamster PrP, which consists of 254 amino acids. After processing of the NH_2 and COOH termini, both PrP^{C} and PrP^{Sc} consist of 209 residues. After limited proteolysis, the NH_2 terminus of PrP^{Sc} is truncated to form PrP 27–30 composed of ~142 amino acids.

Prion strains

The existence of prion strains raised the question of how heritable biologic information can be enciphered in a molecule other than nucleic acid. Various strains of prions have been defined by incubation times and the distribution of neuronal vacuolation. Subsequently, the patterns of PrP^{Sc} deposition were found to correlate with vacuolation profiles, and these patterns were also used to characterize prion strains.

Persuasive evidence that strain-specific information is enciphered in the tertiary structure of PrP^{Sc} comes from transmission of two different inherited human prion diseases to mice expressing a chimeric human-mouse PrP transgene. In FFI, the protease-resistant fragment of PrP^{Sc} after deglycosylation has a molecular mass of 19 kDa, whereas in fCJD and most sporadic prion diseases, it is 21 kDa **(Table 104-3)**. This difference in molecular mass was shown to be due to different sites of proteolytic cleavage at the NH_2 termini of the two human PrP^{Sc} molecules, reflecting different tertiary structures. These distinct conformations were not unexpected because the amino acid sequences of the PrPs differ.

Extracts from the brains of patients with FFI transmitted disease into mice expressing a chimeric human-mouse PrP transgene and induced formation of the 19-kDa PrP^{Sc}, whereas brain extracts from fCJD and sCJD patients produced the 21-kDa PrP^{Sc} in mice expressing the same transgene. On second passage, these differences were maintained, demonstrating that chimeric PrP^{Sc} can exist in two different conformations based on the sizes of the protease-resistant fragments, even though the amino acid sequence of PrP^{Sc} is invariant.

This analysis was extended when patients with sporadic fatal insomnia (sFI) were identified. Although they did not carry a *PRNP* gene mutation, the patients demonstrated a clinical and pathologic phenotype that was indistinguishable from that of patients with FFI. Furthermore, 19-kDa PrP^{Sc} was found in their brains, and on passage of prion disease to mice expressing a chimeric human-mouse PrP transgene, 19-kDa PrP^{Sc} was also found.

TABLE 104-3

DISTINCT PRION STRAINS GENERATED IN HUMANS WITH INHERITED PRION DISEASES AND TRANSMITTED TO TRANSGENIC MICE[a]

INOCULUM	HOST SPECIES	HOST PrP GENOTYPE	INCUBATION TIME [DAYS ± SEM] (n/n_0)	PrP^{Sc} (kDa)
None	Human	FFI(D178N, M129)		19
FFI	Mouse	Tg(MHu2M)	206 ± 7 (7/7)	19
FFI → Tg(MHu2M)	Mouse	Tg(MHu2M)	136 ± 1 (6/6)	19
None	Human	fCJD(E200K)		21
fCJD	Mouse	Tg(MHu2M)	170 ± 2 (10/10)	21
fCJD → Tg(MHu2M)	Mouse	Tg(MHu2M)	167 ± 3 (15/15)	21

[a]Tg(MHu2M) mice express a chimeric mouse-human PrP gene.
Notes: Clinicopathologic phenotype is determined by the conformation of PrP^{Sc} in accord with the results of the transmission of human prions from patients with FFI to transgenic mice. fCJD, familial Creutzfeldt-Jakob disease; FFI, fatal familial insomnia.

These findings indicate that the disease phenotype is dictated by the conformation of PrP^{Sc} and not the amino acid sequence. PrP^{Sc} acts as a template for the conversion of PrP^{C} into nascent PrP^{Sc}. On the passage of prions into mice expressing a chimeric hamster-mouse PrP transgene, a change in the conformation of PrP^{Sc} was accompanied by the emergence of a new strain of prions.

Many new strains of prions were generated using recombinant (rec) PrP produced in bacteria; recPrP was polymerized into amyloid fibrils and inoculated into transgenic mice expressing high levels of wild-type mouse PrP^{C}; about 500 days later, the mice died of prion disease. The incubation times of the "synthetic prions" in mice were dependent on the conditions used for polymerization of the amyloid fibrils. Highly stable amyloids gave rise to stable prions with long incubation times; low-stability amyloids led to prions with short incubation times. Amyloids of intermediate stability gave rise to prions with intermediate stabilities and intermediate incubation times. Such findings are consistent with earlier studies showing that the incubation times of synthetic and naturally occurring prions are directly proportional to the stability of the prion.

Species barrier

Studies on the role of the primary and tertiary structures of PrP in the transmission of prion disease have given new insights into the pathogenesis of these maladies. The amino acid sequence of PrP encodes the species of the prion, and the prion derives its PrP^{Sc} sequence from the last mammal in which it was passaged. While the primary structure of PrP is likely to be the most important or even sole determinant of the tertiary structure of PrP^{C}, PrP^{Sc} seems to function as a template in determining the tertiary structure of nascent PrP^{Sc} molecules as they are formed from PrP^{C}. In turn, prion diversity appears to be enciphered in the conformation of PrP^{Sc}, and thus prion strains seem to represent different conformers of PrP^{Sc}.

In general, transmission of prion disease from one species to another is inefficient, in that not all intracerebrally inoculated animals develop disease, and those that fall ill do so only after long incubation times that can approach the natural life span of the animal. This "species barrier" to transmission is correlated with the degree of similarity between the amino acid sequences of PrP^{C} in the inoculated host and of PrP^{Sc} in the prion inoculum. The importance of sequence similarity between the host and donor PrP argues that PrP^{C} directly interacts with PrP^{Sc} in the prion conversion process.

SPORADIC AND INHERITED PRION DISEASES

Several different scenarios might explain the initiation of sporadic prion disease: (1) A somatic mutation may be the cause and thus follow a path similar to that for germline mutations in inherited disease. In this situation, the mutant PrP^{Sc} must be capable of targeting wild-type PrP^{C}, a process known to be possible for some mutations but less likely for others. (2) The activation energy barrier separating wild-type PrP^{C} from PrP^{Sc} could be crossed on rare occasions when viewed in the context of a population. Most individuals would be spared while presentations in the elderly with an incidence of ~1 per million would be seen. (3) PrP^{Sc} may be present at low levels in some normal cells, where it performs some important, as yet unknown, function. The level of PrP^{Sc} in such cells is hypothesized to be sufficiently low as to be not detected by routine bioassay. In some altered metabolic states, the cellular mechanisms for clearing PrP^{Sc} might become compromised and the rate of PrP^{Sc} formation would then begin to exceed the capacity of the cell to clear it. The third possible mechanism is attractive since it suggests PrP^{Sc} is not simply a misfolded protein, as proposed for the first and second mechanisms, but that it is an alternatively folded molecule with a function. Moreover, the multitude of

conformational states that PrP^{Sc} can adopt, as described earlier, raises the possibility that PrP^{Sc} or another prion-like protein might function in a process like short-term memory where information storage occurs in the absence of new protein synthesis.

More than 40 different mutations resulting in non-conservative substitutions in the human *PRNP* gene have been found to segregate with inherited human prion diseases. Missense mutations and expansions in the octapeptide repeat region of the gene are responsible for familial forms of prion disease. Five different mutations of the *PRNP* gene have been linked genetically to heritable prion disease.

Although phenotypes may vary dramatically within families, specific phenotypes tend to be observed with certain mutations. A clinical phenotype indistinguishable from typical sCJD is usually seen with substitutions at codons 180, 183, 200, 208, 210, and 232. Substitutions at codons 102, 105, 117, 198, and 217 are associated with the GSS variant of prion disease. The normal human PrP sequence contains five repeats of an eight-amino-acid sequence. Insertions from two to nine extra octarepeats frequently cause variable phenotypes ranging from a condition indistinguishable from sCJD to a slowly progressive dementing illness of many years' duration to an early-age-of-onset disorder that is similar to Alzheimer's disease. A mutation at codon 178 resulting in substitution of asparagine for aspartic acid produces FFI if a methionine is encoded at the polymorphic 129 residue on the same allele. Typical CJD is seen if the D178N mutation occurs with a valine encoded at position 129 of the same allele.

HUMAN *PRNP* GENE POLYMORPHISMS

Polymorphisms influence the susceptibility to sporadic, inherited, and infectious forms of prion disease. The methionine/valine polymorphism at position 129 not only modulates the age of onset of some inherited prion diseases but can also determine the clinical phenotype. The finding that homozygosity at codon 129 predisposes to sCJD supports a model of prion production that favors PrP interactions between homologous proteins.

Substitution of the basic residue lysine at position 218 in mouse PrP produced dominant-negative inhibition of prion replication in transgenic mice. This same lysine at position 219 in human PrP has been found in 12% of the Japanese population, and this group appears to be resistant to prion disease. Dominant-negative inhibition of prion replication was also found with substitution of the basic residue arginine at position 171; sheep with arginine are resistant to scrapie prions but are susceptible to BSE prions that were inoculated intracerebrally.

INFECTIOUS PRION DISEASES

IATROGENIC CJD

Accidental transmission of CJD to humans appears to have occurred with corneal transplantation, contaminated electroencephalogram (EEG) electrode implantation, and surgical procedures. Corneas from donors with inapparent CJD have been transplanted to apparently healthy recipients who developed CJD after prolonged incubation periods. The same improperly decontaminated EEG electrodes that caused CJD in two young patients with intractable epilepsy caused CJD in a chimpanzee 18 months after their experimental implantation.

Surgical procedures may have resulted in accidental inoculation of patients with prions, presumably because some instrument or apparatus in the operating theater became contaminated when a CJD patient underwent surgery. Although the epidemiology of these studies is highly suggestive, no proof for such episodes exists.

Dura mater grafts

More than 160 cases of CJD after implantation of dura mater grafts have been recorded. All of the grafts were thought to have been acquired from a single manufacturer whose preparative procedures were inadequate to inactivate human prions. One case of CJD occurred after repair of an eardrum perforation with a pericardium graft.

Human growth hormone and pituitary gonadotropin therapy

The transmission of CJD prions from contaminated human growth hormone (hGH) preparations derived from human pituitaries has been responsible for fatal cerebellar disorders with dementia in >180 patients ranging in age from 10 to 41 years. These patients received injections of hGH every 2–4 days for 4–12 years. If it is thought that these patients developed CJD from injections of prion-contaminated hGH preparations, the possible incubation periods range from 4 to 30 years. Only recombinant hGH is now used therapeutically so that possible contamination with prions is no longer an issue. Four cases of CJD have occurred in women receiving human pituitary gonadotropin.

VARIANT CJD

The restricted geographic occurrence and chronology of vCJD raised the possibility that BSE prions had been transmitted to humans through the consumption of tainted beef. More than 190 cases of vCJD have occurred, with >90% of these in Britain. vCJD has also been reported in people either living in or originating from France, Ireland, Italy, Netherlands, Portugal, Spain, Saudi Arabia, United States, Canada, and Japan.

The steady decline in the number of vCJD cases over the past decade argues that there will not be a prion disease epidemic in Europe, similar to those seen for BSE and kuru. What is certain is that prion-tainted meat should be prevented from entering the human food supply.

The most compelling evidence that vCJD is caused by BSE prions was obtained from experiments in mice expressing the bovine PrP transgene. Both BSE and vCJD prions were efficiently transmitted to these

transgenic mice and with similar incubation periods. In contrast to sCJD prions, vCJD prions did not transmit disease efficiently to mice expressing a chimeric human-mouse PrP transgene. Earlier studies with nontransgenic mice suggested that vCJD and BSE might be derived from the same source because both inocula transmitted disease with similar but very long incubation periods.

Attempts to determine the origin of BSE and vCJD prions have relied on passaging studies in mice, some of which are described earlier, as well as studies of the conformation and glycosylation of PrP^{Sc}. One scenario suggests that a particular conformation of bovine PrP^{Sc} was selected for heat resistance during the rendering process and was then reselected multiple times as cattle infected by ingesting prion-contaminated meat and bone meal (MBM) were slaughtered and their offal rendered into more MBM.

NEUROPATHOLOGY

Frequently the brains of patients with CJD have no recognizable abnormalities on gross examination. Patients who survive for several years have variable degrees of cerebral atrophy.

On light microscopy, the pathologic hallmarks of CJD are spongiform degeneration and astrocytic gliosis. The lack of an inflammatory response in CJD and other prion diseases is an important pathologic feature of these degenerative disorders. Spongiform degeneration is characterized by many 1- to 5-μm vacuoles in the neuropil between nerve cell bodies. Generally the spongiform changes occur in the cerebral cortex, putamen, caudate nucleus, thalamus, and molecular layer of the cerebellum. Astrocytic gliosis is a constant but nonspecific feature of prion diseases. Widespread proliferation of fibrous astrocytes is found throughout the gray matter of brains infected with CJD prions. Astrocytic processes filled with glial filaments form extensive networks.

Amyloid plaques have been found in ~10% of CJD cases. Purified CJD prions from humans and animals exhibit the ultrastructural and histochemical characteristics of amyloid when treated with detergents during limited proteolysis. In first passage from some human Japanese CJD cases, amyloid plaques have been found in mouse brains. These plaques stain with antibodies raised against PrP.

The amyloid plaques of GSS disease are morphologically distinct from those seen in kuru or scrapie. GSS plaques consist of a central dense core of amyloid surrounded by smaller globules of amyloid. Ultrastructurally, they consist of a radiating fibrillar network of amyloid fibrils, with scant or no neuritic degeneration. The plaques can be distributed throughout the brain but are most frequently found in the cerebellum. They are often located adjacent to blood vessels. Congophilic angiopathy has been noted in some cases of GSS disease.

In vCJD, a characteristic feature is the presence of "florid plaques." These are composed of a central core of PrP amyloid, surrounded by vacuoles in a pattern suggesting petals on a flower.

CLINICAL FEATURES

Nonspecific prodromal symptoms occur in about a third of patients with CJD and may include fatigue, sleep disturbance, weight loss, headache, anxiety, vertigo, malaise, and ill-defined pain. Most patients with CJD present with deficits in higher cortical function. These deficits almost always progress over weeks or months to a state of profound dementia characterized by memory loss, impaired judgment, and a decline in virtually all aspects of intellectual function. A few patients present with either visual impairment or cerebellar gait and coordination deficits. Frequently the cerebellar deficits are rapidly followed by progressive dementia. Visual problems often begin with blurred vision and diminished acuity, rapidly followed by dementia.

Other symptoms and signs include extrapyramidal dysfunction manifested as rigidity, masklike facies, or (less commonly) choreoathetoid movements; pyramidal signs (usually mild); seizures (usually major motor) and, less commonly, hypoesthesia; supranuclear gaze palsy; optic atrophy; and vegetative signs such as changes in weight, temperature, sweating, or menstruation.

Myoclonus

Most patients (~90%) with CJD exhibit myoclonus that appears at various times throughout the illness. Unlike other involuntary movements, myoclonus persists during sleep. Startle myoclonus elicited by loud sounds or bright lights is frequent. It is important to stress that myoclonus is neither specific nor confined to CJD and tends to occur later in the course of CJD. Dementia with myoclonus can also be due to Alzheimer's disease (AD), dementia with Lewy bodies, corticobasal degeneration, cryptococcal encephalitis (Chap. 109), or the myoclonic epilepsy disorder Unverricht-Lundborg disease.

Clinical course

In documented cases of accidental transmission of CJD to humans, an incubation period of 1.5–2 years preceded the development of clinical disease. In other cases, incubation periods of up to 40 years have been suggested. Most patients with CJD live 6–12 months after the onset of clinical signs and symptoms, whereas some live for up to 5 years.

DIAGNOSIS

The constellation of dementia, myoclonus, and periodic electrical bursts in an afebrile 60-year-old patient generally indicates CJD. Clinical abnormalities in CJD are confined to the CNS. Fever, elevated sedimentation rate, leukocytosis in blood, or a pleocytosis in cerebrospinal fluid (CSF) should alert the physician to another etiology to explain the patient's CNS dysfunction.

Variations in the typical course appear in inherited and transmitted forms of the disease. fCJD has an

earlier mean age of onset than sCJD. In GSS disease, ataxia is usually a prominent and presenting feature, with dementia occurring late in the disease course. GSS disease typically presents earlier than CJD (mean age 43 years) and is typically more slowly progressive than CJD; death usually occurs within 5 years of onset. FFI is characterized by insomnia and dysautonomia; dementia occurs only in the terminal phase of the illness. Rare sporadic cases have been identified. vCJD has an unusual clinical course, with a prominent psychiatric prodrome that may include visual hallucinations and early ataxia, while frank dementia is usually a late sign of vCJD.

DIFFERENTIAL DIAGNOSIS

Many conditions may mimic CJD superficially. Dementia with Lewy bodies is the most common disorder to be mistaken for CJD. It can present in a subacute fashion with delirium, myoclonus, and extrapyramidal features. Other neurodegenerative disorders to consider include AD, frontotemporal dementia, corticobasal degeneration, progressive supranuclear palsy, ceroid lipofuscinosis, and myoclonic epilepsy with Lafora bodies. The absence of abnormalities on diffusion-weighted and fluid-attenuated inversion recovery (FLAIR) MRI will almost always distinguish these dementing conditions from CJD.

Hashimoto's encephalopathy, which presents as a subacute progressive encephalopathy with myoclonus and periodic triphasic complexes on the EEG, should be excluded in every case of suspected CJD. It is diagnosed by the finding of high titers of antithyroglobulin or antithyroid peroxidase (antimicrosomal) antibodies in the blood and improves with glucocorticoid therapy. Unlike CJD, fluctuations in severity typically occur in Hashimoto's encephalopathy.

Intracranial vasculitides may produce nearly all of the symptoms and signs associated with CJD, sometimes without systemic abnormalities. Myoclonus is exceptional with cerebral vasculitis, but focal seizures may confuse the picture. Prominent headache, absence of myoclonus, stepwise change in deficits, abnormal CSF, and focal white matter changes on MRI or angiographic abnormalities all favor vasculitis.

Paraneoplastic conditions, particularly limbic encephalitis and cortical encephalitis, can also mimic CJD. In many of these patients, dementia appears prior to the diagnosis of a tumor, and in some, no tumor is ever found. Detection of the paraneoplastic antibodies is often the only way to distinguish these cases from CJD.

Other diseases that can simulate CJD include neurosyphilis (Chap. 74), AIDS dementia complex (Chap. 93), progressive multifocal leukoencephalopathy (Chap. 31), subacute sclerosing panencephalitis, progressive rubella panencephalitis, herpes simplex encephalitis (Chap. 31), diffuse intracranial tumor (gliomatosis cerebri), anoxic encephalopathy, dialysis dementia, uremia, hepatic encephalopathy, voltage-gated potassium channel (VGkC) autoimmune encephalopathy and lithium or bismuth intoxication.

LABORATORY TESTS

The only specific diagnostic tests for CJD and other human prion diseases measure PrP^{Sc}. The most widely used method involves limited proteolysis that generates PrP 27-30, which is detected by immunoassay after denaturation. The conformation-dependent immunoassay (CDI) is based on immunoreactive epitopes that are exposed in PrP^{C} but buried in PrP^{Sc}. In humans, the diagnosis of CJD can be established by brain biopsy if PrP^{Sc} is detected. If no attempt is made to measure PrP^{Sc}, but the constellation of pathologic changes frequently found in CJD is seen in a brain biopsy, then the diagnosis is reasonably secure (see "Neuropathology"). The high sensitivity and specificity of cortical ribboning and basal ganglia hyperintensity on FLAIR and diffusion-weighted MRI for the diagnosis of CJD have greatly diminished the need for brain biopsy in patients with suspected CJD. Because PrP^{Sc} is not uniformly distributed throughout the CNS, the apparent absence of PrP^{Sc} in a limited sample such as a biopsy does not rule out prion disease. At autopsy, sufficient brain samples should be taken for both PrP^{Sc} immunoassay, preferably by CDI, and immunohistochemistry of tissue sections.

To establish the diagnosis of either sCJD or familial prion disease, sequencing of the *PRNP* gene must be performed. Finding the wild-type *PRNP* gene sequence permits the diagnosis of sCJD if there is no history to suggest infection from an exogenous source of prions. The identification of a mutation in the *PRNP* gene sequence that encodes a nonconservative amino acid substitution argues for familial prion disease.

CT may be normal or show cortical atrophy. MRI is valuable for distinguishing sCJD from most other conditions. On FLAIR sequences and diffusion-weighted imaging, ~90% of patients show increased intensity in the basal ganglia and cortical ribboning **(Fig. 104-3)**. This pattern is not seen with other neurodegenerative disorders but has been seen infrequently with viral encephalitis, paraneoplastic syndromes, or seizures. When the typical MRI pattern is present, in the proper clinical setting, diagnosis is facilitated. However, some cases of sCJD do not show this typical pattern, and other early diagnostic approaches are still needed.

CSF is nearly always normal but may show protein elevation and, rarely, mild pleocytosis. Although the stress protein 14-3-3 is elevated in the CSF of some patients with CJD, similar elevations of 14-3-3 are found in patients with other disorders; thus this elevation is not specific. Similarly, elevations of CSF neuron-specific enolase and tau occur in CJD but lack specificity for diagnosis.

The EEG is often useful in the diagnosis of CJD, although only about 60% of individuals show the typical pattern. During the early phase of CJD, the EEG is usually normal or shows only scattered theta activity. In most advanced cases, repetitive, high-voltage, triphasic, and polyphasic sharp discharges are seen, but in many cases their presence is transient. The presence of these stereotyped periodic bursts of <200 ms duration,

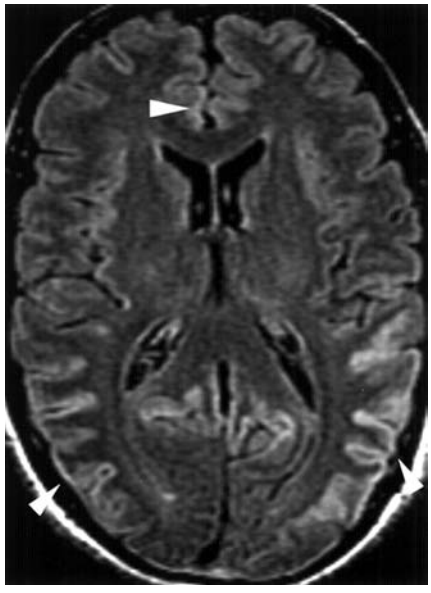


FIGURE 104-3
T2-weighted (FLAIR) MRI showing hyperintensity in the cortex in a patient with sporadic CJD. This so-called "cortical ribboning" along with increased intensity in the basal ganglia on T2 or diffusion-weighted imaging can aid in the diagnosis of CJD.

occurring every 1–2 s, makes the diagnosis of CJD very likely. These discharges are frequently but not always symmetric; there may be a one-sided predominance in amplitude. As CJD progresses, normal background rhythms become fragmentary and slower.

CARE OF CJD PATIENTS

Although CJD should not be considered either contagious or communicable, it is transmissible. The risk of accidental inoculation by aerosols is very small; nonetheless, procedures producing aerosols should be performed in certified biosafety cabinets. Biosafety level 2 practices, containment equipment, and facilities are recommended by the Centers for Disease Control and Prevention and the National Institutes of Health. The primary problem in caring for patients with CJD is the inadvertent infection of health care workers by needle and stab wounds. Electroencephalographic and electromyographic needles should not be reused after studies on patients with CJD have been performed.

There is no reason for pathologists or other morgue employees to resist performing autopsies on patients whose clinical diagnosis was CJD. Standard microbiologic practices outlined here, along with specific recommendations for decontamination, seem to be adequate precautions for the care of patients with CJD and the handling of infected specimens.

DECONTAMINATION OF CJD PRIONS

Prions are extremely resistant to common inactivation procedures, and there is some disagreement about the optimal conditions for sterilization. Some investigators recommend treating CJD-contaminated materials once with 1 *N* NaOH at room temperature, but we believe this procedure may be inadequate for sterilization. Autoclaving at 134°C for 5 h or treatment with 2 *N* NaOH for several hours is recommended for sterilization of prions. The term *sterilization* implies complete destruction of prions; any residual infectivity can be hazardous. Recent studies show that sCJD prions bound to stainless steel surfaces are resistant to inactivation by autoclaving at 134°C for 2 h; exposure of bound prions to an acidic detergent solution prior to autoclaving rendered prions susceptible to inactivation.

PREVENTION AND THERAPEUTICS

There is no known effective regimen for preventing or treating CJD. The finding that phenothiazines and acridines inhibit PrP^{Sc} formation in cultured cells led to clinical studies of quinacrine in CJD patients. Unfortunately, quinacrine failed to slow the rate of cognitive decline in CJD, possibly because therapeutic concentrations in the brain were not achieved. Although inhibition of the P-glycoprotein (Pgp) transport system resulted in substantially increased quinacrine levels in the brains of mice, the prion incubation times were not extended by treatment with the drug. Whether such an approach can be used to treat CJD remains to be established.

Like the acridines, anti-PrP antibodies have been shown to eliminate PrP^{Sc} from cultured cells. Additionally, such antibodies in mice, either administered by injection or produced from a transgene, have been shown to prevent prion disease when prions are introduced by a peripheral route, such as intraperitoneal inoculation. Unfortunately, the antibodies were ineffective in mice inoculated intracerebrally with prions. Several drugs, including pentosan polysulfate as well as porphyrin and phenylhydrazine derivatives, delay the onset of disease in animals inoculated intracerebrally with prions if the drugs are given intracerebrally beginning soon after inoculation.

PRION-LIKE PROTEINS CAUSING OTHER NEURODEGENERATIVE DISEASES

There is mounting evidence that prion-like changes in protein conformation underlie Alzheimer's (AD), Parkinson's (PD), and Huntington's (HD) diseases as well as the frontotemporal dementias (FTDs) and amyotrophic lateral sclerosis (ALS). Experimental studies have shown that transgenic mice expressing mutant amyloid precursor protein (APP) develop amyloid plaques containing fibrils composed of the amyloid beta (Aβ) peptide about a year after inoculation with extracts prepared from the brains of patients with AD. Mutant tau aggregates in transgenic mice and cultured cells can trigger the aggregation of wild-type tau into fibrils that resemble those in

neurofibrillary tangles and Pick bodies that have been found in AD, FTDs, Pick's disease, and some cases of posttraumatic head injury. In patients with advanced PD who received grafts of fetal substantia nigral neurons, Lewy bodies containing β-sheet–rich α-synuclein have been identified in grafted cells about 10 years after transplantation. These findings argue for the axonal transport of misfolded α-synuclein crossing into grafted neurons, where it initiates aggregation of nascent α-synuclein into fibrils that coalesce to form Lewy bodies.

Taken together, a wealth of data argues that all neurodegenerative diseases are caused by proteins that undergo aberrant processing, which results in their assembly into amyloid fibrils. In each degenerative brain disease, prion-like protein processing is responsible for the accumulation of a particular protein in an altered state that leads to neurodegeneration. Interestingly, once these aberrant, prion-like proteins have polymerized into amyloid fibrils, they are probably inert. Amyloid plaques containing PrP^{Sc} are a nonobligatory feature of prion disease in humans and animals. Furthermore, amyloid plaques in AD do not correlate with the level of dementia; however, the level of soluble (oligomeric) Aβ peptide does correlate with memory loss and other intellectual deficits.

SECTION VII

FUNGAL INFECTIONS

CHAPTER 105

DIAGNOSIS AND TREATMENT OF FUNGAL INFECTIONS

John E. Edwards, Jr.

TERMINOLOGY AND MICROBIOLOGY

Traditionally, fungal infections have been classified into specific categories based on both anatomic location and epidemiology. The most common general anatomic categories are mucocutaneous and deep organ infection; the most common general epidemiologic categories are endemic and opportunistic. Although *mucocutaneous infections* can cause serious morbidity, they are rarely fatal. *Deep organ infections* also cause severe illness in many cases and, in contrast to mucocutaneous infections, are often fatal. The *endemic mycoses* (e.g., coccidioidomycosis) are infections caused by fungal organisms that are not part of the normal human microbial flora and are acquired from environmental sources. In contrast, *opportunistic mycoses* are caused by organisms (e.g., *Candida* and *Aspergillus*) that commonly are components of the normal human flora and whose ubiquity in nature renders them easily acquired by the immunocompromised host. Opportunistic fungi cause serious infections when the immunologic response of the host becomes ineffective, allowing the organisms to transition from harmless commensals to invasive pathogens. Frequently, the diminished effectiveness of the immune system is a result of advanced modern therapies that coincidentally either unbalance the host's microflora or directly interfere with immunologic responses. Endemic mycoses cause more severe illness in immunocompromised patients than in immunocompetent individuals.

Patients acquire deep organ infection with endemic fungi almost exclusively by inhalation. Cutaneous infections result either from hematogenous dissemination or, more often, from direct contact with soil—the natural reservoir for the vast majority of endemic mycoses. The dermatophytic fungi may be acquired by human-to-human transmission, but the majority of infections result from environmental contact. In contrast, the opportunistic fungus *Candida* invades the host from normal sites of colonization, usually the mucous membranes of the gastrointestinal tract. In general, innate immunity is the primary defense mechanism against fungi. Although antibodies are formed during many fungal infections (and even during commensalism), they generally do not constitute the primary mode of defense. Nevertheless, in selected infections, as discussed next, measurement of antibody titers may be a useful diagnostic test.

Three other terms frequently used in clinical discussions of fungal infections are *yeast*, *mold*, and *dimorphic fungus*. *Yeasts* are seen as rounded single cells or as budding organisms. *Candida* and *Cryptococcus* are traditionally classified as yeasts. *Molds* grow as filamentous forms called *hyphae* both at room temperature and in invaded tissue. *Aspergillus*, *Rhizopus* (the species that causes mucormycosis [zygomycosis]), and fungi commonly infecting the skin to cause ringworm and related cutaneous conditions are classified as molds. Variations occur within this classification of yeasts and molds. For instance, when *Candida* infects tissue, both yeasts and filamentous forms may occur (except with *C. glabrata*, which forms only yeasts in tissue); in contrast, *Cryptococcus* exists only in yeast form. *Dimorphic* is the term used to describe fungi that grow as yeasts or large spherical structures in tissue but as filamentous forms at room temperature in the environment. Classified in this group are the organisms causing blastomycosis, paracoccidioidomycosis, coccidioidomycosis, histoplasmosis, and sporotrichosis.

The incidence of nearly all fungal infections has risen substantially. Opportunistic infections have increased in frequency as a consequence of intentional immunosuppression in organ and stem cell transplantation and other diseases, the administration of cytotoxic chemotherapy for cancers, and the liberal use of antibacterial agents. The incidence of endemic mycoses has increased in geographic locations where there has been substantial population growth.

DIAGNOSIS

The definitive diagnosis of any fungal infection requires histopathologic identification of the fungus invading tissue,

accompanied by evidence of an inflammatory response. The identification of an inflammatory response has been especially important with regard to *Aspergillus* infection. *Aspergillus* is ubiquitous and can float from the air onto biopsy material. Therefore, in rare but important instances, this fungus is an ex vivo contaminant during processing of a specimen for microscopy, with a consequent incorrect diagnosis. The stains most commonly used to identify fungi are periodic acid–Schiff and Gomori methenamine silver. *Candida*, unlike other fungi, is visible on gram-stained tissue smears. Hematoxylin and eosin stain is not sufficient to identify *Candida* in tissue specimens. When positive, an India ink preparation of cerebrospinal fluid (CSF) is diagnostic for cryptococcosis. Most laboratories now use calcofluor white staining coupled with fluorescent microscopy to identify fungi in fluid specimens.

Extensive investigations of the diagnosis of deep organ fungal infections have yielded a variety of tests with different degrees of specificity and sensitivity. The most reliable tests are the detection of antibody to *Coccidioides immitis* in serum and CSF; of *Histoplasma capsulatum* antigen in urine, serum, and CSF; and of cryptococcal polysaccharide antigen in serum and CSF. These tests have a general sensitivity and specificity of 90%; however, because there is variability among laboratories, testing on multiple occasions is advisable. The test for galactomannan has been used extensively in Europe and is now approved in the United States for diagnosis of aspergillosis. Sources of concern regarding galactomannan are the incidence of false-negative results and the need for multiple serial tests to reduce this incidence. The β-glucan test for *Candida* is also under evaluation but, like the galactomannan test, requires additional validation; this test has a negative predictive value of ~90%. Numerous polymerase chain reaction assays to detect antigens are in the developmental stages, as are nucleic acid hybridization techniques.

Of the fungal organisms, *Candida* is by far the most frequently recovered from blood. Although *Candida* species can be detected with any of the automated blood culture systems widely used at present, the lysis-centrifugation technique increases the sensitivity of blood cultures for *Candida* and for less common organisms (e.g., *H. capsulatum*). Lysis-centrifugation should be used when disseminated fungal infection is suspected.

Except in the cases of coccidioidomycosis, cryptococcosis, and histoplasmosis, there are no fully validated and widely used tests for serodiagnosis of disseminated fungal infection. Skin tests for the endemic mycoses are no longer available.

TREATMENT Fungal Infections

This discussion is intended as a brief overview of general strategies for the use of antifungal agents in the treatment of fungal infections. Regimens, schedules, and strategies are detailed in the chapters on specific mycoses that follow in this section.

Since fungal organisms are eukaryotic cells that contain most of the same organelles (with many of the same physiologic functions) as human cells, the identification of drugs that selectively kill or inhibit fungi but are not toxic to human cells has been highly problematic. Far fewer antifungal than antibacterial agents have been introduced into clinical medicine.

AMPHOTERICIN B The introduction of amphotericin B (AmB) in the late 1950s revolutionized the treatment of fungal infections in deep organs. Before AmB became available, cryptococcal meningitis and other disseminated fungal infections were nearly always fatal. For nearly a decade after AmB was introduced, it was the only effective agent for the treatment of life-threatening fungal infections. AmB remains the broadest-spectrum antifungal agent but carries several disadvantages, including significant nephrotoxicity, lack of an oral preparation, and unpleasant side effects (fever, chills, and nausea) during treatment. To circumvent nephrotoxicity and infusion side effects, lipid formulations of AmB were developed and have virtually replaced the original colloidal deoxycholate formulation in clinical use (although the older formulation is still available). The lipid formulations include liposomal AmB (L-AmB; 3–5 mg/kg per day) and AmB lipid complex (ABLC; 5 mg/kg per day). A third preparation, AmB colloidal dispersion (ABCD; 3–4 mg/kg per day), is rarely used because of the high incidence of side effects associated with infusion. (The doses listed are standard doses for adults with invasive infection.)

The lipid formulations of AmB have the disadvantage of being considerably more expensive than the deoxycholate formulation. Experience is still accumulating on the comparative efficacy, toxicity, and advantages of the different formulations for specific clinical fungal infections (e.g., central nervous system [CNS] infection). Whether there is a clinically significant difference in these drugs with respect to CNS penetration or nephrotoxicity remains controversial. Despite these issues and despite the expense, the lipid formulations are now much more commonly used than AmB deoxycholate in developed countries. In developing countries, AmB deoxycholate is still preferred because of the expense of the lipid formulations.

AZOLES This class of antifungal drugs offers important advantages over AmB: the azoles cause little or no nephrotoxicity and are available in oral preparations. Early azoles included ketoconazole and miconazole, which have been replaced by newer agents for the treatment of deep organ fungal infections. The azoles' mechanism of action is inhibition of ergosterol synthesis in the fungal cell wall. Unlike AmB, these drugs are considered fungistatic, not fungicidal.

Fluconazole Since its introduction, fluconazole has played an extremely important role in the treatment of a wide variety of serious fungal infections. Its major advantages are the availability of both oral and IV formulations, a long half-life, satisfactory penetration of most body fluids (including ocular fluid and CSF), and minimal toxicity (especially relative to that of AmB). Its disadvantages include (usually reversible) hepatotoxicity and—at high doses—alopecia, muscle weakness, and dry mouth with a metallic taste. Fluconazole is not effective for the treatment of aspergillosis, mucormycosis, or *Scedosporium apiospermum* infections. It is less effective than the newer azoles against *C. glabrata* and *C. krusei*.

Fluconazole has become the agent of choice for the treatment of coccidioidal meningitis, although relapses have followed therapy with this drug. In addition, fluconazole is useful for both consolidation and maintenance therapy for cryptococcal meningitis. This agent has been shown to be as efficacious as AmB in the treatment of candidemia. The effectiveness of fluconazole in candidemia and the drug's relatively minimal toxicity, in conjunction with the inadequacy of diagnostic tests for widespread hematogenously disseminated candidiasis, have led to a change in the paradigm for candidemia management. The standard of care is now to treat all candidemic patients with an antifungal agent and to change all their intravascular lines, if feasible, rather than merely to remove a singular suspect intravascular line and then observe the patient. The usual fluconazole regimen for treatment of candidemia is 400 mg/d given until 2 weeks after the last positive blood culture.

Fluconazole is considered effective as fungal prophylaxis in bone marrow transplant recipients and high-risk liver transplant patients. Its general use for prophylaxis in patients with leukemia, in AIDS patients with low CD4+ T cell counts, and in patients on surgical intensive care units remains controversial.

Voriconazole Voriconazole, which is available in both oral and IV formulations, has a broader spectrum than fluconazole against *Candida* species (including *C. glabrata* and *C. krusei*) and is active against *Aspergillus*, *Scedosporium*, and *Fusarium*. It is generally considered the first-line drug of choice for treatment of aspergillosis. A few case reports have shown voriconazole to be effective in individual patients with coccidioidomycosis, blastomycosis, and histoplasmosis, but because of limited data this agent is not recommended for treatment of the endemic mycoses. Among the disadvantages of voriconazole (compared with fluconazole) are its more numerous interactions with many of the drugs used in patients predisposed to fungal infections. Hepatotoxicity, skin rashes (including photosensitivity), and visual disturbances are relatively common. Skin cancer surveillance is now recommended for patients taking voriconazole. Voriconazole is also considerably more expensive than fluconazole. Moreover, it is advisable to monitor voriconazole levels in certain patients since (1) this drug is completely metabolized in the liver by CYP2C9, CYP3A4, and CYP2C19; and (2) human genetic variability in CYP2C19 activity exists. Dosages should be reduced accordingly in those patients with liver failure. Dose adjustments for renal insufficiency are not necessary; however, because the IV formulation is prepared in cyclodextrin, it should not be given to patients with severe renal insufficiency.

Itraconazole Itraconazole is available in IV and oral (capsule and suspension) formulations. Varying blood levels among patients taking oral itraconazole reflect a disadvantage compared with the other azoles. Itraconazole is the drug of choice for mild to moderate histoplasmosis and blastomycosis and has often been used for chronic mucocutaneous candidiasis. It has been approved by the U.S. Food and Drug Administration (FDA) for use in febrile neutropenic patients. Itraconazole has also proved useful for the treatment of chronic coccidioidomycosis, sporotrichosis, and *S. apiospermum* infection. The mucocutaneous and cutaneous fungal infections that have been treated successfully with itraconazole include oropharyngeal candidiasis (especially in AIDS patients), tinea versicolor, tinea capitis, and onychomycosis. Disadvantages of itraconazole include its poor penetration into CSF, the use of cyclodextrin in both the oral suspension and the IV preparation, the variable absorption of the drug in capsule form, and the need for monitoring of blood levels in patients taking capsules for disseminated mycoses. Reported cases of severe congestive heart failure in patients taking itraconazole have been a source of concern. Like the other azoles, itraconazole can cause hepatic toxicity.

Posaconazole Posaconazole is approved by the FDA for prophylaxis of aspergillosis and candidiasis in patients at high risk for developing these infections because of severe immunocompromise. It has also been approved for the treatment of oropharyngeal candidiasis and has been evaluated for the treatment of zygomycosis, fusariosis, aspergillosis, cryptococcosis, and various other forms of candidal infection. The relevant studies of posaconazole in zygomycosis, fusariosis, and aspergillosis have examined salvage therapy. A study of >90 patients whose zygomycosis was refractory to other therapy yielded encouraging results. No trials of posaconazole for the treatment of candidemia have yet been reported. Case reports have described the drug's efficacy in coccidioidomycosis and histoplasmosis. Controlled trials have shown its effectiveness as a prophylactic agent in patients with acute leukemia and in bone marrow transplant recipients. In addition, posaconazole has been found to be effective against fluconazole-resistant *Candida* species. The results of a large-scale study of the use of posaconazole as salvage therapy for aspergillosis indicated that it is an alternative to other agents for salvage

therapy; however, that study predated the use of voriconazole and the echinocandins.

ECHINOCANDINS The echinocandins, including the FDA-approved drugs caspofungin, anidulafungin, and micafungin, have added considerably to the antifungal armamentarium. All three of these agents inhibit β-1,3-glucan synthase, which is necessary for cell wall synthesis in fungi and is not a component of human cells. None of these agents is currently available in an oral formulation. The echinocandins are considered fungicidal for *Candida* and fungistatic for *Aspergillus*. Their greatest use to date is against candidal infections. They offer two advantages: broad-spectrum activity against all *Candida* species and relatively low toxicity. The minimal inhibitory concentrations (MICs) of all the echinocandins are highest against *C. parapsilosis*; it is not clear whether these higher MIC values represent less clinical effectiveness against this species. The echinocandins are among the safest antifungal agents.

In controlled trials, *caspofungin* has been at least as efficacious as AmB for the treatment of candidemia and invasive candidiasis and as efficacious as fluconazole for the treatment of candidal esophagitis. In addition, caspofungin has been efficacious as salvage therapy for aspergillosis. *Anidulafungin* has been approved by the FDA as therapy for candidemia in nonneutropenic patients and for *Candida* esophagitis, intraabdominal infection, and peritonitis. In controlled trials, anidulafungin has been shown to be noninferior and possibly superior to fluconazole against candidemia and invasive candidiasis. It is as efficacious as fluconazole against candidal esophagitis. When anidulafungin is used with cyclosporine, tacrolimus, or voriconazole, no dosage adjustment is required for either drug in the combination. *Micafungin* has been approved for the treatment of esophageal candidiasis and candidemia and for prophylaxis in patients receiving stem cell transplants. In a head-to-head trial, micafungin was noninferior to caspofungin for the treatment of candidemia. Studies thus far have shown that coadministration of micafungin and cyclosporine does not require dose adjustments for either drug. When micafungin is given with sirolimus, the AUC rises for sirolimus, usually necessitating a reduction in its dose. In open-label trials, favorable results have been obtained with micafungin for the treatment of deep-seated *Aspergillus* and *Candida* infections.

FLUCYTOSINE (5-FLUOROCYTOSINE) The use of flucytosine has diminished as newer antifungal drugs have been developed. Flucytosine has a unique mechanism of action based on intrafungal conversion to 5-fluorouracil, which is toxic to the fungal cell. Development of resistance to the compound has limited its use as a single agent. Flucytosine is nearly always used in combination with AmB. Its good penetration into the CSF makes it attractive for use with AmB for treatment of cryptococcal meningitis. Flucytosine has also been recommended for the treatment of candidal meningitis in combination with AmB; comparative trials with AmB alone have not been done. Significant and frequent bone marrow depression is seen with flucytosine when this drug is used with AmB.

GRISEOFULVIN AND TERBINAFINE Historically, griseofulvin has been useful primarily for ringworm infection. This agent is usually given for relatively long periods. Terbinafine has been used primarily for onychomycosis but also for ringworm. In comparative studies, terbinafine has been as effective as itraconazole and more effective than griseofulvin for both conditions.

TOPICAL ANTIFUNGAL AGENTS A detailed discussion of the agents used for the treatment of cutaneous fungal infections and onychomycosis is beyond the scope of this chapter; the reader is referred to the dermatology literature. Many classes of compounds have been used to treat the common fungal infections of the skin. Among the azoles used are clotrimazole, econazole, miconazole, oxiconazole, sulconazole, ketoconazole, tioconazole, butoconazole, and terconazole. In general, topical treatment of vaginal candidiasis has been successful. Since there is considered to be little difference in the efficacy of the various vaginal preparations, the choice of agent is made by the physician and/or the patient on the basis of preference and availability. Fluconazole given orally at 150 mg has the advantage of not requiring repeated intravaginal application. Nystatin is a polyene that has been used for both oropharyngeal thrush and vaginal candidiasis. Useful agents in other classes include ciclopirox olamine, haloprogin, terbinafine, naftifine, tolnaftate, and undecylenic acid.

CHAPTER 106

HISTOPLASMOSIS

Chadi A. Hage ■ L. Joseph Wheat

ETIOLOGY

Histoplasma capsulatum, a thermal dimorphic fungus, is the etiologic agent of histoplasmosis. In most endemic areas, *H. capsulatum* var. *capsulatum* is the causative agent; in Africa, *H. capsulatum* var. *duboisii* is also found. Mycelia—the naturally infectious form of *Histoplasma*—have a characteristic appearance, with microconidial and macroconidial forms. Microconidia are oval and are small enough (2–4 μm) to reach the terminal bronchioles and alveoli. Shortly after infecting the host, mycelia transform into the yeasts that are found inside macrophages and other phagocytes. The yeast forms are characteristically small (2–5 μm), with occasional narrow budding. In the laboratory, mycelia are best grown at room temperature, whereas yeasts are grown at 37°C on enriched media.

EPIDEMIOLOGY

Histoplasmosis is the most prevalent endemic mycosis in North America. Although this fungal disease has been reported throughout the world, its endemicity is particularly notable in certain parts of North, Central, and South America; Africa; and Asia. In the United States, the endemic areas spread over the Ohio and Mississippi river valleys. This pattern is related to the humid and acidic nature of the soil in these areas. Soil enriched with bird or bat droppings promotes the growth and sporulation of *Histoplasma*. Disruption of soil containing the organism leads to aerosolization of the microconidia and exposure of humans nearby. Activities associated with high-level exposure include spelunking, excavation, cleaning of chicken coops, demolition and remodeling of old buildings, and cutting of dead trees. Most cases seen outside of highly endemic areas represent imported disease—e.g., cases reported in Europe after travel to the Americas, Africa, or Asia.

PATHOGENESIS AND PATHOLOGY

Infection follows inhalation of microconidia **(Fig. 106-1)**. Once they reach the alveolar spaces, microconidia are rapidly recognized and engulfed by alveolar macrophages. At this point, the microconidia transform into budding yeasts **(Fig. 106-2)**, a process that is integral to the pathogenesis of histoplasmosis and is dependent on the availability of calcium and iron inside the phagocytes. The yeasts are capable of growing and multiplying inside resting macrophages. Neutrophils and then lymphocytes are attracted to the site of infection. Before the development of cellular immunity, yeasts use the phagosomes as a vehicle for translocation to local draining lymph nodes, whence they spread hematogenously throughout the reticuloendothelial system. Adequate cellular immunity develops ~2 weeks after infection. T cells produce interferon γ to assist the macrophages in killing the organism and controlling the progression of disease. Interleukin 12 and tumor necrosis factor α (TNF-α) play an essential role in cellular immunity to *H. capsulatum*. In the immunocompetent host, macrophages, lymphocytes, and epithelial cells eventually organize and form granulomas that contain the organisms. These granulomas typically fibrose and calcify; calcified mediastinal lymph nodes and hepatosplenic calcifications are frequently found in healthy individuals from endemic areas. In immunocompetent hosts, infection with *H. capsulatum* confers some immunity to

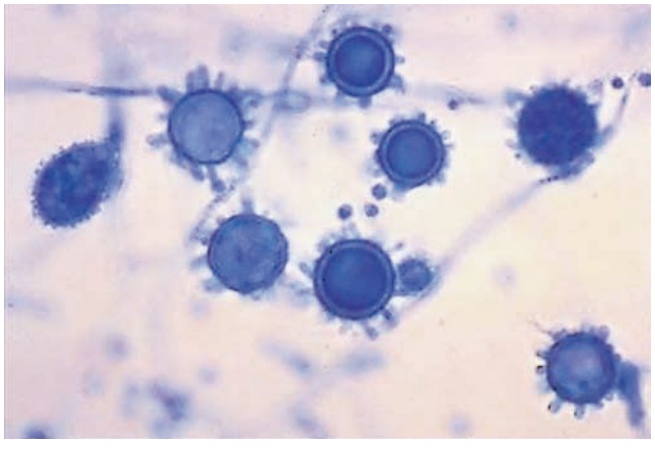


FIGURE 106-1
Spiked spherical conidia of *H. capsulatum* (lacto-phenol cotton blue stain).

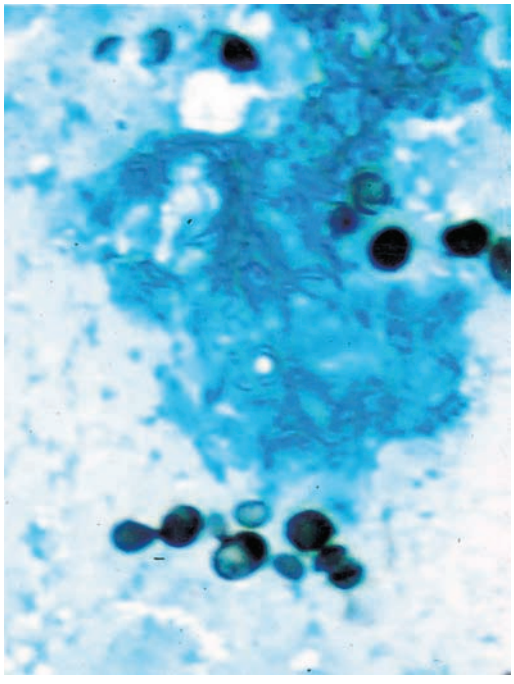


FIGURE 106-2
Small (2–5 μm) narrow budding yeasts of *H. capsulatum* from bronchoalveolar lavage fluid (Grocott's methenamine silver stain).

reinfection. In patients with impaired cellular immunity, the infection is not contained and can disseminate. Progressive disseminated histoplasmosis (PDH) can involve multiple organs, most commonly the bone marrow, spleen, liver **(Fig. 106-3)**, adrenal glands, and mucocutaneous membranes. Unlike latent tuberculosis, latent histoplasmosis rarely reactivates.

Structural lung disease (e.g., emphysema) impairs the clearance of pulmonary histoplasmosis, and chronic pulmonary disease can result. This chronic process is characterized by progressive inflammation, tissue necrosis, and fibrosis mimicking cavitary tuberculosis.

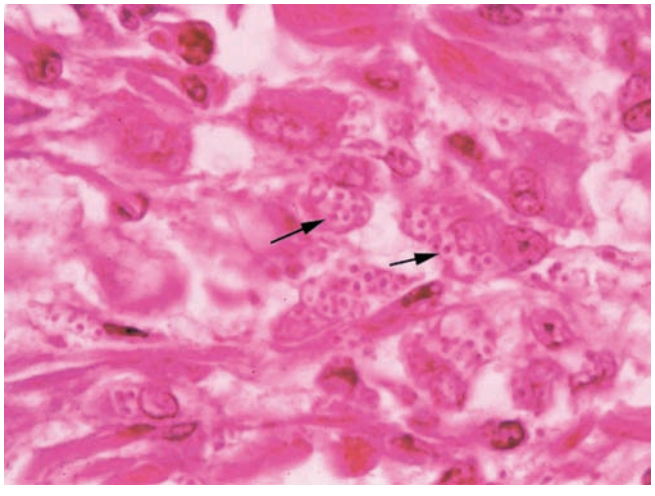


FIGURE 106-3
Intracellular yeasts (*arrows*) of *H. capsulatum* in a liver biopsy specimen (hematoxylin and eosin stain).

CLINICAL MANIFESTATIONS

The clinical spectrum of histoplasmosis ranges from asymptomatic infection to life-threatening illness. The attack rate and the extent and severity of the disease depend on the intensity of exposure, the immune status of the exposed individual, and the underlying lung architecture of the host.

In immunocompetent individuals with low-level exposure, most *Histoplasma* infections are either asymptomatic or mild and self-limited. Of adults residing in endemic areas, 50–80% have skin-test and/or radiographic evidence of previous infection without clinical manifestations. When symptoms do develop, they usually appear 1–4 weeks after exposure. Heavy exposure leads to a flulike illness with fever, chills, sweats, headache, myalgia, anorexia, cough, dyspnea, and chest pain. Chest radiographs usually show signs of pneumonitis with hilar or mediastinal adenopathy. Pulmonary infiltrates may be focal with light exposure or diffuse with heavy exposure. Rheumatologic symptoms of arthralgia or arthritis, often associated with erythema nodosum, occur in 5–10% of patients with acute histoplasmosis. Pericarditis may also develop. These manifestations represent inflammatory responses to the acute infection rather than its direct effects. Hilar or mediastinal lymph nodes may undergo necrosis and coalesce to form large mediastinal masses that can cause compression of great vessels, proximal airways, and the esophagus. These necrotic lymph nodes may also rupture and create fistulas between mediastinal structures (e.g., bronchoesophageal fistulas).

PDH is typically seen in immunocompromised individuals, who account for ~70% of cases. Common risk factors include AIDS (CD4+ T cell count, <200/μL), extremes of age, and the use of immunosuppressive medications such as prednisone, methotrexate, and anti-TNF-α agents. The spectrum of PDH ranges from an acute, rapidly fatal course—with diffuse interstitial or reticulonodular lung infiltrates causing respiratory failure, shock, coagulopathy, and multiorgan failure—to a more subacute course with a focal organ distribution. Common manifestations include fever and weight loss. Hepatosplenomegaly is also common. Other findings may include meningitis or focal brain lesions, ulcerations of the oral mucosa, gastrointestinal ulcerations, and adrenal insufficiency. Prompt recognition of this devastating illness is of paramount importance in patients with more severe manifestations or with underlying immunosuppression, especially AIDS (Chap. 93).

Chronic cavitary histoplasmosis is seen in smokers who have structural lung disease (e.g., bullous emphysema). This chronic illness is characterized by productive cough, dyspnea, low-grade fever, night sweats, and weight loss. Chest radiographs usually show upper-lobe infiltrates, cavitation, and pleural thickening—findings resembling those of tuberculosis. Without treatment, the course is slowly progressive.

Fibrosing mediastinitis is an uncommon and serious complication of histoplasmosis. In certain patients, acute infection is followed for unknown reasons by progressive fibrosis around the hilar and mediastinal lymph nodes. Involvement may be unilateral or bilateral; bilateral

involvement carries a worse prognosis. Major manifestations include superior vena cava syndrome, obstruction of pulmonary vessels, and airway obstruction. Patients may experience recurrent pneumonia, hemoptysis, or respiratory failure. Fibrosing mediastinitis is fatal in up to one-third of cases.

In healed histoplasmosis, calcified mediastinal nodes or lung parenchyma may erode through the walls of the airways and cause hemoptysis. This condition is called *broncholithiasis*.

African histoplasmosis caused by *H. capsulatum* var. *duboisii* is clinically distinct and is characterized by frequent skin and bone involvement.

DIAGNOSIS

Fungal culture remains the gold standard diagnostic test for histoplasmosis. However, culture results may not be known for up to 1 month, and cultures are often negative in less severe cases. Cultures are positive in ~75% of cases of PDH and chronic pulmonary histoplasmosis. Cultures of bronchoalveolar lavage (BAL) fluid are positive in about half of patients with acute pulmonary histoplasmosis causing diffuse infiltrates with hypoxemia. In PDH, the culture yield is highest for BAL fluid, bone marrow aspirate, and blood. Cultures of sputum or bronchial washings are usually positive in chronic pulmonary histoplasmosis. Cultures are typically negative, however, in other forms of histoplasmosis.

Fungal stains of cytopathology or biopsy materials showing structures resembling *Histoplasma* yeasts are helpful in the diagnosis of PDH, yielding positive results in about half of cases. Yeasts can be seen in BAL fluid (Fig. 106-2) from patients with diffuse pulmonary infiltrates, in bone marrow biopsy samples, and in biopsy specimens of other involved organs (e.g., the adrenal glands). Occasionally, yeasts are seen in blood smears from patients with severe PDH. However, staining artifacts and other fungal elements may be misidentified as *Histoplasma* yeasts.

The detection of *Histoplasma* antigen in body fluids is extremely useful in the diagnosis of PDH and acute diffuse pulmonary histoplasmosis. The sensitivity of this technique is >95% in patients with PDH and ~80% in patients with acute pulmonary histoplasmosis if both urine and serum are tested. Antigen can be detected in cerebrospinal fluid from patients with meningitis and in BAL fluid from those with pneumonia. Cross-reactivity occurs with African histoplasmosis, blastomycosis, coccidioidomycosis, paracoccidioidomycosis, and *Penicillium marneffei* infection.

Serologic tests, including immunodiffusion and complement fixation, are especially useful for the diagnosis of self-limited pulmonary histoplasmosis; however, at least 1 month is required for the production of antibodies after acute infection. A fourfold rise in antibody titer may be seen in patients with acute histoplasmosis. Serologic tests are also useful for the diagnosis of chronic pulmonary histoplasmosis. Limitations of serology, however, include insensitivity early in the course of infection and in immunosuppressed patients and the persistence of detectable antibody for several years after infection. Positive results from past infection may lead to a misdiagnosis of active histoplasmosis in a patient with another disease process.

TREATMENT Histoplasmosis

Treatment recommendations for histoplasmosis are summarized in Table 106-1. Treatment is indicated for all patients with PDH or chronic pulmonary histoplasmosis as well as for symptomatic patients with acute pulmonary histoplasmosis causing diffuse infiltrates, especially with hypoxemia. In most cases of pulmonary histoplasmosis, treatment is not recommended because the degree of exposure is not heavy; the infection is asymptomatic or symptoms are mild, subacute, and not progressive; and the illness resolves without therapy.

The preferred treatments for histoplasmosis include the lipid formulations of amphotericin B in more severe cases and itraconazole in others. Liposomal amphotericin B has been more effective than the deoxycholate formulation for treatment of PDH in patients with AIDS. The deoxycholate formulation of amphotericin B is an alternative to a lipid formulation for patients at low risk for nephrotoxicity. Posaconazole, voriconazole, and fluconazole are alternatives for patients who cannot take itraconazole.

In severe cases requiring hospitalization, a lipid formulation of amphotericin B is followed by itraconazole. In patients with meningitis, a lipid formulation of amphotericin B should be given for 4–6 weeks before the switch to itraconazole. In immunosuppressed patients, the degree of immunosuppression should be reduced if possible, although immune reconstitution inflammatory syndrome (IRIS) may ensue. Antiretroviral treatment improves the outcome of PDH in patients with AIDS and is recommended; however, whether antiretroviral treatment should be delayed to avoid IRIS is unknown.

Blood levels of itraconazole should be monitored to ensure adequate drug exposure, with target concentrations of 2–10 μg/mL. Drug interactions should be carefully assessed: itraconazole not only is cleared by cytochrome P450 metabolism but also inhibits cytochrome P450. This profile causes interactions with many other medications.

The duration of treatment for acute pulmonary histoplasmosis is 6–12 weeks, while that for PDH and chronic pulmonary histoplasmosis is ≥1 year. Antigen levels in urine and serum should be monitored during and for at least 1 year after therapy for PDH. Stable or rising antigen levels suggest treatment failure or relapse.

Previously, lifelong itraconazole maintenance therapy was recommended for patients with AIDS once histoplasmosis was diagnosed. Today, however, maintenance therapy is not required for patients who respond well to antiretroviral therapy, with CD4+ T cell counts of at least 150/μL (preferably >250/μL); who complete at least 1 year of itraconazole therapy; and who exhibit neither clinical evidence of active histoplasmosis nor an antigenuria level of >4 ng/mL. Maintenance therapy also appears to be unnecessary in patients receiving immunosuppressive treatment if the degree of immunosuppression can

TABLE 106-1

RECOMMENDATIONS FOR THE TREATMENT OF HISTOPLASMOSIS

TYPE OF HISTOPLASMOSIS	TREATMENT RECOMMENDATIONS	COMMENTS
Acute pulmonary, moderate to severe illness with diffuse infiltrates and/or hypoxemia	Lipid AmB (3–5 mg/kg per day) ± glucocorticoids for 1–2 weeks; then itraconazole (200 mg bid) for 12 weeks. Monitor renal and hepatic function.	Patients with mild cases usually recover without therapy, but itraconazole should be considered if the patient's condition has not improved after 1 month.
Chronic/cavitary pulmonary	Itraconazole (200 mg qd or bid) for at least 12 months. Monitor hepatic function.	Continue treatment until radiographic findings show no further improvement. Monitor for relapse after treatment is stopped.
Progressive disseminated	Lipid AmB (3–5 mg/kg per day) for 1–2 weeks; then itraconazole (200 mg bid) for at least 12 months. Monitor renal and hepatic function.	Liposomal AmB is preferred, but the AmB lipid complex may be used because of cost. Chronic maintenance therapy may be necessary if the degree of immunosuppression cannot be reduced.
Central nervous system	Liposomal AmB (5 mg/kg per day) for 4–6 weeks; then itraconazole (200 mg bid or tid) for at least 12 months. Monitor renal and hepatic function.	A longer course of lipid AmB is recommended because of the high risk of relapse. Itraconazole should be continued until cerebrospinal fluid or CT abnormalities clear.

Abbreviation: AmB, amphotericin B.

be reduced through an approach similar to that used for patients with AIDS.

Fibrosing mediastinitis, which represents a chronic fibrotic reaction to past mediastinal histoplasmosis rather than an active infection, does not respond to antifungal therapy. While treatment is often prescribed for patients with pulmonary histoplasmosis who have not recovered within 1 month and for those with persistent mediastinal lymphadenopathy, the effectiveness of antifungal therapy in these situations is unknown.

CHAPTER 107

COCCIDIOIDOMYCOSIS

Neil M. Ampel

DEFINITION AND ETIOLOGY

Coccidioidomycosis, commonly known as Valley Fever, is caused by dimorphic soil-dwelling fungi of the genus *Coccidioides*. Genetic analysis has demonstrated the existence of two species, *C. immitis* and *C. posadasii*. These species are indistinguishable with regard to the clinical disease they cause and their appearance on routine laboratory media. Thus, the organisms will be referred to simply as *Coccidioides* for the remainder of this chapter.

EPIDEMIOLOGY

Coccidioidomycosis is confined to the Western Hemisphere between the latitudes of 40°N and 40°S. In the United States, areas of high endemicity

include the southern portion of the San Joaquin Valley of California and the south-central region of Arizona. However, infection may be acquired in other areas of the southwestern United States, including the southern coastal counties in California, southern Nevada, southwestern Utah, southern New Mexico, and western Texas, including the Rio Grande Valley. Outside the United States, coccidioidomycosis is endemic to northern Mexico as well as to localized regions of Central America. In South America, there are endemic foci in Colombia, Venezuela, northeastern Brazil, Paraguay, Bolivia, and north-central Argentina.

The risk of infection is increased by direct exposure to soil harboring *Coccidioides*. Because of difficulty in isolating *Coccidioides* from the soil, the precise characteristics of potentially infectious soil are not known. Several outbreaks of coccidioidomycosis have been associated with soil from archaeologic excavations of Amerindian sites both within and outside of the recognized endemic region. These cases often involved alluvial soils in regions of relative aridity with moderate temperature ranges. *Coccidioides* was isolated at depths of 2–20 cm below the surface.

In endemic areas, many cases of *Coccidioides* infection occur without obvious soil or dust exposure. Climatic factors appear to increase the infection rate in these regions. In particular, periods of aridity following rainy seasons have been associated with marked increases in the number of symptomatic cases. The number of cases of symptomatic coccidioidomycosis has increased dramatically in south-central Arizona, where most of the state's population resides. The factors causing this increase have not been fully elucidated; however, an influx of older individuals without prior coccidioidal infection into the region appears to be involved. Other variables, such as climate change, construction activity, and increased awareness and reporting, may also be factors. A similar increase in the incidence of symptomatic cases has recently been observed in the southern San Joaquin Valley of California.

PATHOGENESIS, PATHOLOGY, AND IMMUNE RESPONSE

On agar media and in the soil, *Coccidioides* organisms exist as filamentous molds. Within this mycelial structure, individual filaments (*hyphae*) elongate and branch, some growing upward. Alternating cells within the hyphae degenerate, leaving barrel-shaped viable elements called *arthroconidia*. Measuring ~2 by 5 μm, arthroconidia may become airborne for extended periods. Their small size allows them to evade initial mechanical mucosal defenses and reach deep into the bronchial tree, where infection is initiated in the nonimmune host.

Once in a susceptible host, the arthroconidia enlarge, become rounded, and develop internal septations. The resulting structures, called spherules (Fig. 107-1), may attain sizes of 200 μm and are unique to *Coccidioides*. The septations encompass uninuclear elements called *endospores*. Spherules may rupture and release packets of endospores

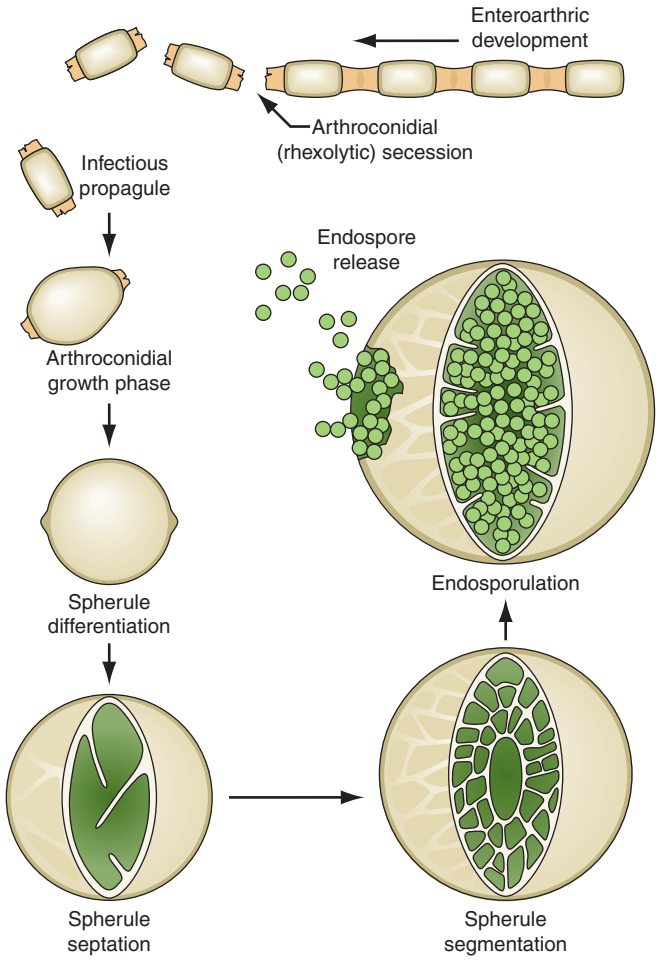


FIGURE 107-1
Life cycle of *Coccidioides*. (*From TN Kirkland, J Fierer: Emerg Infect Dis 2:192, 1996.*)

that can themselves develop into spherules, thus propagating infection locally. If returned to artificial media or the soil, the fungus reverts to its mycelial stage.

Clinical observations and data from studies of animals strongly support the critical role of a robust cellular immune response in the host's control of coccidioidomycosis. Necrotizing granulomas containing spherules are typically identified in patients with resolved pulmonary infection. In disseminated disease, granulomas are generally poorly formed or do not develop at all, and a polymorphonuclear leukocyte response occurs frequently. In patients who are asymptomatic or in whom the initial pulmonary infection resolves, delayed-type hypersensitivity to coccidioidal antigens is routinely documented.

CLINICAL AND LABORATORY MANIFESTATIONS

Coccidioidomycosis is protean in its manifestations. Among infected individuals, 60% are completely asymptomatic, and the remaining 40% have symptoms that are related principally to pulmonary infection, including fever, cough, and pleuritic chest pain. The risk of symptomatic illness

increases with age. Coccidioidomycosis is commonly misdiagnosed as community-acquired bacterial pneumonia.

There are several cutaneous manifestations of primary pulmonary coccidioidomycosis. Toxic erythema consisting of a maculopapular rash has been noted in some cases. Erythema nodosum (see Fig. 11-40)—typically over the lower extremities—or erythema multiforme (see Fig. 11-25)—usually in a necklace distribution—may occur; these manifestations are seen particularly often in women. Arthralgias and arthritis may develop. The diagnosis of primary pulmonary coccidioidomycosis is suggested by a history of night sweats or profound fatigue as well as by peripheral-blood eosinophilia and hilar or mediastinal lymphadenopathy on chest radiography. While pleuritic chest pain is common, pleural effusions occur in fewer than 10% of cases. Such effusions are invariably associated with a pulmonary infiltrate on the same side. The cellular content of these effusions is mononuclear in nature; *Coccidioides* is rarely grown from effusions.

In most patients, primary pulmonary coccidioidomycosis usually resolves without sequelae in several weeks. However, a variety of pneumonic complications may ensue. Pulmonary nodules are residua of primary pneumonia. Generally single, frequently located in the upper lobes, and ≤4 cm in diameter, nodules are often discovered on a routine chest radiograph in an asymptomatic patient. Calcification is uncommon. Coccidioidal pulmonary nodules can be difficult to distinguish radiographically from pulmonary malignancies. Like malignancies, coccidioidal nodules often enhance on positron emission tomography. However, routine CT often demonstrates multiple nodules in coccidioidomycosis. Biopsy is often required to distinguish between these two conditions.

Pulmonary cavities occur when a nodule extrudes its contents into the bronchus, resulting in a thin-walled shell. These cavities can be associated with persistent cough, hemoptysis, and pleuritic chest pain. Rarely, a cavity may rupture into the pleural space, causing pyopneumothorax. In such cases, patients present with acute dyspnea, and the chest radiograph reveals a collapsed lung with a pleural air-fluid level. Chronic or persistent pulmonary coccidioidomycosis manifests with prolonged symptoms of fever, cough, and weight loss and is radiographically associated with pulmonary scarring, fibrosis, and cavities. It occurs in fewer than 1% of patients, many of whom already have chronic lung disease of other etiologies.

In some cases, primary pneumonia presents as a diffuse reticulonodular pulmonary process (detected by plain chest radiography) in association with dyspnea and fever. Primary diffuse coccidioidal pneumonia may occur in settings of intense environmental exposure or profoundly suppressed cellular immunity (e.g., in patients with AIDS), with unrestrained fungal growth that is frequently associated with fungemia.

Clinical dissemination outside the thoracic cavity occurs in fewer than 1% of infected individuals. Dissemination is more likely to occur in male patients, particularly those of African-American or Filipino ancestry, and in persons with depressed cellular immunity, including patients with HIV infection and peripheral-blood CD4+ T cell counts of <250/μL; those receiving chronic glucocorticoid therapy; those with allogeneic solid-organ transplants; and those being treated with tumor necrosis factor α (TNF-α) antagonists. Women who acquire infection during the second or third trimester of pregnancy are also at risk for disseminated disease. Common sites for dissemination include the skin, bone, joints, soft tissues, and meninges. Dissemination may follow symptomatic or asymptomatic pulmonary infection and may involve only one site or multiple anatomic foci. When it occurs, clinical dissemination is usually evident within the first few months after primary pulmonary infection.

Meningitis, if untreated, is uniformly fatal. Patients usually present with a persistent headache, which is occasionally accompanied by lethargy and confusion. Nuchal rigidity, if present, is not severe. Examination of cerebrospinal fluid (CSF) demonstrates lymphocytic pleocytosis with profound hypoglycorrhachia and elevated protein levels. CSF eosinophilia is occasionally documented. With or without appropriate therapy, patients may develop hydrocephalus, which presents clinically as a marked decline in mental status, often with gait disturbances.

DIAGNOSIS

As mentioned earlier, coccidioidomycosis is often misdiagnosed as community-acquired bacterial pneumonia. Serology plays an important role in establishing the diagnosis of coccidioidomycosis. Several techniques are available, including the traditional tube-precipitin (TP) and complement-fixation (CF) assays, immunodiffusion (IDTP and IDCF), and enzyme immunoassay (EIA) to detect IgM and IgG antibodies. TP and IgM antibodies are found in serum soon after infection and persist for weeks. They are not useful for gauging disease progression and are not found in the CSF. The CF and IgG antibodies occur later in the course of the disease and persist longer than TP and IgM antibodies. Rising CF titers are associated with clinical progression, and the presence of CF antibody in CSF is an indicator for coccidioidal meningitis. Antibodies disappear over time in persons whose clinical illness resolves.

Because of its commercial availability, the coccidioidal EIA is frequently used as a screening tool for coccidioidal serology. There has been concern that the IgM EIA is occasionally falsely positive. In addition, while the sensitivity and specificity of the IgG EIA appear to be high when compared with those of the CF and IDCF assays, the optical density obtained in the EIA does not correlate with the serologic titer of either of the latter tests.

Coccidioides grows within 3–7 days at 37°C on a variety of artificial media, including blood agar. Therefore, it is always useful to obtain samples of sputum or other respiratory fluids and tissues for culture in suspected cases of coccidioidomycosis. The clinical laboratory should be alerted to the possibility of this diagnosis, since *Coccidioides* can pose a significant hazard to laboratory workers if it is inadvertently inhaled. The organism can also be identified directly. While treatment of samples with potassium hydroxide is rarely fruitful in establishing the diagnosis, examination of sputum or other respiratory fluids after Papanicolaou or

Gomori methenamine silver staining reveals spherules in a significant proportion of patients with pulmonary coccidioidomycosis. For fixed tissues (e.g., those obtained from biopsy specimens), spherules with surrounding inflammation can be demonstrated with hematoxylin-eosin or Gomori methenamine silver staining.

A commercially available test for coccidioidal antigenuria and antigenemia that appears to be useful for the diagnosis of coccidioidomycosis, particularly in immunosuppressed patients with severe or disseminated disease, has been developed. However, this test can yield false-positive results, especially in cases of histoplasmosis and blastomycosis. Some laboratories offer genomic detection by polymerase chain reaction.

TREATMENT Coccidioidomycosis

Currently, two main classes of antifungal agents are useful for the treatment of coccidioidomycosis (Table 107-1). While once routinely prescribed, amphotericin B in all its formulations is now reserved for only the most severe cases of dissemination and for intrathecal or intraventricular administration to patients with coccidioidal meningitis in whom triazole therapy has failed. The original formulation of amphotericin B, which is dispersed with deoxycholate, is usually administered intravenously in doses of 0.7–1.0 mg/kg either daily or three times per week. The newer lipid-based formulations—amphotericin B lipid complex (ABLC), amphotericin B colloidal dispersion (ABCD), and amphotericin B liposomal complex—appear to offer no therapeutic advantage over the deoxycholate formulation for the treatment of coccidioidomycosis, but are associated with less renal toxicity. The lipid dispersions are administered intravenously at doses of 5 mg/kg daily or three times per week.

Triazole antifungals are the principal drugs now used to treat most cases of coccidioidomycosis. Clinical trials have demonstrated the usefulness of both fluconazole and itraconazole, and evidence indicates that itraconazole may be more efficacious against bone and joint disease. Because of its demonstrated penetration into CSF, fluconazole is the azole of choice for the treatment of coccidioidal meningitis, but itraconazole is also effective. For both drugs, a minimal oral adult dosage of 400 mg/d should be used. The maximal dose of itraconazole is 200 mg three times daily, but higher doses of fluconazole may be given. Two newer triazole antifungals, posaconazole and voriconazole, are now available. However, given the relative paucity of clinical data, the high cost, and (particularly for voriconazole) the potential toxicity, these agents should be reserved for cases that remain recalcitrant when treated with fluconazole or itraconazole. High-dose triazole therapy may be teratogenic, particularly during the first trimester; thus, amphotericin B should be considered as therapy for coccidioidomycosis in pregnant women.

Most patients with focal primary pulmonary coccidioidomycosis require no therapy. Patients for whom antifungal therapy should be considered include those with underlying cellular immunodeficiencies and those with prolonged symptoms and signs of extensive disease. Specific criteria include symptoms persisting for ≥2 months, night sweats occurring for >3 weeks, weight loss of >10%, a serum CF antibody titer of >1:16, and extensive pulmonary involvement apparent on chest radiography.

Diffuse pulmonary coccidioidomycosis represents a special situation. Because most patients with this form of disease are profoundly hypoxemic and critically ill, many clinicians favor beginning therapy with amphotericin B and switching to an oral triazole once clinical improvement occurs.

The nodules that may follow primary pulmonary coccidioidomycosis do not require treatment. As noted earlier, these nodules are not easily distinguished from pulmonary malignancies by means of radiographic imaging. Close clinical follow-up and biopsy may be required to distinguish between these two entities. Most pulmonary cavities do not require therapy. Antifungal treatment should be considered in patients with persistent cough, pleuritic chest pain, and hemoptysis. Occasionally, pulmonary coccidioidal cavities become secondarily infected. This development is usually manifested by an

TABLE 107-1

CLINICAL PRESENTATIONS OF COCCIDIOIDOMYCOSIS, THEIR FREQUENCY, AND RECOMMENDED INITIAL THERAPY FOR THE IMMUNOCOMPETENT HOST

CLINICAL PRESENTATION	FREQUENCY, %	RECOMMENDED THERAPY
Asymptomatic	60	None
Primary pneumonia (focal)	40	In most cases, none[a]
Diffuse pneumonia	<1	Amphotericin B followed by prolonged oral triazole therapy
Pulmonary sequelae	5	
Nodule	—	None
Cavity	—	In most cases, none[b]
Chronic pneumonia	—	Prolonged triazole therapy
Disseminated disease	≤1	
Skin, bone, joint, soft tissue	—	Prolonged triazole therapy[c]
Meningitis	—	Life-long triazole therapy[d]

[a]Treatment is indicated for hosts with depressed cellular immunity as well as for those with prolonged symptoms and signs of increased severity, including night sweats for >3 weeks, weight loss of >10%, a complement-fixation titer of >1:16, and extensive pulmonary involvement on chest radiography.
[b]Treatment (usually with the oral triazoles fluconazole and itraconazole) is recommended for persistent symptoms.
[c]In severe cases, some clinicians would use amphotericin B as initial therapy.
[d]Intraventricular or intrathecal amphotericin B is recommended in cases of triazole failure. Hydrocephalus may occur, requiring a CSF shunt.
Note: See text for dosages and durations.

air-fluid level within the cavity. Bacterial flora or *Aspergillus* species are commonly involved, and therapy directed at these organisms should be considered. Surgery is rarely required except in cases of persistent hemoptysis or pyopneumothorax. For chronic pulmonary coccidioidomycosis, prolonged antifungal therapy—lasting for at least 1 year—is usually required, with monitoring of symptoms, radiographic changes, sputum cultures, and serologic titers.

Most cases of disseminated coccidioidomycosis require prolonged antifungal therapy. Duration of treatment is based on resolution of the signs and symptoms of the lesion in conjunction with a significant decline in serum CF antibody titer. Such therapy routinely is continued for at least several years. Relapse occurs in 15–30% of individuals once therapy is discontinued.

Coccidioidal meningitis poses a special challenge. While most patients with this form of disease respond to treatment with oral triazoles, 80% experience relapse when therapy is stopped. Thus, life-long therapy is recommended. In cases of triazole failure, intrathecal or intraventricular amphotericin B may be used. Installation requires considerable expertise and should be performed only by an experienced health care provider. Shunting of CSF in addition to appropriate antifungal therapy is required in cases of meningitis complicated by hydrocephalus. It is prudent to obtain expert consultation in all cases of coccidioidal meningitis.

PREVENTION

There are no proven methods to reduce the risk of acquiring coccidioidomycosis among residents of an endemic region. Avoidance of direct contact with uncultivated soil or with visible dust containing soil presumably reduces the risk. Targeted prophylactic antifungal therapy is appropriate in patients who have evidence of active or recent coccidioidomycosis and are about to undergo allogeneic solid-organ transplantation. Data on the use of antifungal agents for prophylaxis in other situations are scanty. However, most experts would administer triazole antifungal therapy to patients with a history of active coccidioidomycosis or a positive coccidioidal serology in whom therapy with TNF-α antagonists is being initiated.

CHAPTER 108

BLASTOMYCOSIS

Stanley W. Chapman ■ Donna C. Sullivan

Blastomycosis is a systemic pyogranulomatous infection, involving primarily the lungs, that arises after inhalation of the conidia of *Blastomyces dermatitidis*. Pulmonary blastomycosis varies from an asymptomatic infection to acute or chronic pneumonia. Hematogenous dissemination occurs frequently. Extrapulmonary disease of the skin, bones, and genitourinary system is common, but almost any organ can be infected.

ETIOLOGIC AGENT

B. dermatitidis is the asexual state of *Ajellomyces dermatitidis*. Two serotypes have been identified on the basis of the presence or absence of the A antigen. *B. dermatitidis* exhibits thermal dimorphism, growing as the mycelial phase at room temperature and as the yeast phase at 37°C. Primary isolation is most dependable for the mycelial phase incubated at 30°C. Definitive identification usually requires conversion to the yeast phase at 37°C or, more commonly, the use of nucleic acid amplification techniques (e.g., AccuProbe, Gen-Probe, San Diego, CA) that detect mycelial-phase growth. Yeast cells are usually 8–15 μm in diameter, have thick refractile cell walls, are multinucleate, and reproduce by a single, large, broad-based bud.

EPIDEMIOLOGY

Most cases of blastomycosis have been reported in North America. Endemic areas include the southeastern and south-central states bordering the Mississippi and Ohio river basins, the midwestern states and Canadian provinces bordering the Great Lakes, and a small area in New York and Canada along

the St. Lawrence River. Outside North America, blastomycosis has been reported most frequently in Africa.

Early studies of endemic cases indicated that middle-aged men with outdoor occupations were at greatest risk. Reported outbreaks, however, do not suggest a predilection according to sex, age, race, occupation, or season. *B. dermatitidis* probably grows as microfoci in the warm, moist soil of wooded areas rich in organic debris. Exposure to soil, whether related to work or recreation, appears to be the common factor associated with infection.

PATHOGENESIS

After inhalation, the conidia of *B. dermatitidis* are susceptible to phagocytosis and killing in the lungs by polymorphonuclear leukocytes, monocytes, and alveolar macrophages. This phagocytic response represents innate immunity and probably explains the high frequency of asymptomatic infections in outbreaks. Conidia that escape phagocytosis rapidly convert to the yeast phase in tissue. The greater resistance of the thick-walled yeast form to phagocytosis and killing probably contributes to infection. This yeast-phase conversion also induces the expression of the 120-kDa glycoprotein BAD-1, which is an adhesin, an essential virulence factor, and the major epitope for humoral and cellular immunity. The primary acquired host defense against *B. dermatitidis* is cellular immunity mediated by antigen-specific T cells and lymphokine-activated macrophages.

APPROACH TO THE PATIENT **Blastomycosis**

Whether acute or chronic, blastomycosis mimics many other disease processes. For example, acute pulmonary blastomycosis may present with signs and symptoms indistinguishable from those of bacterial pneumonia or influenza. Chronic pulmonary blastomycosis most commonly mimics malignancy or tuberculosis. Skin lesions are often misdiagnosed as basal cell or squamous cell carcinoma, pyoderma gangrenosum, or keratoacanthoma. Laryngeal lesions are frequently mistaken for squamous cell carcinoma. Thus, the clinician must maintain a high index of suspicion and perform a careful histologic evaluation of secretions or biopsy material from patients who live in or have visited regions endemic for blastomycosis.

CLINICAL MANIFESTATIONS

Acute pulmonary infection is usually diagnosed in association with point-source outbreaks and is accompanied by the abrupt onset of fever, chills, pleuritic chest pain, arthralgias, and myalgias. Cough is initially nonproductive but frequently becomes purulent as disease progresses. Chest radiographs usually reveal alveolar infiltrates with consolidation. Pleural effusions and hilar adenopathy are uncommon. Most patients diagnosed with pulmonary blastomycosis have chronic indolent pneumonia with signs and symptoms of fever, weight loss, productive cough, and hemoptysis. The most common radiologic findings are alveolar infiltrates with or without cavitation, mass lesions that mimic bronchogenic carcinoma, and fibronodular infiltrates. Respiratory failure (adult respiratory distress syndrome) associated with miliary disease or diffuse pulmonary infiltrates is more common among immunocompromised patients, especially those in the late stages of AIDS (Chap. 93). Mortality rates are ≥50% among these patients, and most deaths occur within the first few days of therapy.

Skin disease is the most common extrapulmonary manifestation of blastomycosis. Two types of skin lesions occur: verrucous (more common) and ulcerative. Osteomyelitis is associated with as many as one-fourth of *B. dermatitidis* infections. The vertebrae, pelvis, sacrum, skull, ribs, or long bones are most frequently involved. Patients with *B. dermatitidis* osteomyelitis often present with contiguous soft-tissue abscesses or chronic draining sinuses. In men, blastomycosis may involve the prostate and epididymis. Central nervous system (CNS) disease occurs in <5% of immunocompetent patients with blastomycosis. In AIDS patients, however, CNS disease has been reported in ~40% of cases, usually presenting as a brain abscess. Less common forms of CNS disease are cranial or spinal epidural abscess and meningitis.

DIAGNOSIS

Definitive diagnosis of blastomycosis requires growth of the organism from sputum, pus, or biopsy material. A presumptive diagnosis is made by visualization of the characteristic broad-based budding yeast in clinical specimens. Serologic diagnosis of blastomycosis is of limited usefulness because of cross-reactivity with other fungal antigens.

A *Blastomyces* antigen assay that detects antigen in urine and serum is commercially available (Mira Vista Diagnostics, Indianapolis, IN). Antigen detection in urine appears to be more sensitive than serum antigen detection. This antigen test may be useful for monitoring of patients during therapy or for early detection of relapse. Molecular identification techniques, including DNA probe hybridization, are commercially available but are currently used only to supplement traditional methods of diagnosis.

TREATMENT **Blastomycosis**

The Infectious Diseases Society of America has published guidelines for the treatment of blastomycosis. Selection of an appropriate therapeutic regimen must be based on the clinical form and severity of the disease, the immune status of the patient, and the toxicity of the antifungal agent (Table 108-1). Although spontaneous cures of acute pulmonary infection have been well documented, there are no criteria by which to distinguish patients whose disease will progress or disseminate. Thus, almost all patients with blastomycosis should be treated.

Itraconazole is the agent of choice for immunocompetent patients with mild to moderate pulmonary or non-CNS extrapulmonary disease. Therapy is continued

TABLE 108-1

TREATMENT OF BLASTOMYCOSIS

DISEASE	PRIMARY THERAPY	ALTERNATIVE THERAPY
Immunocompetent Patient/Life-Threatening Disease		
Pulmonary	Lipid AmB, 3–5 mg/kg qd, *or* Deoxycholate AmB, 0.7–1.0 mg/kg qd (total dose: 1.5–2.5 g)	Itraconazole, 200–400 mg/d (once patient's condition has stabilized)
Disseminated		
CNS	Lipid AmB, 3–5 mg/kg qd, *or* Deoxycholate AmB, 0.7–1.0 mg/kg qd (total dose: at least 2 g)	Fluconazole, 800 mg/d (if patient is intolerant to full course of AmB)
Non-CNS	Lipid AmB, 3–5 mg/kg qd, *or* Deoxycholate AmB, 0.7–1.0 mg/kg qd (total dose: 1.5–2.5 g)	Itraconazole, 200–400 mg/d (once patient's condition has stabilized)
Immunocompetent Patient/Non-Life-Threatening Disease		
Pulmonary or disseminated (non-CNS)	Itraconazole, 200–400 mg/d, *or* Lipid AmB, 3–5 mg/kg qd, *or* Deoxycholate AmB, 0.5–0.7 mg/kg qd (in patients intolerant to itraconazole or whose disease progresses despite therapy)	Fluconazole, 400–800 mg/d, *or* Ketoconazole, 400–800 mg/d
Immunocompromised Patient[a]		
All infections	Lipid AmB, 3–5 mg/kg qd, *or* Deoxycholate AmB, 0.7–1.0 mg/kg qd (total dose: 1.5–2.5 g)	Itraconazole, 200–400 mg/d (non-CNS disease, once clinically improved)

[a]Suppressive therapy with itraconazole may be considered for patients whose immunocompromised state continues. Fluconazole (800 mg/d) may be useful for patients who have CNS disease or cannot tolerate itraconazole.
Abbreviations: AmB, amphotericin B; CNS, central nervous system.

for 6–12 months. Amphotericin B is the preferred initial treatment for patients who are severely immunocompromised, who have life-threatening disease or CNS disease, or whose disease progresses during treatment with itraconazole. Although not rigorously studied, lipid formulations of amphotericin B can provide an alternative for patients who cannot tolerate amphotericin B deoxycholate. Most patients with non-CNS disease whose clinical condition improves after an initial course of amphotericin B (usually 2 weeks in duration) can be switched to itraconazole to complete 6–12 months of therapy. Fluconazole, because of its excellent penetration of the CNS, may have a role in the treatment of patients with brain abscess or meningitis after an initial course of amphotericin B.

Voriconazole has been used successfully to treat refractory blastomycosis, blastomycosis in immunosuppressed patients, and—given its good CSF penetration—CNS blastomycosis. There are no data to support the use of posaconazole in human cases of blastomycosis. The echinocandins have variable activity against *B. dermatitidis* and have no place in the treatment of blastomycosis.

PROGNOSIS

Clinical and mycologic response rates are 90–95% among compliant immunocompetent patients given itraconazole for mild to moderate pulmonary and extrapulmonary disease without CNS involvement. Bone and joint disease usually requires 12 months of therapy. The <5% of infections that relapse after an initial course of itraconazole usually respond well to a second treatment course.

CHAPTER 109

CRYPTOCOCCOSIS

Arturo Casadevall

DEFINITION AND ETIOLOGY

Cryptococcus, a genus of yeast-like fungi, is the etiologic agent of cryptococcosis. There are two species, *C. neoformans* and *C. gattii*, each of which can cause cryptococcosis in humans. *C. neoformans* occurs in two varieties known as *grubii* and *neoformans*, which correlate with serotypes A and D, respectively. *C. gattii* has not been divided into varieties but is also antigenically diverse, consisting of serotypes B and C. Most clinical microbiology laboratories do not routinely distinguish between *C. neoformans* and *C. gattii* or among varieties, but rather identify and report all isolates simply as *C. neoformans*.

EPIDEMIOLOGY

Cryptococcosis was first described in the 1890s but remained relatively rare until the mid-twentieth century, when advances in diagnosis and increases in the number of immunosuppressed individuals markedly raised its reported prevalence. The spectrum of disease caused by *Cryptococcus* species consists predominantly of meningoencephalitis and pneumonia, but skin and soft tissue infections also occur. Serologic studies have shown that, although evidence for cryptococcal *infection* is common among immunocompetent individuals, cryptococcal *disease* (cryptococcosis) is relatively rare in the absence of impaired immunity. Individuals at high risk for cryptococcosis include patients with hematologic malignancies, recipients of solid organ transplants who require ongoing immunosuppressive therapy, persons whose medical conditions necessitate glucocorticoid therapy, and patients with advanced HIV infection and CD4 + T lymphocyte counts of <200/μL.

Since the onset of the HIV pandemic in the early 1980s, the overwhelming majority of cryptococcosis cases have occurred in patients with AIDS (Chap. 93). To understand the impact of HIV infection on the epidemiology of cryptococcosis, it is instructive to note that in the early 1990s there were >1000 cases of cryptococcal meningitis each year in New York City—a figure far exceeding that for all cases of bacterial meningitis. With the advent of effective antiretroviral therapy, the incidence of AIDS-related cryptococcosis has been sharply reduced among treated individuals; however, the disease remains distressingly common in regions where antiretroviral therapy is not readily available, such as Africa and Asia, where up to one-third of patients with AIDS have cryptococcosis. The global burden of cryptococcosis was recently estimated at ~1 million cases, with >600,000 deaths annually. Thus cryptococci are major human pathogens.

Cryptococcal infection is acquired from the environment. *C. neoformans* and *C. gattii* inhabit different ecologic niches. *C. neoformans* is frequently found in soils contaminated with avian excreta and can easily be recovered from shaded and humid soils contaminated with pigeon droppings. In contrast, *C. gattii* is not found in bird feces. Instead, it inhabits a variety of arboreal species, including several types of eucalyptus tree. *C. neoformans* strains are found throughout the world; however, var. *grubii* (serotype A) strains are far more common than var. *neoformans* (serotype D) strains among both clinical and environmental isolates. The geographic distribution of *C. gattii* was thought to be largely limited to tropical regions until an outbreak of cryptococcosis caused by a new serotype B strain began in Vancouver in 1999. This outbreak has extended into the United States, and *C. gattii* is now being encountered in several states in the Pacific Northwest. In addition to the different geographic distributions of the two cryptococcal species, individual susceptibility to these species affects epidemiology. Cryptococcosis caused by the *C. neoformans* varieties occurs mostly in individuals with AIDS (Chap. 93) and other forms of impaired immunity. In contrast, *C. gattii*–related disease is not associated with specific immune deficits and often occurs in immunocompetent individuals.

PATHOGENESIS

Cryptococcal infection is acquired by inhalation of aerosolized infectious particles. The exact nature of these particles is not known; the two leading candidate forms

are small desiccated yeast cells and basidiospores. Little is known about the pathogenesis of initial infection. Serologic studies have shown that cryptococcal infection is acquired in childhood, but it is not known whether the initial infection is symptomatic. Given that cryptococcal infection is common while disease is rare, the consensus is that pulmonary defense mechanisms in immunologically intact individuals are highly effective at containing this fungus. It is not clear whether initial infection leads to a state of immunity or whether most individuals are subject throughout life to frequent and recurrent infections that resolve without clinical disease. However, evidence indicates that some human cryptococcal infections lead to a state of latency in which viable organisms are harbored for prolonged periods, possibly in granulomas. Thus the inhalation of cryptococcal cells and/or spores can be followed by either clearance or establishment of the latent state. The consequences of prolonged harboring of cryptococcal cells in the lung are not known, but evidence from animal studies indicates that the organisms' prolonged presence could alter the immunologic milieu in the lung and predispose to allergic airway disease.

Cryptococcosis usually presents clinically as chronic meningoencephalitis. The mechanisms by which the fungus undergoes extrapulmonary dissemination and enters the central nervous system (CNS) remain poorly understood. The mechanism by which cryptococcal cells cross the blood-brain barrier is a subject of intensive study. Current evidence suggests either direct fungal-cell migration across the endothelium or fungal-cell carriage inside macrophages as "Trojan horse" invaders. *Cryptococcus* species have well-defined virulence factors that include the polysaccharide capsule, the ability to make melanin, and the elaboration of enzymes (e.g., phospholipase and urease) that enhance the survival of fungal cells in tissue. Among these virulence factors, the capsule and melanin production have been most extensively studied. The cryptococcal capsule is antiphagocytic, and the capsular polysaccharide has been associated with numerous deleterious effects on host immune function. Cryptococcal infections can elicit little or no tissue inflammatory response. The immune dysfunction seen in cryptococcosis has been attributed to the release of copious amounts of capsular polysaccharide into tissues, where it probably interferes with local immune responses **(Fig. 109-1)**. In clinical practice, the capsular polysaccharide is the antigen that is measured as a diagnostic marker of cryptococcal infection.

APPROACH TO THE PATIENT

Cryptococcosis

Cryptococcosis should be included in the differential diagnosis when any patient presents with findings suggestive of chronic meningitis. Concern about cryptococcosis is heightened by a history of headache and neurologic symptoms in a patient with an underlying immunosuppressive disorder or state that is associated with an increased incidence of cryptococcosis, such as advanced HIV infection or solid organ transplantation.

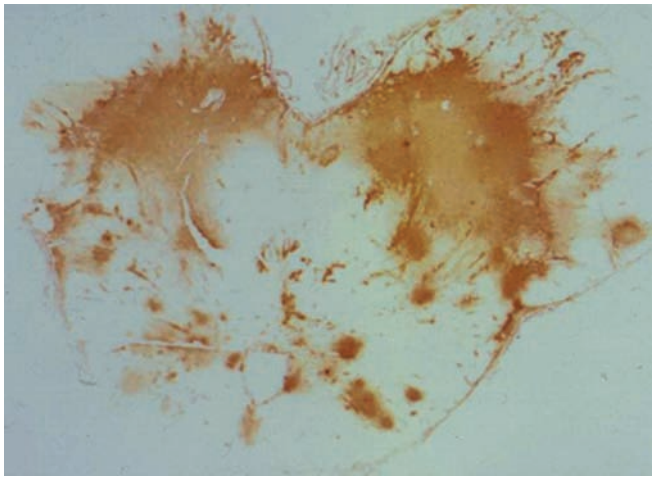


FIGURE 109-1
Cryptococcal antigen in human brain tissue, as revealed by immunohistochemical staining. Brown areas show polysaccharide deposits in the midbrain of a patient who died of cryptococcal meningitis. (*Reprinted with permission from SC Lee et al: Hum Pathol 27:839, 1996.*)

CLINICAL MANIFESTATIONS

The clinical manifestations of cryptococcosis reflect the site of fungal infection. Although infection can affect any tissue or organ, the majority of cases that come to clinical attention involve the CNS and/or the lungs. CNS involvement usually presents as signs and symptoms of chronic meningitis, such as headache, fever, lethargy, sensory deficits, memory deficits, cranial nerve paresis, vision deficits, and meningismus. Cryptococcal meningitis differs from bacterial meningitis in that many *Cryptococcus*-infected patients present with symptoms of several weeks' duration. In addition, classic characteristics of meningeal irritation, such as meningismus, may be absent in cryptococcal meningitis. Indolent cases can present as subacute dementia. Meningeal cryptococcosis can lead to sudden catastrophic vision loss.

Pulmonary cryptococcosis usually presents as cough, increased sputum production, and chest pain. Patients infected with *C. gattii* can present with granulomatous pulmonary masses known as *cryptococcomas*. Fever develops in a minority of cases. Like CNS disease, pulmonary cryptococcosis can follow an indolent course, and the majority of cases probably do not come to clinical attention. In fact, many cases are discovered incidentally during the workup of an abnormal chest radiograph obtained for other diagnostic purposes. Pulmonary cryptococcosis can be associated with antecedent diseases such as malignancy, diabetes, and tuberculosis.

Skin lesions are common in patients with disseminated cryptococcosis and can be highly variable, including papules, plaques, purpura, vesicles, tumor-like lesions, and rashes. The spectrum of cryptococcosis in HIV-infected patients is so varied and has changed so much since the advent of antiretroviral therapy that a distinction between HIV-related and HIV-unrelated cryptococcosis is no longer pertinent. In patients with AIDS and solid organ transplant recipients, the lesions

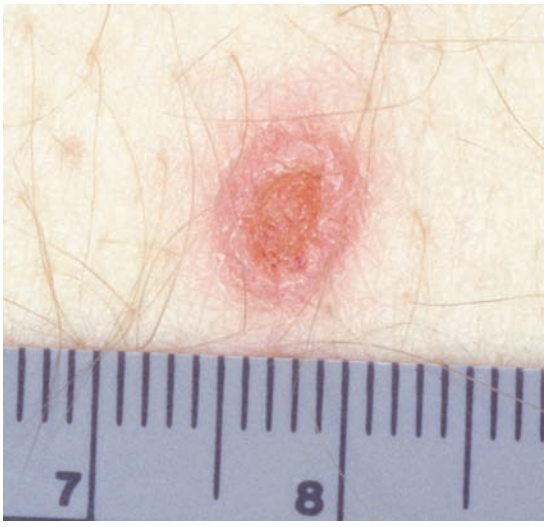


FIGURE 109-2
Disseminated fungal infection. A liver transplant recipient developed six cutaneous lesions similar to the one shown. Biopsy and serum antigen testing demonstrated *Cryptococcus*. Important features of the lesion include a benign-appearing fleshy papule with central umbilication resembling molluscum contagiosum. (*Photo courtesy of Dr. Lindsey Baden; with permission.*)

of cutaneous cryptococcosis often resemble those of molluscum contagiosum (Fig. 109-2; Chap. 88).

DIAGNOSIS

A diagnosis of cryptococcosis requires the demonstration of yeast cells in normally sterile tissues. Visualization of the capsule of fungal cells in cerebrospinal fluid (CSF) mixed with india ink is a useful rapid diagnostic technique. Cryptococcal cells in india ink have a distinctive appearance because their capsules exclude ink particles. However, the CSF india ink examination may yield negative results in patients with a low fungal burden. This examination should be performed by a trained individual, since leukocytes and fat globules can sometimes be mistaken for fungal cells. Cultures of CSF and blood that are positive for cryptococcal cells are diagnostic for cryptococcosis. In cryptococcal meningitis, CSF examination usually reveals evidence of chronic meningitis with mononuclear cell pleocytosis and increased protein levels. A particularly useful test is cryptococcal antigen (CRAg) detection in CSF and blood. The assay is based on serologic detection of cryptococcal polysaccharide and is both sensitive and specific. A positive cryptococcal antigen test provides strong presumptive evidence for cryptococcosis; however, because the result is often negative in pulmonary cryptococcosis, the test is less useful in the diagnosis of pulmonary disease.

TREATMENT Cryptococcosis

Both the site of infection and the immune status of the host must be considered in the selection of therapy for cryptococcosis. The disease has two general patterns of manifestation: (1) pulmonary cryptococcosis, with no evidence of extrapulmonary dissemination; and (2) extrapulmonary (systemic) cryptococcosis, with or without meningoencephalitis. Pulmonary cryptococcosis in an immunocompetent host sometimes resolves without therapy. However, given the propensity of *Cryptococcus* species to disseminate from the lung, the inability to gauge the host's immune status precisely, and the availability of low-toxicity therapy in the form of fluconazole, the current recommendation is for pulmonary cryptococcosis in an immunocompetent individual to be treated with fluconazole (200–400 mg/d for 3–6 months). Extrapulmonary cryptococcosis without CNS involvement in an immunocompetent host can be treated with the same regimen, although amphotericin B (AmB; 0.5–1 mg/kg daily for 4–6 weeks) may be required for more severe cases. In general, extrapulmonary cryptococcosis without CNS involvement requires less intensive therapy—with the caveat that morbidity and death in cryptococcosis are associated with meningeal involvement. Thus the decision to categorize cryptococcosis as "extrapulmonary without CNS involvement" should be made only after careful evaluation of the CSF reveals no evidence of cryptococcal infection. For CNS involvement in a host without AIDS or obvious immune impairment, most authorities recommend initial therapy with AmB (0.5–1 mg/kg daily) during an induction phase, which is followed by prolonged therapy with fluconazole (400 mg/d) during a consolidation phase. For cryptococcal meningoencephalitis without a concomitant immunosuppressive condition, the recommended regimen is AmB (0.5–1 mg/kg) plus flucytosine (100 mg/kg) daily for 6–10 weeks. Alternatively, patients can be treated with AmB (0.5–1 mg/kg) plus flucytosine (100 mg/kg) daily for 2 weeks and then with fluconazole (400 mg/d) for at least 10 weeks. Patients with immunosuppression are treated with the same initial regimens except that consolidation therapy with fluconazole is given for a prolonged period to prevent relapse.

Cryptococcosis in patients with HIV infection always requires aggressive therapy and is considered incurable unless immune function improves. Consequently, therapy for cryptococcosis in the setting of AIDS has two phases: induction therapy (intended to reduce the fungal burden and alleviate symptoms) and lifelong maintenance therapy (to prevent a symptomatic clinical relapse). Pulmonary and extrapulmonary cryptococcosis without evidence of CNS involvement can be treated with fluconazole (200–400 mg/d). In patients who have more extensive disease, flucytosine (100 mg/kg per day) may be added to the fluconazole regimen for 10 weeks, with lifelong fluconazole maintenance therapy thereafter. For HIV-infected patients with evidence of CNS involvement, most authorities recommend induction therapy with AmB. An acceptable regimen is AmB (0.7–1 mg/kg) plus flucytosine (100 mg/kg) daily for 2 weeks followed by fluconazole (400 mg/d) for at least 10 weeks and then by lifelong maintenance therapy with fluconazole (200 mg/d). Fluconazole (400–800 mg/d) plus flucytosine (100 mg/kg per day) for 6–10 weeks followed by fluconazole (200 mg/d) as maintenance therapy can

be used as an alternative. Newer triazoles like voriconazole are highly active against cryptococcal strains, but clinical experience with these agents in the treatment of cryptococcosis is limited. Lipid formulations of AmB can be substituted for AmB deoxycholate in patients with renal impairment. Neither caspofungin nor micafungin is effective against *Cryptococcus* species; consequently, neither drug has a role in the treatment of cryptococcosis. Cryptococcal meningoencephalitis is often associated with increased intracranial pressure, which is believed to be responsible for damage to the brain and cranial nerves. Appropriate management of CNS cryptococcosis requires careful attention to the management of intracranial pressure, including the reduction of pressure by repeated therapeutic lumbar puncture and the placement of shunts.

In HIV-infected patients with previously treated cryptococcosis who are receiving fluconazole maintenance therapy, it may be possible to discontinue antifungal drug treatment if antiretroviral therapy results in immunologic improvement. However, certain recipients of maintenance therapy who have a history of successfully treated cryptococcosis can develop a troublesome immune reconstitution syndrome when antiretroviral therapy produces a rebound in immunologic function.

PROGNOSIS AND COMPLICATIONS

Even with antifungal therapy, cryptococcosis is associated with high rates of morbidity and death. For the majority of patients with cryptococcosis, the most important prognostic factor is the extent and the duration of the underlying immunologic deficits that predisposed them to develop the disease. Therefore, cryptococcosis is often curable with antifungal therapy in individuals with no apparent immunologic dysfunction, but, in patients with severe immunosuppression (e.g., those with AIDS), the best that can be hoped for is that antifungal therapy will induce remission, which can then be maintained with lifelong suppressive therapy. Before the advent of antiretroviral therapy, the median overall survival period for AIDS patients with cryptococcosis was <1 year. Cryptococcosis in patients with underlying neoplastic disease has a particularly poor prognosis. For CNS cryptococcosis, poor prognostic markers are a positive CSF assay for yeast cells by initial india ink examination (evidence of a heavy fungal burden), high CSF pressure, low CSF glucose levels, low CSF pleocytosis (<2/μL), recovery of yeast cells from extraneural sites, absence of antibody to capsular polysaccharide, a CSF or serum cryptococcal antigen level of ≥1:32, and concomitant glucocorticoid therapy or hematologic malignancy. A response to treatment does not guarantee cure since relapse of cryptococcosis is common even among patients with relatively intact immune systems. Complications of CNS cryptococcosis include cranial nerve deficits, vision loss, and cognitive impairment.

PREVENTION

No vaccine is available for cryptococcosis. In patients at high risk (e.g., those with advanced HIV infection and CD4+ T lymphocyte counts of <200/μL), primary prophylaxis with fluconazole (200 mg/d) is effective in reducing the prevalence of disease. Since antiretroviral therapy raises the CD4+ T lymphocyte count, it constitutes an immunologic form of prophylaxis. However, cryptococcosis in the setting of immune reconstitution has been reported in patients with HIV infection and recipients of solid organ transplants.

CHAPTER 110

CANDIDIASIS

John E. Edwards, Jr.

The genus *Candida* encompasses more than 150 species, only a few of which cause disease in humans. With rare exceptions, the human pathogens are *C. albicans, C. guilliermondii, C. krusei, C. parapsilosis, C. tropicalis, C. kefyr, C. lusitaniae, C. dubliniensis,* and *C. glabrata*. Ubiquitous in nature, these organisms are found on inanimate objects, in foods, and on animals and are normal commensals of humans. They inhabit the

gastrointestinal tract (including the mouth and oropharynx), the female genital tract, and the skin. Although cases of candidiasis have been described since antiquity in debilitated patients, the advent of *Candida* species as common human pathogens dates to the introduction of modern therapeutic approaches that suppress normal host defense mechanisms. Of these relatively recent advances, the most important is the use of antibacterial agents that alter the normal human microbial flora and allow nonbacterial species to become more prevalent in the commensal flora. With the introduction of antifungal agents, the causes of *Candida* infections shifted from an almost complete dominance of *C. albicans* to the common involvement of *C. glabrata* and the other species listed earlier. The non-*albicans* species now account for approximately half of all cases of candidemia and hematogenously disseminated candidiasis. Recognition of this change is clinically important, since the various species differ in susceptibility to the newer antifungal agents. In developed countries, where medical therapeutics are commonly used, *Candida* species are now among the most common nosocomial pathogens. In the United States, these species are the fourth most common isolates from the blood of hospitalized patients.

Candida is a small, thin-walled, ovoid yeast that measures 4–6 μm in diameter and reproduces by budding. Organisms of this genus occur in three forms in tissue: blastospores, pseudohyphae, and hyphae. *Candida* grows readily on simple medium; lysis centrifugation enhances its recovery from blood. Species are identified by biochemical testing (currently with automated devices) or on special agar.

PATHOGENESIS

In the most serious form of *Candida* infection, the organisms disseminate hematogenously and form microabscesses and small macroabscesses in major organs. Although the exact mechanism is not known, *Candida* probably enters the bloodstream from mucosal surfaces after growing to large numbers as a consequence of bacterial suppression by antibacterial drugs; alternatively, in some instances, the organism may enter from the skin. A change from the blastospore stage to the pseudohyphal and hyphal stages is generally considered integral to the organism's penetration into tissue. However, *C. glabrata* can cause extensive infection even though it does not transform into pseudohyphae or hyphae. Numerous reviews of cases of hematogenously disseminated candidiasis have identified the following predisposing factors or conditions: antibacterial agents, indwelling intravascular catheters, hyperalimentation fluids, indwelling urinary catheters, parenteral glucocorticoids, respirators, neutropenia, abdominal and thoracic surgery, cytotoxic chemotherapy, and immunosuppressive agents for organ transplantation. Patients with severe burns, low-birthweight neonates, and persons using illicit IV drugs are also susceptible. HIV-infected patients with low CD4+ T cell counts and patients with diabetes are susceptible to mucocutaneous infection, which may eventually develop into the disseminated form when other predisposing factors are encountered. Women who receive antibacterial agents may develop vaginal candidiasis.

Innate immunity is the most important defense mechanism against hematogenously disseminated candidiasis, and the neutrophil is the most important component of this defense. Although many immunocompetent individuals have antibodies to *Candida*, the role of these antibodies in defense against the organism is not clear.

CLINICAL MANIFESTATIONS

Mucocutaneous candidiasis

Thrush is characterized by white, adherent, painless, discrete or confluent patches in the mouth, tongue, or esophagus, occasionally with fissuring at the corners of the mouth. This form of *Candida* disease may also occur at points of contact with dentures. Organisms are identifiable in gram-stained scrapings from lesions. The occurrence of thrush in a young, otherwise healthy-appearing person should prompt an investigation for underlying HIV infection. More commonly, thrush is seen as a nonspecific manifestation of severe debilitating illness. Vulvovaginal candidiasis is accompanied by pruritus, pain, and vaginal discharge that is usually thin but may contain whitish "curds" in severe cases.

Other *Candida* skin infections include *paronychia*, a painful swelling at the nail-skin interface; *onychomycosis*, a fungal nail infection rarely caused by this genus; *intertrigo*, an erythematous irritation with redness and pustules in the skin folds; *balanitis*, an erythematous-pustular infection of the glans penis; *erosio interdigitalis blastomycetica*, an infection between the digits of the hands or toes; *folliculitis*, with pustules developing most frequently in the area of the beard; *perianal candidiasis*, a pruritic, erythematous, pustular infection surrounding the anus; and *diaper rash*, a common erythematous-pustular perineal infection in infants. *Generalized disseminated cutaneous candidiasis*, another form of infection that occurs primarily in infants, is characterized by widespread eruptions over the trunk, thorax, and extremities. The diagnostic macronodular lesions of hematogenously disseminated candidiasis **(Fig. 110-1)** indicate a high probability of dissemination to multiple organs as well as the skin. While the lesions are seen predominantly in immunocompromised patients treated with cytotoxic drugs, they may also develop in patients without neutropenia.

Chronic mucocutaneous candidiasis is a heterogeneous infection of the hair, nails, skin, and mucous membranes that persists despite intermittent therapy. The onset of disease usually comes in infancy or within the first two decades of life but in rare cases can come in later life. The condition may be mild and limited to a specific area of the skin or nails, or it may take a severely disfiguring form (*Candida* granuloma) characterized by exophytic outgrowths on the skin. The condition is usually associated with specific immunologic dysfunction; most frequently reported is a failure of T lymphocytes to proliferate or to stimulate cytokines in response to stimulation by *Candida* antigens in vitro.

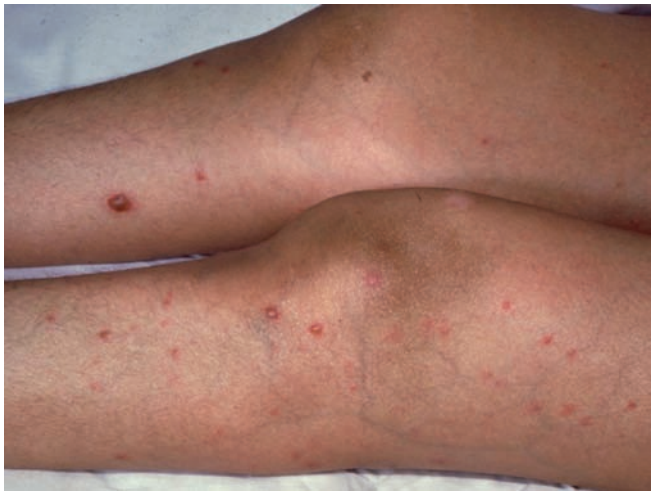


FIGURE 110-1
Macronodular skin lesions associated with hematogenously disseminated candidiasis. *Candida* organisms are usually but not always visible on histopathologic examination. The fungi grow when a portion of the biopsied specimen is cultured. Therefore, for optimal identification, both histopathology and culture should be performed. (*Image courtesy of Dr. Noah Craft and the Victor Newcomer collection at UCLA, archived by Logical Images, Inc.; with permission.*)

Approximately half of patients have associated endocrine abnormalities that together are designated the autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy (APECED) syndrome. This syndrome is due to mutations in the autoimmune regulator (AIRE) gene and is most prevalent among Finns, Iranian Jews, Sardinians, northern Italians, and Swedes. Conditions that usually follow the onset of the disease include hypoparathyroidism, adrenal insufficiency, autoimmune thyroiditis, Graves' disease, chronic active hepatitis, alopecia, juvenile-onset pernicious anemia, malabsorption, and primary hypogonadism. In addition, dental enamel dysplasia, vitiligo, pitted nail dystrophy, and calcification of the tympanic membranes may occur. Patients with chronic mucocutaneous candidiasis rarely develop hematogenously disseminated candidiasis, probably because their neutrophil function remains intact.

Deeply invasive candidiasis

Deeply invasive *Candida* infections may or may not be due to hematogenous seeding. Deep esophageal infection may result from penetration by organisms from superficial esophageal erosions; joint or deep wound infection from contiguous spread of organisms from the skin; kidney infection from catheter-initiated spread of organisms through the urinary tract; infection of intraabdominal organs and the peritoneum from perforation of the gastrointestinal tract; and gallbladder infection from retrograde migration of organisms from the gastrointestinal tract into the biliary drainage system.

However, far more commonly, deeply invasive candidiasis is a result of hematogenous seeding of various organs as a complication of candidemia. Once the organism gains access to the intravascular compartment (either from the gastrointestinal tract or, less often, from the skin through the site of an indwelling intravascular catheter), it may spread hematogenously to a variety of deep organs. The brain, chorioretina **(Fig. 110-2)**, heart, and kidneys are most commonly infected and the liver and spleen less commonly so (most often in neutropenic patients). In fact, nearly any organ can become involved, including the endocrine glands, pancreas, heart valves (native or prosthetic), skeletal muscle, joints (native or prosthetic), bone, and meninges. *Candida* organisms may also spread hematogenously to the skin and cause classic macronodular lesions (Fig. 110-1). Frequently, painful muscular involvement is also evident beneath the area of affected skin. Chorioretinal involvement and skin involvement are highly significant, since both findings are associated with a very high probability of abscess formation in multiple deep organs as a result of generalized hematogenous seeding. Ocular involvement (Fig. 110-2) may require specific treatment (e.g., partial vitrectomy or intraocular injection of antifungal agents) to prevent permanent blindness. An ocular examination is indicated for all patients with candidemia, whether or not they have ocular manifestations.

DIAGNOSIS

The diagnosis of *Candida* infection is established by visualization of pseudohyphae or hyphae on wet mount (saline and 10% KOH), tissue Gram's stain, periodic acid–Schiff stain, or methenamine silver stain in the presence of inflammation. Absence of organisms on hematoxylin-eosin staining does not reliably exclude *Candida* infection. The most challenging aspect of

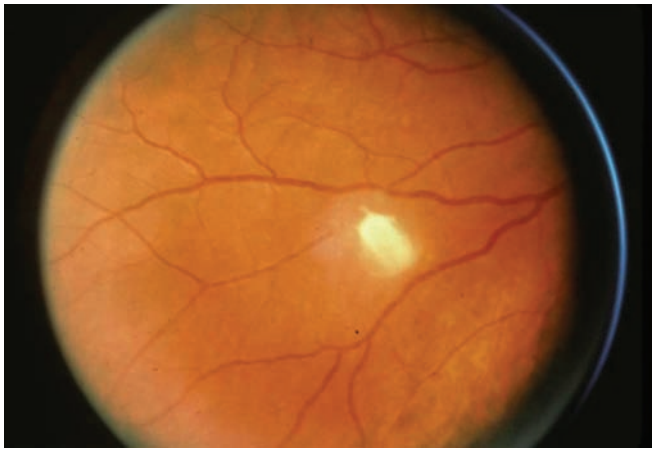


FIGURE 110-2
Hematogenous *Candida* endophthalmitis. A classic off-white lesion projecting from the chorioretina into the vitreous causes the surrounding haze. The lesion is composed primarily of inflammatory cells rather than organisms. Lesions of this type may progress to cause extensive vitreal inflammation and eventual loss of the eye. Partial vitrectomy, combined with IV and possibly intravitreal antifungal therapy, may be helpful in controlling the lesions. (*Image courtesy of Dr. Gary Holland; with permission.*)

diagnosis is determining which patients with *Candida* isolates have hematogenously disseminated candidiasis. For instance, recovery of *Candida* from sputum, urine, or peritoneal catheters may indicate mere colonization rather than deep-seated infection, and *Candida* isolation from the blood of patients with indwelling intravascular catheters may reflect inconsequential seeding of the blood from or growth of the organisms on the catheter. Despite extensive research into both antigen and antibody detection systems, there is currently no widely available and validated diagnostic test to distinguish patients with inconsequential seeding of the blood from those whose positive blood cultures represent hematogenous dissemination to multiple organs. Many studies are under way to establish the utility of the β-glucan test; at present, its greatest utility is its negative predictive value (~90%). Meanwhile, the presence of ocular or macronodular skin lesions is highly suggestive of widespread infection of multiple deep organs.

TREATMENT *Candida* Infections

MUCOCUTANEOUS *CANDIDA* INFECTION The treatment of mucocutaneous candidiasis is summarized in Table 110-1.

CANDIDEMIA AND SUSPECTED HEMATOGENOUSLY DISSEMINATED CANDIDIASIS All patients with candidemia are now treated with a systemic antifungal agent. A certain percentage of patients, including many of those who have candidemia associated with an indwelling intravascular catheter, probably have "benign" candidemia rather than deep-organ seeding. However, because there is no reliable way to distinguish benign candidemia from deep-organ infection, and because antifungal drugs less toxic than amphotericin B are available, it has become the standard of practice to treat all patients with candidemia, whether or not there is clinical evidence of deep-organ involvement. In addition, if an indwelling intravascular catheter may be involved, it is best to remove or replace the device whenever possible.

TABLE 110-1

TREATMENT OF MUCOCUTANEOUS CANDIDAL INFECTIONS

DISEASE	PREFERRED TREATMENT	ALTERNATIVES
Cutaneous	Topical azole	Topical nystatin
Vulvovaginal	Oral fluconazole (150 mg) or azole cream or suppository	Nystatin suppository
Thrush	Clotrimazole troches	Nystatin
Esophageal	Fluconazole tablets (100–200 mg/d) or itraconazole solution (200 mg/d)	Caspofungin, micafungin, or amphotericin B

The drugs used for the treatment of candidemia and suspected disseminated candidiasis are listed in Table 110-2. Various lipid formulations of amphotericin B, three echinocandins, and the azoles fluconazole and voriconazole are used; no agent within a given class has been clearly identified as superior to the others. Most institutions choose an agent from each class on the basis of their own specific microbial epidemiology, strategies to minimize toxicities, and cost considerations. Unless azole resistance is considered likely, fluconazole is the agent of choice for the treatment of candidemia and suspected disseminated candidiasis in nonneutropenic, hemodynamically stable patients. Initial treatment in the context of likely azole resistance depends, as mentioned earlier, on the epidemiology of the individual hospital. For example, certain hospitals have a high rate of recovery of *C. glabrata*, while others do not. At institutions where non-*albicans Candida* spp. are frequently recovered, therapy with an echinocandin is typically started while the results of sensitivity testing are awaited. For hemodynamically unstable or neutropenic patients, initial treatment with broader-spectrum agents is desirable; these drugs include polyenes, echinocandins, or later-generation azoles such as voriconazole. Once the clinical response has been assessed and the pathogen specifically identified, the regimen can be altered accordingly. At present, the vast majority of *C. albicans* isolates are sensitive to fluconazole. Isolates of *C. glabrata* and *C. krusei* are less sensitive to fluconazole and more sensitive to polyenes and echinocandins. *C. parapsilosis* is less sensitive to echinocandins in vitro, although the clinical significance of this finding is not known.

Some generalizations about the management of specific *Candida* infections are possible. Recovery of *Candida* from sputum is almost never indicative of underlying pulmonary candidiasis and does not by itself warrant antifungal treatment. Similarly, *Candida* in the urine of a patient with an indwelling bladder catheter may represent colonization only rather than bladder or kidney infection; however, the threshold for systemic treatment is lower in severely ill patients in this category since it is not possible to distinguish colonization from lower or upper urinary tract infection. If the isolate is *C. albicans*, most clinicians use oral fluconazole rather than a bladder washout with amphotericin, which was more commonly used in the past. Caspofungin has been used with success; although they are poorly excreted into the urine, echinocandins may be an option, especially for non-albicans isolates. The doses and duration are the same as for disseminated candidiasis. The significance of the recovery of *Candida* from abdominal drains in postoperative patients is also unclear, but again the threshold for treatment is generally low because most of the affected patients have been subjected to factors predisposing to disseminated candidiasis.

Removal of the infected valve and long-term antifungal therapy constitute appropriate treatment for *Candida* endocarditis. Although definitive studies are not available, patients usually are treated for weeks with a systemic antifungal agent (Table 110-2) and then given

TABLE 110-2

AGENTS FOR THE TREATMENT OF DISSEMINATED CANDIDIASIS

AGENT	ROUTE OF ADMINISTRATION	DOSE[a]	COMMENT
Amphotericin B deoxycholate	IV only	0.5–1.0 mg/kg daily	Being replaced by lipid formulations
Amphotericin B lipid formulations			Not FDA approved as primary therapy, but used commonly because less toxic than amphotericin B deoxycholate
Liposomal (AmBiSome, Abelcet)	IV only	3.0–5.0 mg/kg daily	
Lipid complex (ABLC)	IV only	3.0–5.0 mg/kg daily	
Colloidal dispersion (ABCD)	IV only	3.0–5.0 mg/kg daily	Associated with frequent infusion reactions
Azoles			
Fluconazole	IV and oral	400 mg/d	Most commonly used
Voriconazole	IV and oral	400 mg/d	Multiple drug interactions; approved for candidemia in nonneutropenic patients
Echinocandins			Broad spectrum against *Candida* species; approved for disseminated candidiasis
Caspofungin	IV only	50 mg/d	
Anidulafungin	IV only	100 mg/d	
Micafungin	IV only	100 mg/d	

[a]See Pappas et al. (2009) for loading doses and adjustments in renal failure. The recommended duration of therapy is 2 weeks beyond the last positive blood cultures and resolution of signs and symptoms of infection.

Note: Although ketoconazole is approved for the treatment of disseminated candidiasis, it has been replaced by the newer agents listed in this table. Posaconazole has been approved for prophylaxis in neutropenic patients and for oropharyngeal candidiasis. FDA, U.S. Food and Drug Administration.

chronic suppressive therapy for months or years (and sometimes indefinitely) with an oral azole (usually fluconazole at 400–800 mg/d).

Hematogenous *Candida* endophthalmitis is a special problem requiring ophthalmologic consultation. In lesions that are expanding or that threaten the macula, an IV polyene combined with flucytosine (25 mg/kg four times daily) has been the regimen of choice. However, as more data on the azoles and echinocandins become available, new strategies involving these agents are developing. Of paramount importance is the decision to perform a partial vitrectomy. This procedure debulks the infection and can preserve sight, which may otherwise be lost as a result of vitreal scarring. All patients with candidemia should undergo ophthalmologic examination because of the relatively high frequency of this ocular complication. Not only can this examination detect a developing eye lesion early in its course; in addition, identification of a lesion signifies a probability of ~90% of deep-organ abscesses and may prompt prolongation of therapy for candidemia beyond the recommended 2 weeks after the last positive blood culture.

Although the basis for the consensus is a very small data set, the recommended treatment for *Candida* meningitis is a polyene (Table 110-2) plus flucytosine (25 mg/kg four times daily). Successful treatment of *Candida*-infected prosthetic material (e.g., an artificial joint) nearly always requires removal of the infected material followed by long-term administration of an antifungal agent selected on the basis of the isolate's sensitivity and the logistics of administration.

PROPHYLAXIS

The use of antifungal agents to prevent *Candida* infections has been controversial, but some general principles have emerged. Most centers administer prophylactic fluconazole (400 mg/d) to recipients of allogeneic stem cell transplants. High-risk liver transplant recipients are also given fluconazole prophylaxis in most centers. The use of prophylaxis for neutropenic patients has varied considerably from center to center; most centers that elect to give prophylaxis to this population use either fluconazole (200–400 mg/d) or a lipid formulation of amphotericin B (AmBiSome, 1–2 mg/d). Caspofungin (50 mg/d) has also been recommended. Some centers have used itraconazole suspension (200 mg/d). Posaconazole (200 mg three times daily) has also been approved by the FDA for prophylaxis in neutropenic patients.

Prophylaxis is sometimes given to surgical patients at very high risk. The widespread use of prophylaxis for nearly all patients in general surgical or medical intensive care units is not—and should not be—a common practice for three reasons: (1) the incidence of disseminated candidiasis is relatively low, (2) the cost-benefit ratio is suboptimal, and (3) increased resistance with widespread prophylaxis is a valid concern.

Prophylaxis for oropharyngeal or esophageal candidiasis in HIV-infected patients is not recommended unless there are frequent recurrences.

CHAPTER 111

ASPERGILLOSIS

David W. Denning

Aspergillosis is the collective term used to describe all disease entities caused by any one of ~35 pathogenic and allergenic species of *Aspergillus*. Only those species that grow at 37°C can cause invasive infection, although some species without this capability can cause allergic syndromes. *A. fumigatus* is responsible for most cases of invasive aspergillosis, almost all cases of chronic aspergillosis, and most allergic syndromes. *A. flavus* is more prevalent in some hospitals and causes a higher proportion of cases of sinus and cutaneous infections and keratitis than *A. fumigatus*. *A. niger* can cause invasive infection but more commonly colonizes the respiratory tract and causes external otitis. *A. terreus* causes only invasive disease, usually with a poor prognosis. *A. nidulans* occasionally causes invasive infection, primarily in patients with chronic granulomatous disease.

EPIDEMIOLOGY AND ECOLOGY

Aspergillus has a worldwide distribution, most commonly growing in decomposing plant materials (i.e., compost) and in bedding. This hyaline (nonpigmented), septate, branching mold produces vast numbers of conidia (spores) on stalks above the surface of mycelial growth. Aspergilli are found in indoor and outdoor air, on surfaces, and in water from surface reservoirs. Daily exposures vary from a few to many millions of conidia; the latter high numbers of conidia are encountered in hay barns and other very dusty environments. The required size of the infecting inoculum is uncertain; however, only intense exposures (e.g., during construction work, handling of moldy bark or hay, or composting) are sufficient to cause disease in healthy immunocompetent individuals. Allergic syndromes may be exacerbated by continuous antigenic exposure arising from sinus or airway colonization or from nail infection. High-efficiency particulate air (HEPA) filtration is often protective against infection; thus HEPA filters should be installed and monitored for efficiency in operating rooms and in hospital environments that house high-risk patients.

The incubation period of invasive aspergillosis after exposure is highly variable, extending in documented cases from 2 to 90 days. Thus community-acquired acquisition of an infecting strain frequently manifests as invasive infection during hospitalization, although nosocomial acquisition is also common. Outbreaks usually are directly related to a contaminated air source in the hospital.

RISK FACTORS AND PATHOGENESIS

The primary risk factors for invasive aspergillosis are profound neutropenia and glucocorticoid use; risk increases with longer duration of these conditions. Higher doses of glucocorticoids increase the risk of both acquisition of invasive aspergillosis and death from the infection. Neutrophil and/or phagocyte dysfunction is also an important risk factor, as evidenced by aspergillosis in chronic granulomatous disease, advanced HIV infection, and relapsed leukemia. An increasing incidence of invasive aspergillosis in medical intensive care units suggests that, in patients who are not immunocompromised, temporary abrogation of protective responses as a result of glucocorticoid use or a general anti-inflammatory state is a significant risk factor. Many patients have some evidence of prior pulmonary disease—typically, a history of pneumonia or chronic obstructive pulmonary disease. Glucocorticoid use does not appear to predispose to invasive *Aspergillus* sinusitis but probably increases the risk of dissemination after pulmonary infection. Anti–tumor necrosis factor therapy also carries an increased risk of infection.

Patients with chronic pulmonary aspergillosis have a wide spectrum of underlying pulmonary disease, often tuberculosis or sarcoidosis. Patients are immunocompetent except for some cytokine regulation defects, most of which are consistent with an inability to mount an inflammatory immune (T_H1-like) response. Glucocorticoids accelerate disease progression.

Allergic bronchopulmonary aspergillosis (ABPA) is associated with polymorphisms of interleukin (IL) 4Ra, IL-10, and SPA2 genes (and others) and

with heterozygosity of the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. These associations suggest a strong genetic basis for the development of a T_H2-like and "allergic" response to *A. fumigatus*.

CD4+CD25+ T (T_{reg}) cells also appear to be pivotal in determining the disease phenotype. Remarkably, high-dose glucocorticoid treatment for exacerbations of ABPA almost never leads to invasive aspergillosis.

CLINICAL FEATURES AND APPROACH TO THE PATIENT

(Table 111-1)

Invasive pulmonary aspergillosis

Both the frequency of invasive disease and the pace of its progression increase with greater degrees of immunocompromise (Fig. 111-1). Invasive aspergillosis is arbitrarily divided into acute and subacute forms that have courses of ≤1 month and 1–3 months, respectively. More than 80% of cases of invasive aspergillosis involve the lungs. The most common clinical features are no symptoms at all, fever, cough (sometimes productive), nondescript chest discomfort, trivial hemoptysis, and shortness of breath. Although the fever often responds to glucocorticoids, the disease progresses. The keys to early diagnosis in at-risk patients are a high index of suspicion, screening for circulating antigen (in leukemia), and urgent CT of the thorax.

Invasive sinusitis

The sinuses are involved in 5–10% of cases of invasive aspergillosis, especially in patients with leukemia and recipients of hematopoietic stem cell transplants. In addition to fever, the most common features are nasal or facial discomfort, blocked nose, and nasal discharge (sometimes bloody). Endoscopic examination of the nose reveals pale, dusky or necrotic-looking tissue in any location. CT or MRI of the sinuses is essential but does not distinguish invasive *Aspergillus* sinusitis from preexisting allergic or bacterial sinusitis early in the disease process.

Tracheobronchitis

Occasionally, only the airways are infected by *Aspergillus*. The resulting manifestations range from acute or chronic bronchitis to ulcerative or pseudomembranous tracheobronchitis. These entities are particularly common among lung transplant recipients. Obstruction with mucous plugs occurs in normal individuals, persons with ABPA, and immunocompromised patients.

Disseminated aspergillosis

In the most severely immunocompromised patients, *Aspergillus* disseminates from the lungs to multiple organs—most often to the brain but also to the skin, thyroid, bone, kidney, liver, gastrointestinal tract, eye (endophthalmitis), and heart valve. Aside from cutaneous lesions, the most common features are gradual clinical

TABLE 111-1

MAJOR MANIFESTATIONS OF ASPERGILLOSIS

	TYPE OF DISEASE			
ORGAN	INVASIVE (ACUTE AND SUBACUTE)	CHRONIC	SAPROPHYTIC	ALLERGIC
Lung	Angioinvasive in neutropenia, non-angioinvasive, granulomatous	Chronic cavitary, chronic fibrosing	Aspergilloma (single), airway colonization	Allergic bronchopulmonary, severe asthma with fungal sensitization, extrinsic allergic alveolitis
Sinus	Acute invasive	Chronic invasive, chronic granulomatous	Maxillary fungal ball	Allergic fungal sinusitis, eosinophilic fungal rhinosinusitis
Brain	Abscess, hemorrhagic infarction, meningitis	Granulomatous, meningitis	None	None
Skin	Acute disseminated, locally invasive (trauma, burns, IV access)	External otitis, onychomycosis	None	None
Heart	Endocarditis (native or prosthetic), pericarditis	None	None	None
Eye	Keratitis, endophthalmitis	None	None	None described

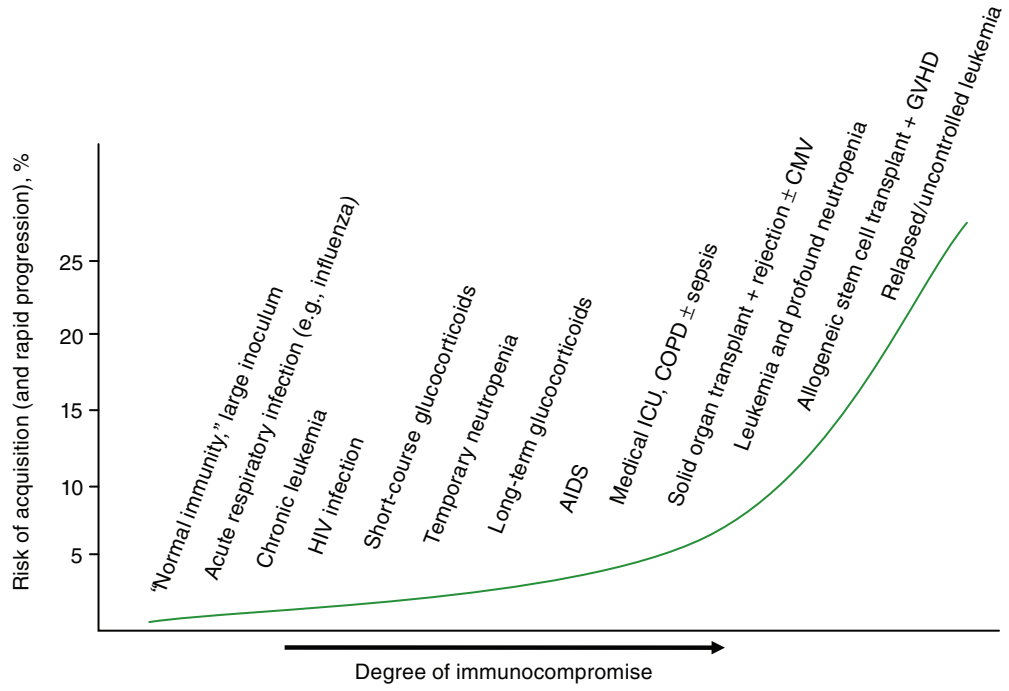


FIGURE 111-1
Invasive aspergillosis: conditions placing patients at elevated risk of acquisition and relatively rapid progression. CMV, cytomegalovirus; COPD, chronic obstructive pulmonary disease; GVHD, graft-versus-host disease; ICU, intensive care unit.

deterioration over 1–3 days, with low-grade fever and features of mild sepsis, and nonspecific abnormalities in laboratory tests. In most cases, at least one localization becomes apparent before death occurs. Blood cultures are almost always negative.

Cerebral aspergillosis

Hematogenous dissemination to the brain is a devastating complication of invasive aspergillosis. Single or multiple lesions may develop. In acute disease, hemorrhagic infarction is most typical, and cerebral abscess is common. Rarer manifestations include meningitis, mycotic aneurysm, and cerebral granuloma. Local spread from cranial sinuses also occurs. Postoperative infection occurs rarely and is exacerbated by glucocorticoids, which are often given after neurosurgery. The presentation can be either acute or subacute, with mood changes, focal signs, seizures, and decline in mental status. Cerebral granuloma can mimic a primary or secondary tumor. MRI is the most useful immediate investigation; unenhanced CT of the brain is usually nonspecific, and contrast is often contraindicated because of poor renal function.

Endocarditis

Most cases of *Aspergillus* endocarditis are prosthetic valve infections resulting from contamination during surgery. Native valve disease is reported, especially as a feature of disseminated infection and in persons using illicit IV drugs. Culture-negative endocarditis with large vegetations is the most common presentation, but embolectomy reveals the diagnosis in a few cases.

Cutaneous aspergillosis

Dissemination of *Aspergillus* occasionally results in cutaneous features, usually an erythematous or purplish nontender area that progresses to a necrotic eschar. Direct invasion of the skin occurs in neutropenic patients at the site of IV catheter insertion and in burn patients. Rapidly progressive local aspergillosis of the skin and underlying tissue may follow trauma, and wounds may become infected with *Aspergillus* (especially *A. flavus*) after surgery.

Chronic pulmonary aspergillosis

The hallmark of chronic cavitary pulmonary aspergillosis (also called semi-invasive aspergillosis, chronic necrotizing aspergillosis, or complex aspergilloma) **(Fig. 111-2)** is one or more pulmonary cavities expanding over a period of months or years in association with pulmonary symptoms and systemic manifestations such as fatigue and weight loss. (Pulmonary aspergillosis developing over <3 months is better classified as subacute invasive aspergillosis.) Often mistaken initially for tuberculosis, almost all cases occur in patients with prior pulmonary disease (e.g., tuberculosis, atypical mycobacterial infection, sarcoidosis, rheumatoid lung disease, pneumothorax, bullae) or lung surgery. The onset is insidious, and systemic features may be more prominent than pulmonary symptoms. Cavities may have a fluid level or a well-formed fungal ball, but pericavitary

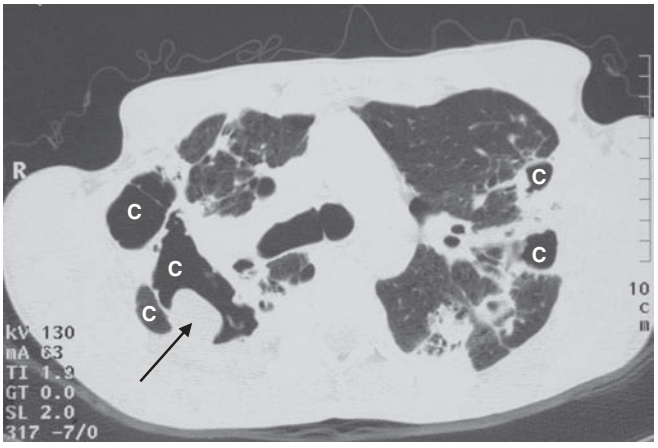


FIGURE 111-2
CT scan image of the chest in a patient with longstanding bilateral chronic cavitary pulmonary aspergillosis. He had a prior history of several bilateral pneumothoraces and required bilateral pleurodesis (1990). CT scan then demonstrated multiple bullae, and sputum cultures grew *A. fumigatus*. The patient had initially weakly and later strongly positive serum *Aspergillus* antibody tests (precipitins). This scan (2003) shows a mixture of thick- and thin-walled cavities in both lungs (each marked with *C*), with a probable fungal ball (*black arrow*) protruding into the large cavity on the patient's right side (*R*). There is also considerable pleural thickening bilaterally.

infiltrates and multiple cavities—with or without pleural thickening—are typical. IgG antibodies (usually precipitating) to *Aspergillus* are almost always detectable in blood. Some patients have concurrent infections—even without a fungal ball—with atypical mycobacteria and/or other bacterial pathogens. If untreated, chronic pulmonary aspergillosis typically progresses (sometimes relatively rapidly) to unilateral or upper-lobe fibrosis. This end-stage entity is termed *chronic fibrosing pulmonary aspergillosis*.

Aspergilloma

Aspergilloma (fungal ball) occurs in up to 20% of residual pulmonary cavities ≥2.5 cm in diameter. Signs and symptoms associated with single (simple) aspergillomas are minor, including a cough (sometimes productive), hemoptysis, wheezing, and mild fatigue. More significant signs and symptoms are associated with chronic cavitary pulmonary aspergillosis and should be treated as such. The vast majority of fungal balls are caused by *A. fumigatus*, but *A. niger* has been implicated, particularly in diabetic patients; aspergillomas due to *A. niger* can lead to oxalosis with renal dysfunction. The most significant complication of aspergilloma is life-threatening hemoptysis, which may be the presenting manifestation. Some fungal balls resolve spontaneously, but the cavity may still be infected.

Chronic sinusitis

Three entities are subsumed under this broad label: sinus aspergilloma, chronic invasive sinusitis, and chronic granulomatous sinusitis. *Sinus aspergilloma* is limited to the maxillary sinus and consists of a chronic saprophytic entity in which the sinus cavity is filled with a fungal ball. This form of disease is associated with prior upper-jaw root canal work and chronic (bacterial) sinusitis. About 90% of CT scans show focal hyperattenuation related to concretions; on MRI scans, the T2-weighted signal is decreased, whereas it is increased in bacterial sinusitis. Removal of the fungal ball is curative. No tissue invasion is demonstrable histologically or radiologically.

In contrast, *chronic invasive sinusitis* is a slowly destructive process that most commonly affects the ethmoid and sphenoid sinuses but can involve any sinus. Patients are usually but not always immunocompromised to some degree (e.g., as a result of diabetes or HIV infection). Imaging of the cranial sinuses shows opacification of one or more sinuses, local bone destruction, and invasion of local structures. The differential diagnosis is wide, as numerous other fungi may cause a similar disease and sphenoid sinusitis is often caused by bacteria. Apart from a history of chronic nasal discharge and blockage, loss of the sense of smell, and persistent headache, the usual presenting features are related to local involvement of critical structures. The orbital apex syndrome (blindness and proptosis) is characteristic. Facial swelling, cavernous sinus thrombosis, carotid artery occlusion, pituitary fossa, and brain and skull base invasion have been described.

Chronic granulomatous sinusitis due to *Aspergillus* is most commonly seen in the Middle East and India and is often caused by *A. flavus*. It typically presents late, with facial swelling and unilateral proptosis. The prominent granulomatous reaction histologically distinguishes this disease from chronic invasive sinusitis, in which tissue necrosis with a low-grade mixed-cell infiltrate is typical.

Allergic bronchopulmonary aspergillosis

In almost all cases, ABPA represents a hypersensitivity reaction to *A. fumigatus*; rare cases are due to other aspergilli and other fungi. ABPA occurs in ~1% of patients with asthma and in up to 15% of adults with cystic fibrosis; occasional cases are reported in patients with neither of the latter. Episodes of bronchial obstruction with mucous plugs leading to coughing fits, "pneumonia," consolidation, and breathlessness are typical. Many patients report coughing up thick sputum casts, usually brown or clear. Eosinophilia commonly develops before systemic glucocorticoids are given. The cardinal diagnostic tests include an elevated serum level of total IgE (usually >1000 IU/mL), a positive skin-prick test to *A. fumigatus* extract, or detection of *Aspergillus*-specific IgE and IgG (precipitating) antibodies. Central bronchiectasis is characteristic, but patients may present before it becomes apparent.

Severe asthma with fungal sensitization

Many adults with severe asthma do not fulfill the criteria for ABPA and yet are allergic to fungi. Although *A. fumigatus* is a common allergen, numerous other fungi (e.g., *Cladosporium* and *Alternaria* spp.) are implicated by skin-prick testing and/or specific IgE radioallergosorbent testing.

Allergic sinusitis

Like the lungs, the sinuses manifest allergic responses to *Aspergillus* and other fungi. The affected patients present with chronic (i.e., perennial) sinusitis typically requiring multiple courses of antibiotics that are of only limited benefit. Many of these patients have nasal polyps, and all have congested nasal mucosae and sinuses full of mucoid material. The histologic hallmark of allergic fungal sinusitis is local eosinophilia and Charcot-Leyden crystals (the breakdown products of eosinophils). Removal of abnormal mucus and polyps, with local and occasionally systemic administration of glucocorticoids, usually leads to resolution. Persistent or recurrent signs and symptoms may require more extensive surgery (ethmoidectomy) and possibly local antifungal therapy.

Superficial aspergillosis

Aspergillus can cause keratitis and otitis externa. The former may be difficult to diagnose early enough to save the patient's sight. Treatment requires local surgical debridement as well as both systemic and topical antifungal therapy. Otitis externa usually resolves with debridement and local application of antifungal agents.

DIAGNOSIS

Several techniques are required to establish the diagnosis of any form of aspergillosis with confidence. Patients with acute invasive aspergillosis have a relatively heavy load of fungus in the affected organ; thus culture, molecular diagnosis, antigen detection, and histopathology usually confirm the diagnosis. However, the pace of progression leaves only a narrow window for making the diagnosis without losing the patient, and some invasive procedures are not possible because of coagulopathy, respiratory compromise, and other factors. Currently, ~40% of cases of invasive aspergillosis are missed clinically and are diagnosed only at autopsy. Histologic examination of affected tissue reveals either infarction, with invasion of blood vessels by many fungal hyphae, or acute necrosis, with limited inflammation and hyphae. *Aspergillus* hyphae are hyaline, narrow, and septate, with branching at 45°; no yeast forms are present in infected tissue. Hyphae can be seen in cytology or microscopy preparations, which therefore provide a rapid means of presumptive diagnosis.

Culture is important in confirming the diagnosis, given that multiple other (rarer) fungi can mimic *Aspergillus* spp. histologically. Bacterial agar is less sensitive than fungal media for culture. Thus, if physicians do not request fungal culture, the diagnosis may be missed. Culture may be falsely positive (e.g., in patients whose airways are colonized by *Aspergillus*) or falsely negative. Only 10–30% of patients with invasive aspergillosis have a positive culture at any time. Molecular diagnostic techniques are faster and much more sensitive than culture of respiratory samples and blood.

The *Aspergillus* antigen test relies on detection of galactomannan release from *Aspergillus* spp. during growth. Antigen testing in high-risk patients is best done prospectively, as positive results usually precede clinical or radiologic features by several days. Antigen testing may be falsely positive in patients receiving certain β-lactam/β-lactamase inhibitor antibiotic combinations. Antigen and molecular testing on bronchoalveolar lavage fluid and cerebrospinal fluid are useful if performed before antifungal therapy has been given for more than a few days. The sensitivity of antigen detection is reduced by antifungal prophylaxis.

Definitive confirmation of the diagnosis requires (1) a positive culture of a sample taken directly from an ordinarily sterile site (e.g., a brain abscess) or (2) positive results of both histologic testing and culture of a sample taken from an affected organ (e.g., sinuses or skin). Most diagnoses of invasive aspergillosis are inferred from fewer data, including the presence of the *halo* sign on a high-resolution thoracic CT scan, in which a localized ground-glass appearance representing hemorrhagic infarction surrounds a nodule. While a halo sign may be produced by other fungi, *Aspergillus* spp. are by far the most common cause. Halo signs are present for ~7 days early in the course of infection in neutropenic patients and are a good prognostic feature. Thick CT sections can give the false appearance of a halo sign, as can other technical factors. Other common radiologic features of invasive pulmonary aspergillosis include pleural-based infarction or cavitation.

For chronic invasive aspergillosis, *Aspergillus* antibody testing is invaluable although relatively imprecise. Titers fall with successful therapy. Cultures are infrequently positive. Some patients with chronic pulmonary aspergillosis also have elevated titers of total serum IgE and *Aspergillus*-specific IgE.

ABPA and severe asthma with fungal sensitization are diagnosed serologically with elevated total and specific serum IgE levels and with skin-prick tests. Allergic *Aspergillus* sinusitis is usually diagnosed histologically, although precipitating antibodies in blood may also be useful.

TREATMENT Aspergillosis

Antifungal drugs active against *Aspergillus* include voriconazole, itraconazole, posaconazole, caspofungin, micafungin, and amphotericin B. Initial IV administration is preferred for acute invasive aspergillosis and oral administration for all other disease that requires antifungal therapy. Current recommendations are shown in Table 111-2. Voriconazole is the preferred agent for invasive aspergillosis; caspofungin, posaconazole, and lipid-associated amphotericin B are second-line agents. Amphotericin B is not active against *A. terreus* or *A. nidulans*. An infectious disease consultation is advised for patients with invasive disease, given the complexity of management. It is not clear whether combination therapy for acute invasive aspergillosis is beneficial, but it is widely used for very ill patients and for those with a poor prognosis. Commonly used combinations include an azole with either caspofungin or micafungin. The interactions of voriconazole and itraconazole with many drugs must be considered before these agents are prescribed. In addition, the plasma concentrations of both drugs vary substantially from one patient to another, and many authorities recommend monitoring to ensure that drug concentrations are adequate but not excessive. The duration of therapy for invasive aspergillosis varies from ~3 months to several years, depending on the patient's immune status and response to therapy. Relapse occurs if the response is suboptimal and immune reconstitution is not complete.

Itraconazole is the preferred oral agent for chronic and allergic forms of aspergillosis. Voriconazole or posaconazole can be substituted when failure, emergence of resistance, or adverse events occur. An itraconazole dose of

TABLE 111-2

TREATMENT OF ASPERGILLOSIS

INDICATION	PRIMARY TREATMENT	EVIDENCE LEVEL[a]	PRECAUTIONS	SECONDARY TREATMENT	COMMENTS
Invasive[b]	Voriconazole	AI	Drug interactions (especially with rifampin), renal failure (IV only)	AmB, caspofungin, posaconazole, micafungin	As primary therapy, voriconazole carries 20% more responses than AmB. If azole prophylaxis fails, it is unclear whether a class change is required for therapy.
Prophylaxis	Posaconazole, itraconazole solution	AI	Diarrhea and vomiting with itraconazole, vincristine interaction	Micafungin, aerosolized AmB	Some centers monitor plasma levels of itraconazole and posaconazole.
ABPA	Itraconazole	AI	Some glucocorticoid interactions, including with inhaled formulations	Voriconazole, posaconazole	Long-term therapy is helpful in most patients. No evidence indicates whether therapy modifies progression to bronchiectasis/fibrosis.
Single aspergilloma	Surgery	BII	Multicavity disease: poor outcome of surgery; medical therapy preferable	Itraconazole, voriconazole, intracavity AmB	Single large cavities with an aspergilloma are best resected.
Chronic pulmonary[b]	Itraconazole, voriconazole	BII	Poor absorption of capsules with proton pump inhibitors or H_2 blockers	Posaconazole, IV AmB, IV micafungin	Resistance may emerge during treatment, especially if plasma drug levels are subtherapeutic.

[a]Evidence levels are those used in treatment guidelines (Walsh TJ et al: Treatment of aspergillosis: Clinical practice guidelines of the Infectious Diseases Society of America [IDSA]. Clin Infect Dis 46:327, 2008).

[b]An infectious disease consultation is appropriate for these patients.

Note: The oral dose is usually 200 mg bid for voriconazole and itraconazole and 400 mg bid for posaconazole. The IV dose of voriconazole is 6 mg/kg twice at 12-h intervals (loading doses) followed by 4 mg/kg q12h. Plasma monitoring is helpful in optimizing the dosage. Caspofungin is given as a single loading dose of 70 mg and then at 50 mg/d; some authorities use 70 mg/d for patients weighing >80 kg, and lower doses are required with hepatic dysfunction. Micafungin is given as 50 mg/d for prophylaxis and as at least 150 mg/d for treatment; this drug is not yet approved by the U.S. Food and Drug Administration (FDA) for this indication. AmB deoxycholate is given at a daily dose of 1 mg/kg if tolerated. Several strategies are available for minimizing renal dysfunction. Lipid-associated AmB is given at 3 mg/kg (AmBisome) or 5 mg/kg (Abelcet). Different regimens are available for aerosolized AmB, but none is FDA approved. Other considerations that may alter dose selection or route include age; concomitant medications; renal, hepatic, or intestinal dysfunction; and drug tolerability. ABPA, allergic bronchopulmonary aspergillosis; AmB, amphotericin B.

200 mg twice daily is recommended, with monitoring of drug concentrations in the blood. Chronic cavitary pulmonary aspergillosis probably requires life-long therapy, whereas the duration of treatment for other forms of chronic and allergic aspergillosis requires case-by-case evaluation.

Resistance to one or more azoles, although uncommon, may develop during long-term treatment, and a positive culture during antifungal therapy is an indication for susceptibility testing. Glucocorticoids should be used with caution in chronic cavitary pulmonary aspergillosis.

Surgical treatment is important in several forms of aspergillosis, including maxillary fungal ball and single aspergillomas, in which surgery is curative; invasive aspergillosis involving bone, heart valve, sinuses, and proximal areas of the lung; brain abscess; keratitis; and endophthalmitis. In allergic fungal sinusitis, removal of abnormal mucus and polyps, with local and occasionally systemic glucocorticoid treatment, usually leads to resolution. Persistent or recurrent signs and symptoms may require more extensive surgery (ethmoidectomy) and possibly local antifungal therapy. Surgery is problematic in chronic pulmonary aspergillosis, usually resulting in serious complications. Bronchial artery embolization is preferred for problematic hemoptysis.

PROPHYLAXIS

In situations in which moderate or high risk is predicted (e.g., after induction therapy for acute myeloid leukemia), the need for antifungal prophylaxis for superficial and systemic candidiasis and for invasive aspergillosis is generally accepted. Fluconazole is commonly used in these situations but has no activity against *Aspergillus* spp. Itraconazole capsules are ineffective, and itraconazole solution offers only modest efficacy. Posaconazole solution is more effective. Some data support the use of IV micafungin. No prophylactic regimen is completely successful.

OUTCOME

Invasive aspergillosis is curable if immune reconstitution occurs, whereas allergic and chronic forms are not. The mortality rate for invasive aspergillosis is ~50% if the infection is treated but is 100% if the diagnosis is missed. Cerebral aspergillosis, *Aspergillus* endocarditis, and bilateral extensive invasive pulmonary aspergillosis have very poor outcomes, as does invasive infection in persons with late-stage AIDS or relapsed uncontrolled leukemia and in recipients of allogeneic hematopoietic stem cell transplants.

CHAPTER 112

MUCORMYCOSIS

Brad Spellberg ■ Ashraf S. Ibrahim

Mucormycosis represents a group of life-threatening infections caused by fungi of the order Mucorales. Recent reclassification has abolished the class Zygomycetes and placed the order Mucorales in the subphylum Mucoromycotina. Therefore, infection caused by the Mucorales is most accurately referred to as mucormycosis, although the term *zygomycosis* may still be used by some sources. Mucormycosis is highly invasive and relentlessly progressive, resulting in higher rates of morbidity and mortality (>40%) than many other infections. A high index of suspicion is critical for diagnosis, and early initiation of therapy—often before confirmation of the diagnosis—is necessary to optimize outcomes.

ETIOLOGY

Fungi of the order Mucorales belong to six families, all of which can cause mucormycosis. Among the Mucorales, *Rhizopus oryzae* (in the family Mucoraceae) is by far the most common cause of infection. Less frequently isolated species of the Mucoraceae family that cause a similar spectrum of infections include *Rhizopus microsporus*, *Rhizomucor pusillus*, *Mycocladus corymbifer* (formerly *Absidia corymbifera*), *Apophysomyces elegans*, and *Mucor* species (which, despite its name, is a rare cause of mucormycosis). Increasing numbers of cases of mucormycosis due to infection with *Cunninghamella* species (family Cunninghamellaceae) have also been reported. Rare case reports have

demonstrated the ability of fungi in the remaining families of the Mucorales to cause mucormycosis.

PATHOGENESIS

The Mucorales are ubiquitous environmental fungi to which humans are constantly exposed. These fungi cause infection primarily in patients with diabetes or defects in phagocytic function (e.g., associated with neutropenia or glucocorticoid treatment). Patients with elevated levels of free iron, which supports fungal growth in serum and tissues, are likewise at increased risk for mucormycosis. In iron-overloaded patients with end-stage renal failure, treatment with deferoxamine predisposes to the development of rapidly fatal disseminated mucormycosis; this agent, an iron chelator for the human host, serves as a fungal siderophore, directly delivering iron to the Mucorales. Furthermore, patients with diabetic ketoacidosis (DKA) are at high risk of developing rhinocerebral mucormycosis. The acidosis causes dissociation of iron from sequestering proteins in serum, resulting in enhanced fungal survival and virulence. It is likely that hyperglycemia during DKA also contributes to the risk of mucormycosis through its association with poorly characterized defects in phagocytic function.

EPIDEMIOLOGY

Mucormycosis typically occurs in patients with diabetes mellitus, solid organ or hematopoietic stem cell transplantation (HSCT), prolonged neutropenia, or malignancy. In patients undergoing HSCT, mucormycosis develops at least as commonly during nonneutropenic as during neutropenic periods, probably because of glucocorticoid treatment of graft-versus-host disease. Mucormycosis can occur as isolated cutaneous or subcutaneous infection in immunologically normal individuals after traumatic implantation of soil or vegetation, after maceration of the skin by a moist surface, or in nosocomial settings via direct access through intravenous catheters or subcutaneous injections.

Patients receiving antifungal prophylaxis with either itraconazole or voriconazole may be at increased risk of mucormycosis. These patients typically present with disseminated mucormycosis, the most lethal form of disease. Breakthrough mucormycosis has been described repeatedly in patients receiving posaconazole or echinocandin prophylaxis.

CLINICAL MANIFESTATIONS

Mucormycosis can be divided into at least six clinical categories based on clinical presentation and the involvement of a particular anatomic site: rhinocerebral, pulmonary, cutaneous, gastrointestinal, disseminated, and miscellaneous. These categories of invasive mucormycosis tend to affect patients with specific defects in host defense. For example, patients with DKA typically develop the rhinocerebral form and much more rarely develop pulmonary or disseminated disease. In contrast, pulmonary mucormycosis occurs most commonly in leukemic patients who are receiving chemotherapy and in patients undergoing HSCT.

Rhinocerebral mucormycosis continues to be the most common form of the disease. Most cases occur in patients with diabetes, although such cases (probably due to glucocorticoid use) are increasingly being described in the transplantation setting. The initial symptoms of rhinocerebral mucormycosis are nonspecific and include eye or facial pain and facial numbness followed by the onset of conjunctival suffusion, blurry vision, and soft tissue swelling. Fever may be absent in up to half of cases, while white blood cell counts are typically elevated as long as the patient has functioning bone marrow. If untreated, infection usually spreads from the ethmoid sinus to the orbit, resulting in compromise of extraocular muscle function and proptosis, typically with chemosis. Onset of signs and symptoms in the contralateral eye, with resulting bilateral proptosis, chemosis, vision loss, and ophthalmoplegia, is ominous and suggests the development of cavernous sinus thrombosis.

Upon visual inspection, infected tissue may appear to be normal during the earliest stages of fungal spread and then progresses through an erythematous phase, with or without edema, before the onset of a violaceous appearance and finally the development of a black necrotic eschar. Infection can sometimes extend from the sinuses into the mouth and produce painful necrotic ulcerations of the hard palate, but this is a late finding that suggests extensive, well-established infection.

Pulmonary mucormycosis is the second most common manifestation. Symptoms include dyspnea, cough, and chest pain; fever is often but not invariably present. Angioinvasion results in necrosis, cavitation, and/or hemoptysis. Lobar consolidation, isolated masses, nodular disease, cavities, or wedge-shaped infarcts may be seen on chest radiography. High-resolution chest CT is the best method for determining the extent of pulmonary mucormycosis and may demonstrate evidence of infection before it is seen on the chest x-ray. In the setting of cancer, where mucormycosis may be difficult to differentiate from aspergillosis, the presence of ≥10 pulmonary nodules, pleural effusion, or concomitant sinusitis makes mucormycosis more likely. It is critical to distinguish mucormycosis from aspergillosis as rapidly as possible, as treatments for these infections differ. Indeed, voriconazole—the first-line treatment for aspergillosis—exacerbates mucormycosis in mouse and fly models.

Cutaneous mucormycosis may result from external implantation of the fungus or conversely from hematogenous dissemination. External implantation–related infection has been described in the setting of soil exposure from trauma (e.g., in a motor vehicle accident), penetrating injury with plant material (e.g., a thorn), injections of medications (e.g., insulin), catheter insertion, contaminated surgical dressings, and use of tape to secure endotracheal tubes. Cutaneous disease can be highly invasive, penetrating into muscle, fascia, and even bone. In mucormycosis, necrotizing fasciitis carries a mortality rate approaching 80%. Necrotic cutaneous lesions in the setting of hematogenous dissemination are also associated with an extremely high mortality rate. However, with prompt, aggressive

surgical debridement, isolated cutaneous mucormycosis has a favorable prognosis and a low mortality rate.

Gastrointestinal mucormycosis has occurred in premature neonates in association with disseminated disease and necrotizing enterocolitis; more rarely, it has been described in adults with neutropenia or other immunocompromising conditions. In addition, gastrointestinal disease has been reported as a nosocomial process following administration of medications mixed with contaminated wooden applicator sticks. Nonspecific abdominal pain and distention associated with nausea and vomiting are the most common symptoms. Gastrointestinal bleeding is common, and fungating masses may be seen in the stomach at endoscopy. The disease may progress to visceral perforation, with extremely high mortality rates.

Hematogenously disseminated mucormycosis may originate from any primary site of infection. The most common site of dissemination is the brain, but metastatic lesions may also be found in any other organ. The mortality rate associated with dissemination to the brain approaches 100%. Even without central nervous system (CNS) involvement, mortality rates for disseminated mucormycosis exceed 90%. Miscellaneous forms of mucormycosis may affect any body site, including bones, mediastinum, trachea, kidneys, and (in association with dialysis) peritoneum.

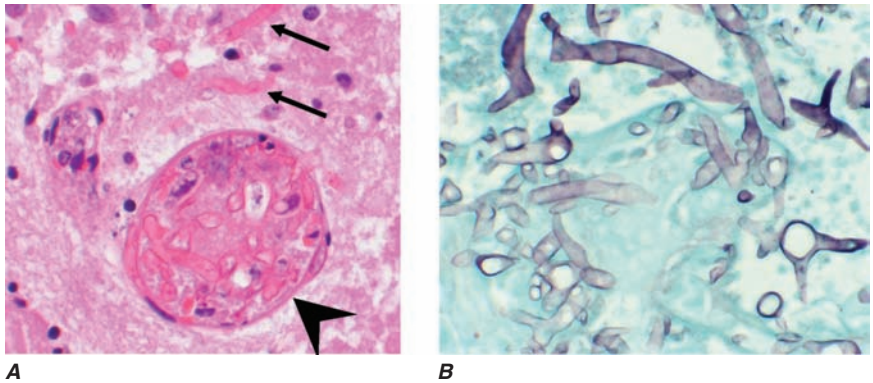
DIAGNOSIS

A high index of suspicion is required for diagnosis of mucormycosis. Unfortunately, autopsy series have shown that up to half of cases are diagnosed only post-mortem. Because the Mucorales are environmental isolates, definitive diagnosis requires a positive culture from a sterile site (e.g., a needle aspirate, a tissue biopsy specimen, or pleural fluid) or histopathologic evidence of invasive mucormycosis. A probable diagnosis of mucormycosis can be established by culture from a nonsterile site (e.g., sputum or bronchoalveolar lavage) when a patient has appropriate risk factors as well as clinical and radiographic evidence of disease. However, given the urgency of administering therapy early, the patient should be treated while confirmation of the diagnosis is awaited.

Biopsy with histopathologic examination remains the most sensitive and specific modality for definitive diagnosis **(Fig. 112-1)**. Biopsy reveals characteristic wide (≥6- to 30-μm), thick-walled, ribbon-like, aseptate hyphal elements that branch at right angles. Other fungi, including *Aspergillus*, *Fusarium*, and *Scedosporium* species, have septae, are thinner, and branch at acute angles. Because artificial septae may result from folding of tissue during processing (which may also alter the appearance of the angle of branching), the width and the ribbon-like form of the fungus are the most reliable features distinguishing mucormycosis. The Mucorales are visualized most effectively with periodic acid–Schiff or methenamine silver stain or, if the organism burden is high, with hematoxylin and eosin. While histopathology can identify the Mucorales, species can be identified only by culture. PCR is being investigated as a diagnostic tool for mucormycosis but is not yet approved by the U.S. Food and Drug Administration (FDA) for this purpose and is not generally available.

Unfortunately, cultures are positive in fewer than half of cases of mucormycosis. Nevertheless, the Mucorales are not fastidious organisms and tend to grow quickly (i.e., within 48 h) on culture media. The likely explanation for the low sensitivity of culture is that the Mucorales form long filamentous structures that are killed by tissue homogenization—the standard method for preparing tissue cultures in the clinical microbiology laboratory. Thus the laboratory should be advised when a diagnosis of mucormycosis is suspected, and the tissue should be cut into sections and placed in the center of culture dishes rather than homogenized.

Imaging techniques often yield subtle findings that underestimate the extent of disease. For example, the most common finding on CT or MRI of the head or sinuses of a patient with rhino-orbital mucormycosis is sinusitis that is indistinguishable from bacterial sinusitis. It is also common to detect no abnormalities in sinus bones despite clinical evidence of progressive disease. MRI is more sensitive (~80%) for detecting orbital and CNS disease than is



A ***B***

FIGURE 112-1
Histopathology sections of *Rhizopus oryzae* in infected brain. ***A.*** Broad, ribbon-like, nonseptate hyphae in the parenchyma (*arrows*) and a thrombosed blood vessel with extensive intravascular hyphae (*arrowhead*) (hematoxylin and eosin). ***B***. Extensive, broad, ribbon-like hyphae invading the parenchyma (Gomori methenamine silver).

CT. High-risk patients should always undergo endoscopy and/or surgical exploration, with biopsy of the areas of suspected infection. If mucormycosis is suspected, initial empirical therapy with a polyene antifungal agent should be initiated while the diagnosis is being confirmed.

DIFFERENTIAL DIAGNOSIS

Other mold infections, including aspergillosis, scedosporiosis, fusariosis, and infections caused by the dematiaceous fungi (brown-pigmented soil organisms), can cause clinical syndromes identical to mucormycosis. Histopathologic examination usually allows distinction of the Mucorales from these other organisms, and a positive culture permits definitive species identification. It is important to distinguish the Mucorales from these other fungi, as the preferred antifungal treatments differ (i.e., polyenes for the Mucorales vs. expanded-spectrum triazoles for most septate molds). The entomophthoromycoses caused by *Basidiobolus* and *Conidiobolus* (fungi formerly grouped with the Mucorales in the class Zygomycetes) can also cause identical clinical syndromes. These fungi may appear similar to the Mucorales on histopathology and can be reliably distinguished from the latter only by culture.

In a patient with sinusitis and proptosis, orbital cellulitis and cavernous sinus thrombosis caused by bacterial pathogens (most commonly *Staphylococcus aureus*, but also streptococcal and gram-negative species) must be excluded. *Klebsiella rhinoscleromatis* is a rare cause of an indolent facial rhinoscleroma syndrome that may appear similar to mucormycosis. Finally, the Tolosa-Hunt syndrome causes painful ophthalmoplegia, ptosis, headache, and cavernous sinus inflammation; biopsies and clinical follow-up may be needed to distinguish the Tolosa-Hunt syndrome from mucormycosis by the lack of progression of the former entity.

TREATMENT Mucormycosis

GENERAL PRINCIPLES The successful treatment of mucormycosis requires four steps: (1) early diagnosis; (2) reversal of underlying predisposing risk factors, if possible; (3) surgical debridement; and (4) prompt antifungal therapy. Early diagnosis of mucormycosis is critical, since early initiation of therapy is associated with improved outcomes. It is also crucial to reverse (or prevent) underlying defects in host defense during treatment (e.g., by stopping or reducing the dosage of immunosuppressive medications or by rapidly restoring euglycemia and normal acid-base status). Finally, it is advisable to avoid administration of iron to patients with active mucormycosis, as iron exacerbates infection in animal models.

Blood vessel thrombosis and resulting tissue necrosis during mucormycosis can result in poor penetration of antifungal agents to the site of infection. Therefore, debridement of necrotic tissues may be critical for complete eradication of disease. Surgery has been found (by logistic regression and in multiple case series) to be an independent variable for favorable outcome in patients with mucormycosis. The extent and timing of surgical debridement necessary to optimize outcomes of mucormycosis have not been defined. Limited data from a retrospective study support the use of intraoperative frozen sections to delineate the margins of infected tissues, with sparing of tissues lacking evidence of infection. A multidisciplinary team, including an internist, an infectious disease specialist, and surgical specialists relevant to the sites of infection, is typically required for the management of mucormycosis.

ANTIFUNGAL THERAPY Primary antifungal therapy for mucormycosis should be based on a polyene antibiotic (Table 112-1), except perhaps for mild localized infection (e.g., isolated suprafascial cutaneous infection) in immunocompetent patients, which has been eradicated surgically. Amphotericin B (AmB) deoxycholate remains the only licensed antifungal agent for the treatment of mucormycosis. However, lipid formulations of AmB are significantly less nephrotoxic, can be administered at higher doses, and may be more efficacious than AmB deoxycholate for this purpose.

The optimal dosages for antifungal treatment of mucormycosis are not known. Starting dosages of 1 mg/kg per day for AmB deoxycholate and 5–7.5 mg/kg per day for liposomal AmB (LAmB) and amphotericin B lipid complex (ABLC) are commonly given to adults and children. Whether higher dosages provide any additional benefit is unclear. However, dose escalation of LAmB to 10 mg/kg per day for CNS mucormycosis may be considered in light of the limited penetration of polyenes into the brain. ABLC dose escalation above 7.5 mg/kg per day is not advisable given the lack of relevant data.

Echinocandin–lipid polyene combinations improved survival rates among mice with disseminated mucormycosis (including CNS disease) and were associated with significantly better outcomes than polyene monotherapy in a small retrospective study involving primarily diabetic patients with rhino-orbital-cerebral mucormycosis. Although combination therapy may be considered on the basis of these limited data sets, definitive clinical trials are needed to establish whether it offers any real advantage over monotherapy for mucormycosis.

In contrast to deferoxamine, the iron chelator deferasirox is fungicidal for clinical isolates of the Mucorales. In mice with DKA and disseminated mucormycosis, combination deferasirox-LAmB therapy resulted in synergistic improvement of survival rates. Enrollment in a double-blind, randomized, placebo-controlled, phase II safety/exploratory efficacy study of adjunctive deferasirox therapy (20 mg/kg per day for 14 days) [the Deferasirox-AmBisome Therapy for Mucormycosis (DEFEAT Mucor) Study, NCT00419770] has recently been completed; this study is likely to elucidate the potential risks and benefits of iron chelation therapy for mucormycosis.

Posaconazole is the only FDA-approved azole with in vitro activity against the Mucorales. However, pharmacokinetic/pharmacodynamic data raise concerns about the reliability of achieving adequate in vivo levels of orally administered posaconazole. Furthermore, posaconazole

TABLE 112-1

FIRST-LINE ANTIFUNGAL OPTIONS FOR THE TREATMENT OF MUCORMYCOSIS[a]

DRUG	RECOMMENDED DOSAGE	ADVANTAGES AND SUPPORTING STUDIES	DISADVANTAGES
Primary Antifungal Therapy			
AmB deoxycholate	• 1.0–1.5 mg/kg qd	• >5 decades of clinical experience • Inexpensive • Only licensed agent for treatment of mucormycosis	• Highly toxic • Poor CNS penetration
LAmB	• 5–10 mg/kg qd	• Less nephrotoxic than AmB deoxycholate • Better CNS penetration than AmB deoxycholate or ABLC • Better outcomes than with AmB deoxycholate in murine models and a retrospective clinical review	• Expensive
ABLC	• 5–7.5 mg/kg qd	• Less nephrotoxic than AmB deoxycholate • Murine and retrospective clinical data suggest benefit of combination therapy with echinocandins.	• Expensive • Possibly less efficacious than LAmB for CNS infection
Primary Combination Therapy[b]			
Caspofungin *plus* Lipid polyene	• 70-mg IV loading dose, then 50 mg/d for ≥2 weeks • 50 mg/m^2 IV in children	• Favorable toxicity profile • Synergistic in murine disseminated mucormycosis • Retrospective clinical data suggest superior outcomes for rhino-orbital-cerebral mucormycosis.	• Very limited clinical data on combination therapy
Micafungin or anidulafungin *plus* Lipid polyene	• 100 mg/d for ≥2 weeks • Micafungin: 4 mg/kg qd in children • Micafungin: 10 mg/kg qd in low-birth-weight infants • Anidulafungin: 1.5 mg/kg qd in children	• Favorable toxicity profile • Synergistic with LAmB in murine model of disseminated mucormycosis	• No clinical data
Deferasirox *plus* Lipid polyene	• 20 mg/kg PO qd for 2–4 weeks	• Highly fungicidal against Mucorales in vitro • Synergistic with LAmB in murine model of disseminated mucormycosis	• Only available for enteral administration • No clinical data; phase 2 clinical trial completed

[a]Primary therapy should generally include a polyene. Non-polyene-based regimens may be appropriate for patients who refuse polyene therapy or for relatively immunocompetent patients with mild disease (e.g., isolated suprafascial cutaneous infection) that can be surgically eradicated.
[b]Prospective randomized trials are necessary to confirm the suggested benefit (from animal and small retrospective human studies) of combination therapy for mucormycosis. Dose escalation of any echinocandin is not recommended because of a paradoxical loss of benefit of combination therapy at echinocandin doses of ≥3 mg/kg qd.
Abbreviations: ABLC, AmB lipid complex; AmB, amphotericin B; CNS, central nervous system; LAmB, liposomal AmB.
Source: Reprinted from B Spellberg et al: Clin Infect Dis 48:1743, 2009.

has been found to be inferior in efficacy to AmB for the treatment of murine mucormycosis and is not superior to placebo for treatment of murine infection with *R. oryzae*. Moreover, posaconazole-polyene combination therapy is not superior to polyene monotherapy for murine mucormycosis.

The roles of recombinant cytokines and neutrophil transfusions in the primary treatment of mucormycosis are not clear. Limited data indicate that hyperbaric oxygen may be useful in centers with the appropriate technical expertise and facilities.

In general, antifungal therapy for mucormycosis should be continued until all of the following objectives are attained: (1) resolution of clinical signs and symptoms of infection; (2) resolution or stabilization of residual radiographic signs of disease on serial imaging; and (3) resolution of underlying immunosuppression. For patients with mucormycosis who are receiving immunosuppressive medications, secondary antifungal prophylaxis is typically continued for as long as the immunosuppressive regimen is administered.

CHAPTER 113

SUPERFICIAL MYCOSES AND LESS COMMON SYSTEMIC MYCOSES

Carol A. Kauffman

ENDEMIC MYCOSES (DIMORPHIC FUNGI)

Dimorphic fungi exist in discrete environmental niches as molds that produce conidia, which are their infectious form. In tissues and at temperatures of >35°C, the mold converts to the yeast form. Other endemic mycoses—histoplasmosis, coccidioidomycosis, and blastomycosis—are discussed in Chaps. 106, 107, and 108, respectively.

SPOROTRICHOSIS

Etiologic agent

Sporothrix schenckii is a thermally dimorphic fungus that is found worldwide in sphagnum moss, decaying vegetation, and soil.

Epidemiology and pathogenesis

Sporotrichosis most commonly infects persons who participate in outdoor activities such as landscaping, gardening, and tree farming. Infected animals, especially cats, can transmit *S. schenckii* to humans. Sporotrichosis is primarily a localized infection of skin and subcutaneous tissues that follows traumatic inoculation of conidia. Osteoarticular sporotrichosis is uncommon, occurring most often in middle-aged men who abuse alcohol, and pulmonary sporotrichosis occurs almost exclusively in persons with chronic obstructive pulmonary disease who have inhaled the organism from the environment. Dissemination occurs rarely, almost always in markedly immunocompromised patients, especially those with AIDS.

Clinical manifestations

Days or weeks after inoculation, a papule develops at the site and then usually ulcerates but is not very painful. Similar lesions develop sequentially along the lymphatic channels proximal to the original lesion. Some patients develop a fixed cutaneous lesion that can be verrucous or ulcerative and that remains localized without lymphatic extension. The differential diagnosis of lymphocutaneous sporotrichosis includes nocardiosis, tularemia, nontuberculous mycobacterial infection (especially that due to *Mycobacterium marinum*), and leishmaniasis. Osteoarticular sporotrichosis can present as chronic synovitis or septic arthritis. Pulmonary sporotrichosis must be differentiated from tuberculosis or other fungal pneumonias. Numerous ulcerated skin lesions, with or without spread to visceral organs [including the central nervous system (CNS)], are characteristic of disseminated sporotrichosis.

Diagnosis

S. schenckii usually grows readily as a mold when material from a cutaneous lesion is incubated at room temperature. Histopathologic examination of biopsy material shows a mixed granulomatous and pyogenic reaction, and tiny oval or cigar-shaped yeasts are sometimes visualized with special stains. Serologic testing is not useful.

Treatment and prognosis

Guidelines for the management of the various forms of sporotrichosis have been published by the Infectious Diseases Society of America **(Table 113-1)**. Itraconazole is the drug of choice for lymphocutaneous sporotrichosis. Fluconazole is less effective; voriconazole and posaconazole have not been used for sporotrichosis. Saturated solution of potassium iodide (SSKI) is also effective for lymphocutaneous infection and costs much less than itraconazole. However, SSKI is poorly tolerated because of adverse reactions, including metallic taste, salivary gland swelling, rash, and fever. Terbinafine appears to be effective but has been used in few patients. Treatment for lymphocutaneous sporotrichosis is continued for 2–4 weeks after all lesions have resolved, usually for a total of 3–6 months. Pulmonary and osteoarticular forms

TABLE 113-1

SUGGESTED TREATMENT FOR ENDEMIC MYCOSES

DISEASE	FIRST-LINE THERAPY	ALTERNATIVES/COMMENTS
Sporotrichosis		
Cutaneous, lymphocutaneous	Itraconazole, 200 mg/d until 2–4 weeks after lesions resolve	SSKI, increasing doses[a] Terbinafine, 500 mg bid
Pulmonary, osteoarticular	Itraconazole, 200 mg bid for 12 months	Lipid AmB[b] for severe pulmonary disease until stable; then itraconazole
Disseminated, central nervous system	Lipid AmB[b] for 4–6 weeks	Itraconazole, 200 mg bid after AmB for 12 months Itraconazole maintenance for AIDS patients: 200 mg/d until CD4+ T cell count is >200/μL for 12 months
Paracoccidioidomycosis		
Chronic (adult form)	Itraconazole, 100–200 mg/d for 6–12 months	TMP-SMX, 160/800 mg bid for 12–36 months
Acute (juvenile form)	AmB[c] until improvement	Itraconazole, 200 mg bid after AmB for 12 months
Penicilliosis		
Mild or moderate	Itraconazole, 200 mg bid for 12 weeks	Itraconazole maintenance for AIDS patients: 200 mg/d until CD4+ T cell count is >100/μL for 6 months
Severe	AmB[c] until improvement	Itraconazole, 200 mg bid after AmB for 12 weeks Itraconazole maintenance: as for mild or moderate disease

[a] The starting dosage is 5–10 drops tid in water or juice. The dosage is increased weekly by 10 drops per dose, as tolerated, up to 40–50 drops tid.
[b] The dosage of lipid AmB is 3–5 mg/kg daily; the higher dosage should be used when the central nervous system is involved.
[c] The dosage of AmB deoxycholate is 0.6–1.0 mg/kg daily.
Abbreviations: AmB, amphotericin B; SSKI, saturated solution of potassium iodide; TMP-SMX, trimethoprim-sulfamethoxazole.

of sporotrichosis are treated with itraconazole for at least 1 year. Severe pulmonary infection and disseminated sporotrichosis, including that involving the CNS, are treated initially with amphotericin B (AmB), which is followed by itraconazole after improvement has been noted. Lifelong suppressive therapy with itraconazole is required for AIDS patients. The success rate for treatment of lymphocutaneous sporotrichosis is 90–100%, but other forms of the disease respond poorly to antifungal therapy.

PARACOCCIDIOIDOMYCOSIS

Etiologic agent

Paracoccidioides brasiliensis is a thermally dimorphic fungus that is endemic in humid areas of Central and South America, especially in Brazil.

Epidemiology and pathogenesis

A striking male-to-female ratio varies from 14:1 to as high as 70:1 (in rural Brazil). Most patients are middle-aged or elderly men from rural areas. Paracoccidioidomycosis develops after the inhalation of aerosolized conidia encountered in the environment. For most patients, disease rarely develops at the time of the initial infection but appears years later, presumably after reactivation of a latent infection.

Clinical manifestations

Two major syndromes are associated with paracoccidioidomycosis: the acute or juvenile form and the chronic or adult form. The acute form is uncommon, occurs mostly in persons <30 years old, and manifests as disseminated infection of the reticuloendothelial system. Immunocompromised individuals can also manifest this type of rapidly progressive disease. The chronic form of paracoccidioidomycosis accounts for ~90% of cases and predominantly affects older men. The primary manifestation is progressive pulmonary disease, primarily in the lower lobes, with fibrosis. Ulcerative and nodular mucocutaneous lesions in the nares and mouth—another common manifestation of chronic paracoccidioidomycosis—must be differentiated from leishmaniasis (Chap. 122) and squamous cell carcinoma.

Diagnosis

The diagnosis is established by growth of the organism in culture. A presumptive diagnosis can be made by detection of the distinctive thick-walled yeast, with multiple narrow-necked buds attached circumferentially, in purulent material or tissue biopsies.

Treatment and prognosis

Itraconazole is the treatment of choice for paracoccidioidomycosis (Table 113-1). Ketoconazole is also effective but more toxic; voriconazole and posaconazole have been used with success in a few cases. Sulfonamides are also effective and are the least costly agents, but the response is slower and the relapse rate higher. Seriously ill patients should be treated with AmB initially. Patients with paracoccidioidomycosis have an excellent response to therapy, but pulmonary fibrosis is often progressive in those with chronic disease.

PENICILLIOSIS

Etiologic agent

Penicillium marneffei is a thermally dimorphic fungus that is endemic in the soil in certain areas of Vietnam, Thailand, and several other southeastern Asian countries.

Epidemiology and pathogenesis

The epidemiology of penicilliosis is linked to bamboo rats, which are infected with the fungus but rarely manifest disease. The disease occurs most often among persons living in rural areas in which the rats are found, but there is no evidence for transmission of the infection directly from rats to humans. Infection is rare in immunocompetent hosts, and most cases are reported in persons who have advanced AIDS. Infection results from the inhalation of conidia from the environment. The organism converts to the yeast phase in the lungs and then spreads hematogenously to the reticuloendothelial system.

Clinical manifestations

The clinical manifestations of penicilliosis mimic those of disseminated histoplasmosis and include fever, fatigue, weight loss, dyspnea, diarrhea (in some cases), lymphadenopathy, hepatosplenomegaly, and skin lesions, which appear as papules that often umbilicate and resemble molluscum contagiosum (Chap. 88).

Diagnosis

Penicilliosis is diagnosed by culture of *P. marneffei* from blood or from biopsy samples of skin, bone marrow, or lymph node. The organism usually grows within 1 week as a mold that produces a distinctive red pigment. Histopathologic examination of tissues and smears of blood or material from skin lesions shows oval or elliptical yeast-like organisms with central septation and can quickly establish a presumptive diagnosis.

Treatment and prognosis

Patients who have severe disease should be treated initially with AmB until their condition improves; therapy can then be changed to itraconazole (Table 113-1). Patients who have mild symptoms can be treated from the start with itraconazole. For patients with AIDS, suppressive therapy with itraconazole is recommended until immune reconstitution (related to successful therapy for HIV infection with antiretroviral drugs) is evident. Disseminated penicilliosis is usually fatal if not treated. With treatment, the mortality rate is ~10%.

PHAEOHYPHOMYCOSES

In these common soil organisms (also called *dematiaceous* fungi), melanin causes the hyphae and/or conidia to be darkly pigmented (brown/black). The term *phaeohyphomycosis* is used to describe any infection with a pigmented mold. This definition encompasses two specific syndromes—eumycetoma and chromoblastomycosis—as well as all other types of infections caused by these organisms. It is important to note that eumycetomas can be caused by hyaline molds as well as brown-black molds and that only about half of all mycetomas are due to fungi. Actinomycetes cause the remainder (Chap. 67). Most of these fungi cause localized subcutaneous infections after direct inoculation, but disseminated infection and serious visceral focal infections also occur, especially in immunocompromised patients.

Etiologic agents

A large number of pigmented molds can cause human infection. All are found in the soil or on plants, and some cause economically important plant diseases. The most common cause of eumycetoma is *Madurella* species, but hyaline molds such as *Scedosporium* species also cause this syndrome. *Fonsecaea* and *Cladophialophora* species are responsible for most cases of chromoblastomycosis. Disseminated infection and focal visceral infections are caused by a variety of dematiaceous fungi; *Alternaria*, *Exophiala*, *Curvularia*, and *Wangiella* species are among the more common molds reported to cause human infection.

Epidemiology and pathogenesis

Most infections, including all cases of eumycetoma and chromoblastomycosis, are acquired by inoculation through the skin. These two syndromes are seen almost entirely in tropical and subtropical areas and occur mostly in rural laborers who are frequently exposed to the organisms. Inhalation into the upper or lower respiratory tract leads to localized infection of sinuses and, in immunocompromised patients, to pneumonia and sometimes hematogenous

dissemination. Several organisms, specifically *Cladophialophora bantiana* and *Rhinocladiella mackensiei*, are neurotropic and likely to cause CNS infection.

Clinical manifestations

Eumycetoma is a chronic subcutaneous and cutaneous infection that usually occurs on the lower extremities and that is characterized by swelling, development of sinus tracts, and the appearance of grains that are actually colonies of fungi discharged from the sinus tract. As the infection progresses, adjacent fascia and bony structures become involved. The disease is indolent and disfiguring, progressing slowly over years. Complications include fractures of infected bone and bacterial superinfections.

Chromoblastomycosis is an indolent subcutaneous infection characterized by nodular, verrucous, or plaque-like painless lesions that occur predominantly on the lower extremities and grow slowly over months or years. There is hardly ever extension to adjacent structures, as is seen with eumycetoma. Long-term consequences include bacterial superinfection, chronic lymphedema, and (rarely) the development of squamous cell carcinoma.

Dematiaceous molds are the most common cause of allergic fungal sinusitis and a less common cause of invasive fungal sinusitis. Keratitis occurs with corneal inoculation. Many patients, including some who are immunocompromised, develop only localized infection manifested by cyst-like subcutaneous lesions at the site of inoculation. Other immunocompromised patients have pneumonia and disseminated infection, including CNS involvement, and are quite ill.

Diagnosis

The specific diagnosis of infection with a pigmented mold is established by growth of the organism in culture. However, in eumycetoma, a tentative clinical diagnosis can be made when a patient presents with a lesion characterized by swelling, sinus tracts, and grains. Histopathologic examination and culture are necessary to ensure that the etiologic agent is a mold and not an actinomycete. In chromoblastomycosis, the diagnosis rests on the histologic demonstration of sclerotic bodies in the tissues; culture merely establishes which pigmented mold is causing the infection. Sclerotic bodies are dark brown, thick-walled, septate fungal forms that resemble large yeasts and define the syndrome. For disseminated infections and nonsubcutaneous focal infections, growth of the organism is essential to differentiate infection with a hyaline mold (e.g., *Aspergillus* or *Fusarium*) from that due to a pigmented mold. No serologic or non-culture-based methods are currently available to aid in the diagnosis of phaeohyphomycoses.

Treatment and prognosis

Treatment of eumycetoma and chromoblastomycosis involves both surgical extirpation of the lesion and use of antifungal agents. Surgical removal of the lesions of both eumycetoma and chromoblastomycosis is most effective if performed before extensive spread has occurred. In chromoblastomycosis, cryosurgery and laser therapy have been used with variable success. The antifungal agents of choice are itraconazole, voriconazole, and posaconazole. The most experience has accrued with itraconazole; there is less experience with the newer azoles, which are active in vitro and have been reported to be effective in a few patients. Flucytosine and terbinafine also have been used to treat chromoblastomycosis.

Disseminated and focal visceral infections are treated with the appropriate antifungal agent; the choice of agent is based on the location and extent of the infection, in vitro testing, and clinical experience with the specific infecting organism. AmB is not effective against many of these organisms but has been used successfully against others. Again, the most experience has been obtained with itraconazole, which is effective for localized infections. Voriconazole and posaconazole are likely to play an increasing role in therapy for both localized and disseminated infections. Chromoblastomycosis and eumycetoma are chronic indolent infections that are difficult to cure without surgical excision, but these are not life-threatening diseases. Disseminated or focal visceral infections with pigmented molds in immunocompromised patients are associated with high mortality rates unless immunosuppression can be diminished and effective antifungal agents prescribed promptly.

OPPORTUNISTIC FUNGAL INFECTIONS

Many environmental fungi can cause infection in markedly immunocompromised hosts, but two genera of hyaline (nonpigmented) molds, *Fusarium* and *Scedosporium*, and one yeast-like genus, *Trichosporon*, have become particularly prominent pathogens among such patients. *Fusarium* and *Scedosporium* species overlap with invasive aspergillosis in their clinical manifestations and, when seen in tissues, appear similar to *Aspergillus*. In the immunocompetent host, these fungi cause localized infections of skin, skin structures, and subcutaneous tissues, but their role in disseminated infection will be emphasized in this section.

FUSARIOSIS

Etiologic agent

Fusarium species, which are found worldwide in soil and on plants, have emerged as major opportunists in markedly immunocompromised patients.

Epidemiology and pathogenesis

Most human infections follow inhalation of conidia, but ingestion and direct inoculation can also lead to disease. An outbreak of severe *Fusarium* keratitis among soft contact lens wearers was traced back to a particular brand of contact lens solution and individual contact lens cases

that had been contaminated. Disseminated infection is reported most often in patients who have a hematologic malignancy, are neutropenic, have received a stem cell or solid organ transplant, or have a severe burn.

Clinical manifestations

In immunocompetent persons, *Fusarium* species cause localized infections of various organs. These organisms commonly cause fungal keratitis, which can extend into the anterior chamber of the eye, cause loss of vision, and require corneal transplantation. Onychomycosis due to *Fusarium* species, while basically an annoyance in immunocompetent patients, is a source of subsequent hematogenous dissemination and should be aggressively sought and treated in neutropenic patients. In profoundly immunocompromised patients, fusariosis is angioinvasive, and clinical manifestations mimic those of aspergillosis. Pulmonary infection is characterized by multiple nodular lesions. Sinus infection is likely to lead to invasion of adjacent structures. Disseminated fusariosis occurs primarily in neutropenic patients with hematologic malignancies and in allogeneic stem cell transplant recipients, especially those with graft-versus-host disease. Disseminated fusariosis differs from disseminated aspergillosis in that skin lesions are extremely common with fusariosis; the lesions are nodular or necrotic, are usually painful, and appear over time in different locations.

Diagnosis

The diagnostic approach usually includes both documentation of the growth of *Fusarium* species from involved tissue and demonstration of invasion by histopathologic or microbiologic techniques that show septate hyphae in tissues or aspirates. The organism is difficult to differentiate from *Aspergillus* species in tissues; thus, identification with culture is imperative. An extremely helpful diagnostic clue is growth in blood cultures, which are positive in as many as 50% of patients with disseminated fusariosis. No serologic or non-culture-based techniques are currently available to aid in diagnosis.

Treatment and prognosis

Fusarium species are resistant to many antifungal agents. A lipid formulation of AmB (at least 5 mg/kg daily), voriconazole (200–400 mg twice daily), or posaconazole (400 mg twice daily) is recommended. Many physicians use both a lipid formulation of AmB and either voriconazole or posaconazole because susceptibility information is not available when therapy must be initiated. Serum drug levels should be monitored with either azole to ensure that absorption is adequate and with voriconazole to avoid toxicity. Mortality rates for disseminated fusariosis have been as high as 85%. With the antifungal therapy noted earlier, mortality rates have fallen to ~50%. However, if neutropenia persists, the mortality rate approaches 100%.

SCEDOSPORIOSIS

Etiologic agent

The genus *Scedosporium* includes several pathogens. The major causes of human infections are *Scedosporium apiospermum*, which in its sexual state is termed *Pseudallescheria boydii*, and *S. prolificans*. The *S. apiospermum* complex encompasses several species but will be referred to here simply as *S. apiospermum*.

Epidemiology and pathogenesis

S. apiospermum is found worldwide in temperate climates in tidal flats, swamps, ponds, manure, and soil. This organism is known as a cause of pneumonia, disseminated infection, and brain abscess in near-drowning victims. *S. prolificans* is also found in soil but is more geographically restricted; most cases are reported from Spain and Australia. Infection occurs predominantly through inhalation of conidia, but direct inoculation through the skin or into the eye also can occur.

Clinical manifestations

Among immunocompetent persons, *Scedosporium* species are a prominent cause of eumycetoma. Keratitis as a result of accidental corneal inoculation is a sight-threatening infection. In patients who have hematologic malignancies (especially acute leukemia with neutropenia), recipients of solid organ or stem cell transplants, and patients receiving glucocorticoids, *Scedosporium* species are angioinvasive, causing pneumonia and widespread dissemination with abscesses. Pulmonary infection mimics that caused by aspergillosis; nodules, cavities, and lobar infiltrates are common. Disseminated infection involves the skin, heart, brain, and many other organs. Skin lesions are not as common or as painful as those of fusariosis.

Diagnosis

Diagnosis depends on the growth of *Scedosporium* species from involved tissue and the demonstration of invasion by histopathologic or microbiologic techniques that show septate hyphae in tissues or aspirates. Culture evidence is essential because *Scedosporium* species are difficult to differentiate from *Aspergillus* in tissues. Demonstration of tissue invasion is essential because these ubiquitous environmental molds can be mere contaminants or colonizers. *S. prolificans* can grow in blood cultures, but *S. apiospermum* usually does not. No serologic or non-culture-based diagnostic methods are available to aid in diagnosis.

Treatment and prognosis

Scedosporium species are resistant to AmB, echinocandins, and some azoles. Voriconazole is the agent of choice for *S. apiospermum*, and posaconazole has also been used for this infection. *S. prolificans* is resistant in vitro to almost every available antifungal agent; the addition of agents such as terbinafine to a voriconazole

regimen has been attempted because in vitro data suggest possible synergy against some strains of *S. prolificans*. Mortality rates have been as high as 65–75% for *S. apiospermum* and 85–100% for *S. prolificans*. Mortality rates for *S. apiospermum* infection have decreased to 40–50% with the use of voriconazole, but those for disseminated *S. prolificans* infection remain extremely high.

TRICHOSPORONOSIS

Etiologic agent

The genus *Trichosporon* contains many species, some of which cause localized infection of hair and nails. The major pathogen responsible for invasive infection is *Trichosporon asahii*. *Trichosporon* species grow as yeast-like colonies in vitro; in vivo, however, hyphae, pseudohyphae, and arthroconidia can also be seen.

Epidemiology and pathogenesis

These yeasts are commonly found in soil, sewage, and water and in rare instances can colonize human skin and the human gastrointestinal tract. Most infections follow fungal inhalation or entry via central venous catheters. Systemic infection occurs almost exclusively in immunocompromised hosts, including those who have hematologic malignancies, are neutropenic, have received a solid organ transplant, or are receiving glucocorticoids.

Clinical manifestations

Disseminated trichosporonosis resembles invasive candidiasis, and fungemia is often the initial manifestation of infection. Pneumonia, skin lesions, and sepsis syndrome are common. The skin lesions begin as papules or nodules surrounded by erythema and progress to central necrosis. A chronic form of infection mimics hepatosplenic candidiasis (chronic disseminated candidiasis).

Diagnosis

The diagnosis of systemic *Trichosporon* infection is established by growth of the organism from involved tissues or from blood. Histopathologic examination of a skin lesion showing a mixture of yeast forms, arthroconidia, and hyphae can lead to an early presumptive diagnosis of trichosporonosis. The serum cryptococcal antigen latex agglutination test may be positive in patients with disseminated trichosporonosis because *T. asahii* and *Cryptococcus neoformans* share polysaccharide antigens.

Treatment and prognosis

Rates of response to AmB have been disappointing, and many *Trichosporon* isolates are resistant in vitro. Voriconazole appears to be the antifungal agent of choice and is used at a dosage of 200–400 mg twice daily. The mortality rates for disseminated *Trichosporon* infection have been as high as 70% but should decrease with the use of newer azoles, such as voriconazole; however, patients who remain neutropenic are likely to succumb to this infection.

SUPERFICIAL CUTANEOUS INFECTIONS

Fungal infections of the skin and skin structures are caused by molds and yeasts that do not invade deeper tissues but rather cause disease merely by inhabiting the superficial layers of skin, hair follicles, and nails. These agents are the most common cause of fungal diseases of humans but only rarely cause serious infections.

YEAST INFECTIONS

Etiologic agents

The lipophilic yeast *Malassezia* is actually dimorphic in that it lives on the skin in the yeast phase but transforms to the mold phase as it causes disease. Of the seven species, six are grouped together in some classification systems as the *M. furfur* complex; all six of these species require exogenous lipids for growth. The seventh species, *M. pachydermatis*, is also lipophilic but does not have an absolute requirement for lipids.

Epidemiology and pathogenesis

Malassezia species are part of the indigenous human flora found in the stratum corneum of the back, chest, scalp, and face—areas rich in sebaceous glands. Disease is more common in moist humid areas of the world. The organisms do not invade below the stratum corneum and generally elicit little if any inflammatory response.

Clinical manifestations

Malassezia species cause tinea versicolor (also called *pityriasis versicolor*), folliculitis, and seborrheic dermatitis. Tinea versicolor presents as flat round scaly patches of hypo- or hyperpigmented skin on the neck, chest, or upper arms. The lesions are usually asymptomatic but can be pruritic. They can be mistaken for vitiligo, but the latter is not scaly. Folliculitis occurs over the back and chest and mimics bacterial folliculitis. Seborrheic dermatitis manifests as erythematous pruritic scaly lesions in the eyebrows, moustache, nasolabial folds, and scalp. The scalp lesions are termed cradle cap in babies and dandruff in adults. Seborrheic dermatitis can be severe in patients with advanced AIDS. Fungemia and disseminated infection occur rarely with *Malassezia* species—almost always in premature neonates receiving parenteral lipid preparations through a central venous catheter.

Diagnosis

Malassezia infections are diagnosed clinically in most cases. If scrapings are collected on a microscope slide on which a drop of potassium hydroxide has been placed, a

mixture of budding yeasts and short septate hyphae are seen. In order to culture *M. furfur* from those patients in whom disseminated infection is suspected, sterile olive oil must be added to the medium.

Treatment and prognosis

Topical creams and lotions, including selenium sulfide shampoo, ketoconazole shampoo or cream, terbinafine cream, and ciclopirox cream, are effective in treating *Malassezia* infections and are usually given for 2 weeks. Mild topical steroid creams are sometimes used to treat seborrheic dermatitis. For extensive disease, itraconazole (200 mg/d) or fluconazole (200 mg/d) can be used for 5–7 days. The rare cases of fungemia caused by *Malassezia* species are treated with AmB or fluconazole, prompt removal of the catheter, and discontinuance of parenteral lipid infusions. *Malassezia* skin infections are benign and self-limited, although recurrences are the rule. The outcome of systemic infection depends on the host's underlying conditions, but most infants do well.

DERMATOPHYTE (MOLD) INFECTIONS

Etiologic agents

The molds that cause skin infections in humans include the genera *Trichophyton*, *Microsporum*, and *Epidermophyton*. These organisms, which are not components of the normal skin flora, can live within the keratinized structures of the skin—hence the term *dermatophytes*.

Epidemiology and pathogenesis

Dermatophytes occur worldwide, and infections with these organisms are extremely common. Some organisms cause disease only in humans and can be transmitted by person-to-person contact and by fomites, such as hairbrushes or wet floors that have been contaminated by infected individuals. Several species cause infections in cats and dogs and can readily be transmitted from these animals to humans. Finally, some dermatophytes are spread from contact with soil. The characteristic ring shape of cutaneous lesions is the result of the organisms' outward growth in a centrifugal pattern in the stratum corneum. Fungal invasion of the nails usually occurs through the lateral or superficial nail plates and then spreads throughout the nails; when hair shafts are invaded, the organisms can be found either within the shaft or surrounding it. Symptoms are caused by the inflammatory reaction elicited by fungal antigens and not by tissue invasion. Dermatophyte infections occur more commonly in male than in female patients, and progesterone has been shown to inhibit dermatophyte growth.

Clinical manifestations

Dermatophyte infection of the skin is often called *ringworm*. This term is confusing because worms are not involved. *Tinea*, the Latin word for *worm*, describes the serpentine nature of the skin lesions and is a less confusing designation that is used in conjunction with the name of the body part affected—e.g., tinea capitis (head), tinea pedis (feet), tinea corporis (body), tinea cruris (crotch), and tinea unguium (nails, although infection at this site is more often termed *onychomycosis*).

Tinea capitis occurs most commonly in children 3–7 years old. Children with tinea capitis usually present with well-demarcated scaly patches in which hair shafts are broken off right above the skin; alopecia can result. Tinea corporis is manifested by well-demarcated, annular, pruritic, scaly lesions that undergo central clearing. Usually one or several small lesions are present. In some cases, tinea corporis can involve much of the trunk or manifest as folliculitis with pustule formation. The rash should be differentiated from contact dermatitis, eczema, and psoriasis. Tinea cruris is seen almost exclusively in men. The perineal rash is erythematous and pustular, has a discrete scaly border, is without satellite lesions, and is usually pruritic. The rash must be differentiated from intertriginous candidiasis, erythrasma, and psoriasis.

Tinea pedis also is more common among men than among women. It usually starts in the web spaces of the toes; peeling, maceration, and pruritus are followed by development of a scaly pruritic rash along the lateral and plantar surfaces of the feet. Hyperkeratosis of the soles of the feet often ensues. Tinea pedis has been implicated in lower-extremity cellulitis, as streptococci and staphylococci can gain entrance to the tissues through fissures between the toes. Onychomycosis affects toenails more often than fingernails and is most common among persons who have tinea pedis. The nail becomes thickened and discolored and may crumble; onycholysis almost always occurs. Onychomycosis is more common in older adults and in persons with vascular disease, diabetes mellitus, and trauma to the nails. Fungal infection must be differentiated from psoriasis, which can mimic onychomycosis but usually has associated skin lesions.

Diagnosis

Many dermatophyte infections are diagnosed by their clinical appearance. If the diagnosis is in doubt, as is often the case in children with tinea capitis, scrapings should be taken from the edge of a lesion with a scalpel blade, transferred to a slide to which a drop of potassium hydroxide is added, and examined under a microscope for the presence of hyphae. Cultures are indicated if an outbreak is suspected or the patient does not respond to therapy. Culture of the nail is especially useful as an aid to decisions about both diagnosis and treatment.

Treatment and prognosis

Dermatophyte infections usually respond to topical therapy. Lotions or sprays are easier than creams to apply to large or hairy areas. Particularly for tinea cruris, the affected area should be kept as dry as possible. When patients have

TABLE 113-2

SUGGESTED TREATMENT FOR EXTENSIVE TINEA INFECTIONS AND ONYCHOMYCOSIS

ANTIFUNGAL AGENT	SUGGESTED DOSAGE	COMMENTS
Extensive tinea skin infection		
Terbinafine	250 mg/d for 1–2 weeks	Adverse reactions minimal with short treatment period
Itraconazole[a]	200 mg/d for 1–2 weeks	Adverse reactions minimal with short treatment period except for drug interactions
Onychomycosis		
Terbinafine	250 mg/d for 3 months	Slightly superior to itraconazole; monitor for hepatotoxicity
Itraconazole[a]	200 mg/d for 3 months or 200 mg bid for 1 week each month for 3 months	Drug interactions frequent; monitor for hepatotoxicity; rarely causes hypokalemia, hypertension, edema; use with caution in patients with congestive heart failure

[a]Itraconazole capsules require food and gastric acid for absorption, whereas itraconazole solution is taken on an empty stomach.

extensive skin lesions, oral itraconazole or terbinafine can hasten resolution (Table 113-2). Terbinafine interacts with fewer drugs than itraconazole and is generally the first-line agent. Onychomycosis does not respond to topical therapy, although ciclopirox nail lacquer applied daily for a year is occasionally beneficial. Itraconazole and terbinafine both accumulate in the nail plate and can be used to treat onychomycosis (Table 113-2). These agents are more effective and better tolerated than griseofulvin and ketoconazole. The major decision to be made with regard to therapy is whether the extent of nail involvement justifies the use of systemic antifungal agents that have adverse effects, may interact with other drugs, and are costly. Treating for cosmetic reasons alone is discouraged. Relapses of tinea cruris and tinea pedis are common and should be treated early with topical creams to avoid development of more extensive disease. Relapses of onychomycosis follow treatment in 25–30% of cases.

CHAPTER 114

PNEUMOCYSTIS INFECTIONS

A. George Smulian ■ Peter D. Walzer

DEFINITION AND DESCRIPTION

Pneumocystis is an opportunistic fungal pulmonary pathogen that is an important cause of pneumonia in the immunocompromised host. Although organisms within the *Pneumocystis* genus are morphologically very similar, they are genetically diverse and host-specific. *P. jirovecii* infects humans, whereas *P. carinii*—the original species described in 1909—infects rats. For clarity, only the genus designation *Pneumocystis* will be used in this chapter.

Developmental stages of the organism include the trophic form, the cyst, and the precyst (an intermediate stage). The life cycle of *Pneumocystis* probably involves sexual and asexual reproduction, although definitive

proof awaits the development of a reliable culture system. *Pneumocystis* contains several different antigen groups, the most prominent of which are the 95- to 140-kDa major surface glycoprotein (MSG) and kexin (KEX1).

EPIDEMIOLOGY

Serologic surveys have demonstrated that *Pneumocystis* has a worldwide distribution and that most healthy children have been exposed to the organism by 3–4 years of age. Airborne transmission of *Pneumocystis* has been documented in animal studies; person-to-person transmission has been suggested by hospital outbreaks of *Pneumocystis* pneumonia (PcP) and by molecular epidemiologic analysis of isolates. Data suggest that the cyst is the transmissible form.

PATHOGENESIS AND PATHOLOGY

Studies over the past several years have shown that *Pneumocystis* commonly colonizes patients who are immunosuppressed or who have chronic obstructive pulmonary disease. This colonization elicits an inflammatory response and is associated with a decline in lung function.

The host factors that predispose to the development of PcP include defects in cellular and humoral immunity. The risk of PcP among HIV-infected patients rises markedly when circulating CD4+ T cell counts fall below 200/μL. Other persons at risk for PcP are patients receiving immunosuppressive agents (particularly glucocorticoids) for cancer and organ transplantation; those receiving biologic agents such as infliximab and etanercept for rheumatoid arthritis and inflammatory bowel disease; children with primary immunodeficiency diseases; and premature malnourished infants.

The principal host effector cells against *Pneumocystis* are alveolar macrophages, which ingest and kill the organism, releasing a variety of inflammatory mediators. Proliferating organisms remain extracellular within the alveolus, attaching tightly to type I cells. Alveolar damage results in increased alveolar-capillary permeability and surfactant abnormalities, including a fall in phospholipids and an increase in surfactant proteins A and D. The host inflammatory response to lung injury leads to increases in levels of interleukin 8 and in neutrophil counts in bronchoalveolar lavage (BAL) fluid. These changes correlate with disease severity.

On lung sections stained with hematoxylin and eosin, the alveoli are filled with a typical foamy, vacuolated exudate. Severe disease may include interstitial edema, fibrosis, and hyaline membrane formation. The host inflammatory changes usually consist of hypertrophy of alveolar type II cells, a typical reparative response, and a mild mononuclear cell interstitial infiltrate. Malnourished infants display an intense plasma cell infiltrate that gave the disease its early name: interstitial plasma cell pneumonia.

CLINICAL FEATURES

Patients with PcP develop dyspnea, fever, and nonproductive cough. HIV-infected patients are usually ill for several weeks and may have relatively subtle manifestations. Symptoms in non-HIV-infected patients are of shorter duration and often begin after the glucocorticoid dose has been tapered. A high index of suspicion and a thorough history are key factors in early detection.

Physical findings include tachypnea, tachycardia, and cyanosis, but lung auscultation reveals few abnormalities. Reduced arterial oxygen pressure (Pa_{O2}), increased alveolar-arterial oxygen gradient ($PA_{O2} - Pa_{O2}$), and respiratory alkalosis are evident. Diffusion capacity is reduced, and heightened uptake with nonspecific nuclear imaging techniques (gallium scan) may be noted. Elevated serum concentrations of lactate dehydrogenase, reflecting lung parenchymal damage, and β-D-glucan, a component of the fungal cell wall, have been reported; however, these elevations are not specific for PcP infection.

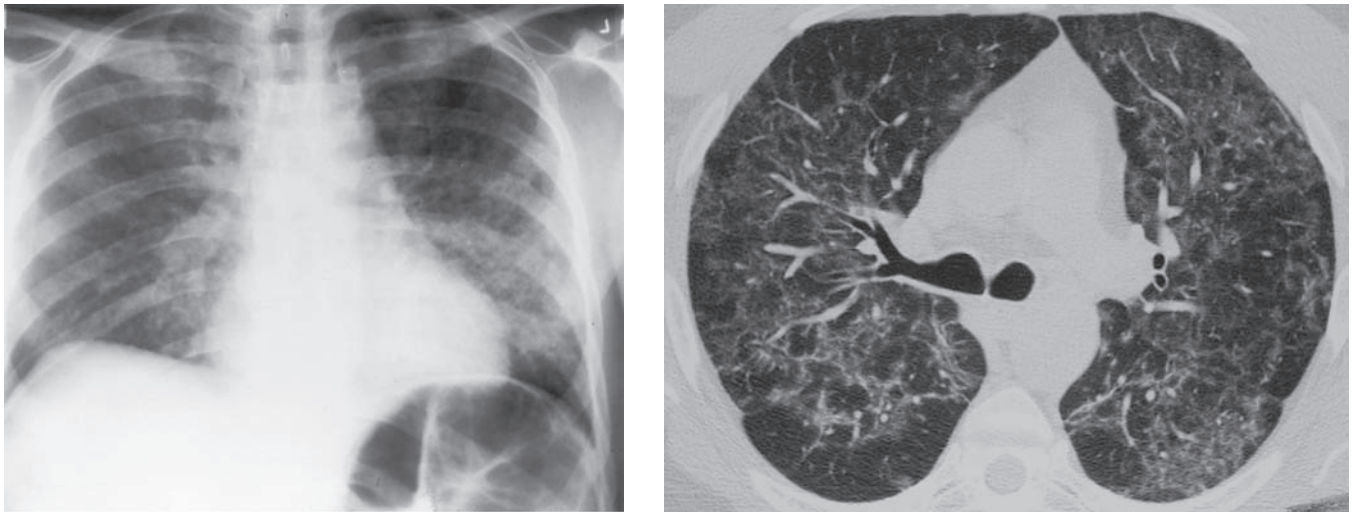
The classic findings on chest radiography consist of bilateral diffuse infiltrates beginning in the perihilar regions **(Fig. 114-1*A*)**, but various atypical manifestations (nodular densities, cavitary lesions) have also been reported. Pneumothorax occurs, and its management is often difficult. Early in the course of PcP, the chest radiograph may be normal, although high-resolution CT of the lung may reveal ground-glass opacities at this stage (Fig. 114-1*B*).

While *Pneumocystis* usually remains confined to the lungs, cases of disseminated infection have occurred in both HIV-infected and non-HIV-infected patients. Common sites of involvement include the lymph nodes, spleen, liver, and bone marrow.

DIAGNOSIS

Because of the nonspecific nature of the clinical picture, the diagnosis must be based on specific identification of the organism. A definitive diagnosis is made by histopathologic staining. Traditional cell wall stains such as methenamine silver selectively stain the wall of *Pneumocystis* cysts, while reagents such as Wright-Giemsa stain the nuclei of all developmental stages. Immunofluorescence with monoclonal antibodies is more sensitive and specific than histologic staining. DNA amplification by PCR may become part of routine diagnostics but may not distinguish colonization from infection.

The successful diagnosis of PcP depends on the collection of proper specimens. In general, the yield from different diagnostic procedures is higher for HIV-infected patients than for non-HIV-infected patients because of the higher organism burden in the former group. Sputum induction and oral washes have gained popularity as simple, noninvasive techniques; however, these procedures require trained and dedicated personnel. Fiberoptic bronchoscopy with BAL, which provides information about the organism burden, the host inflammatory response, and the presence of other opportunistic infections, continues to be the mainstay of *Pneumocystis* diagnosis. Transbronchial biopsy and open lung biopsy, the most invasive procedures, are used only when a diagnosis cannot be made by BAL.



A **B**

FIGURE 114-1

A. Chest radiograph depicting diffuse infiltrates in an HIV-infected patient with PcP. ***B.*** High-resolution CT of the lung showing ground-glass opacification in an HIV-infected patient with PcP. (*Courtesy of Dr. Cristopher Meyer, with permission.*)

COURSE AND PROGNOSIS

In the typical case of untreated PcP, progressive respiratory embarrassment leads to death. Therapy is most effective when instituted early, before there is extensive alveolar damage. If examination of induced sputum is nondiagnostic and BAL cannot be performed in a timely manner, empirical therapy for PcP is reasonable. However, this practice does not eliminate the need for a specific etiologic diagnosis. With improved management of HIV and its complications, mortality rates from PcP among HIV-infected patients are 0–15%. In contrast, rates of early death remain high among patients who require mechanical ventilation (60%) and among non-HIV-infected patients (40%).

TREATMENT *Pneumocystis* Infections

Trimethoprim-sulfamethoxazole (TMP-SMX), which acts by inhibiting folic acid synthesis, is considered the drug of choice for all forms of PcP (Table 114-1). Therapy is continued for 14 days in non-HIV-infected patients and for 21 days in persons infected with HIV. Since HIV-infected patients respond more slowly than non-HIV-infected patients, it is prudent to wait at least 7 days after the initiation of treatment before concluding that therapy has failed. TMP-SMX is well tolerated by non-HIV-infected patients, whereas more than half of HIV-infected patients experience serious adverse reactions.

Several alternative regimens are available for the treatment of mild to moderate cases of PcP (a Pa_{O2} of >70 mmHg or a $PA_{O2} - Pa_{O2}$ of <35 mmHg while breathing room air). TMP plus dapsone and clindamycin plus primaquine are about as effective as TMP-SMX. Dapsone and primaquine should not be administered to patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Atovaquone is less effective than TMP-SMX but is better tolerated. Since *Pneumocystis* lacks ergosterol, it is not susceptible to antifungal agents that inhibit ergosterol synthesis.

Alternative regimens that are recommended for the treatment of moderate to severe PcP (a Pa_{O2} of ≤70 mmHg or a $PA_{O2} - Pa_{O2}$ of ≥35 mmHg) are parenteral pentamidine, parenteral clindamycin plus primaquine, or trimetrexate plus leucovorin. Parenteral clindamycin plus primaquine may be more efficacious than pentamidine.

Molecular evidence of resistance to sulfonamides and to atovaquone has emerged among clinical *Pneumocystis* isolates. Although prior sulfonamide exposure is a risk factor, this resistance has also occurred in HIV-infected patients who have never received sulfonamides. The outcome of therapy appears to be linked more strongly to traditional measures—e.g., high Acute Physiology, Age, and Chronic Health Evaluation III (APACHE III) scores, need for positive-pressure ventilation, delayed intubation, and development of pneumothorax—than to the presence of molecular markers of sulfonamide resistance.

Early institution of antiretroviral therapy when HIV patients present with PcP has been associated with improved survival rates, but careful attention should be devoted to the possible development of the immune reconstitution inflammatory syndrome. HIV-infected patients frequently experience deterioration of respiratory function shortly after receiving anti-*Pneumocystis* drugs. The adjunctive administration of tapering doses of glucocorticoids to HIV-infected patients with moderate to severe PcP can prevent this problem and improve the rate of survival (Table 114-1). For maximal benefit, this adjunctive therapy should be started early in the course of the illness. The use of steroids as adjunctive therapy in HIV-infected patients with mild PcP or in non-HIV-infected patients remains to be evaluated.

TABLE 114-1

TREATMENT OF PNEUMOCYSTOSIS

DRUG(S), DOSE, ROUTE	ADVERSE EFFECTS
First Choice[a]	
TMP-SMX (TMP: 5 mg/kg; SMX: 25 mg/kg[b]) q6–8 h PO or IV	Fever, rash, cytopenias, hepatitis, hyperkalemia, GI disturbances
Other Agents[a]	
TMP, 5 mg/kg q6–8h; plus dapsone, 100 mg qd PO	Hemolysis (G6PD deficiency), methemoglobinemia, fever, rash, GI disturbances
Atovaquone, 750 mg bid PO	Rash, fever, GI and hepatic disturbances
Clindamycin, 300–450 mg q6h PO or 600 mg q6–8h IV; plus primaquine, 15–30 mg qd PO	Hemolysis (G6PD deficiency), methemoglobinemia, rash, colitis, neutropenia
Pentamidine, 3–4 mg/kg qd IV	Hypotension, azotemia, cardiac arrhythmias, pancreatitis, dysglycemias, hypocalcemia, neutropenia, hepatitis
Trimetrexate, 45 mg/m^2 qd IV; plus leucovorin,[c] 20 mg/kg q6h PO or IV	Cytopenias, peripheral neuropathy, hepatic disturbances
Adjunctive Agent	
Prednisone, 40 mg bid × 5 d, 40 mg qd × 5 d, 20 mg qd × 11 d; PO or IV	Immunosuppression, peptic ulcer, hyperglycemia, mood changes, hypertension

[a]Therapy is administered for 14 days to non-HIV-infected patients and for 21 days to HIV-infected patients.
[b]Equivalent of 2 double-strength (DS) tablets. (One DS tablet contains 160 mg of TMP and 800 mg of SMX.)
[c]Leucovorin prevents bone marrow toxicity from trimetrexate.
Abbreviations: GI, gastrointestinal; G6PD, glucose-6-phosphate dehydrogenase; TMP-SMX, trimethoprim-sulfamethoxazole.

TABLE 114-2

PROPHYLAXIS OF PNEUMOCYSTOSIS[a]

DRUG(S), DOSE, ROUTE	COMMENTS
First Choice	
TMP-SMX, 1 DS tablet or 1 SS tablet qd PO[b]	TMP-SMX can be safely reintroduced for treatment of some patients who have had mild to moderate side effects.
Other Agents	
Dapsone, 50 mg bid or 100 mg qd PO	—
Dapsone, 50 mg qd PO; plus pyrimethamine, 50 mg weekly PO; plus leucovorin, 25 mg weekly PO	Leucovorin prevents bone marrow toxicity from pyrimethamine.
Dapsone, 200 mg weekly PO; plus pyrimethamine, 75 mg weekly PO; plus leucovorin, 25 mg weekly PO	Leucovorin prevents bone marrow toxicity from pyrimethamine.
Pentamidine, 300 mg monthly via Respirgard II nebulizer	Adverse reactions include cough and bronchospasm.
Atovaquone, 1500 mg qd PO	—
TMP-SMX, 1 DS tablet three times weekly PO	TMP-SMX can be safely reintroduced for treatment of some patients who have had mild to moderate side effects.

[a]For a list of adverse effects, see Table 114-1.
[b]One DS tablet contains 160 mg of TMP and 800 mg of SMX.
Abbreviations: DS, double-strength; SS, single-strength; TMP-SMX, trimethoprim-sulfamethoxazole.

PREVENTION

Prophylaxis is indicated for HIV-infected patients with CD4+ T cell counts of <200/μL or a history of oropharyngeal candidiasis and for both HIV-infected and non-HIV-infected patients who have recovered from PcP. Prophylaxis may be discontinued in HIV-infected patients once CD4+ T cell counts have risen to >200/μL and remained at that level for ≥3 months. Primary prophylaxis guidelines for immunocompromised hosts not infected with HIV are less clear.

TMP-SMX is the drug of choice for primary and secondary prophylaxis (Table 114-2). This agent also provides protection against toxoplasmosis and some bacterial infections. Alternative regimens are available for individuals intolerant of TMP-SMX (Table 114-2). Although there are no specific recommendations for preventing the spread of *Pneumocystis* in health care facilities, it seems prudent to prevent direct contact between patients with PcP and other susceptible hosts.

This page intentionally left blank

SECTION VIII

PROTOZOAL AND HELMINTHIC INFECTIONS

CHAPTER 115

LABORATORY DIAGNOSIS OF PARASITIC INFECTIONS

Sharon L. Reed ■ Charles E. Davis

The cornerstone for the diagnosis of parasitic infections is a thorough history of the patient's illness. Epidemiologic aspects of the illness are especially important because the risks of acquiring many parasites are closely related to occupation, recreation, or travel to areas of high endemicity. Without a basic knowledge of the epidemiology and life cycles of the major parasites, it is difficult to approach the diagnosis of parasitic infections systematically. Accordingly, the medical classification of important human parasites in this chapter emphasizes their geographic distribution, their transmission, and the anatomic location and stages of their life cycle in humans. The text and tables are intended to serve as a guide to the correct diagnostic procedures for the major parasitic infections; in addition, the reader is referred to other chapters that contain more comprehensive information about each infection (Chaps. 118–130). **Tables 115-1, 115-2,** and **115-3** summarize the geographic distributions, the anatomic locations, and the methods employed for the diagnosis of flatworm, roundworm, and protozoal infections, respectively.

In addition to selecting the correct diagnostic procedures, physicians must counsel their patients to ensure that specimens are collected properly and arrive at the laboratory promptly. For example, the diagnosis of bancroftian filariasis is unlikely to be confirmed by the laboratory unless blood is drawn near midnight, when the nocturnal microfilariae are active. Laboratory personnel and surgical pathologists should be notified in advance when a parasitic infection is suspected. Continuing interaction with the laboratory staff and the surgical pathologists increases the likelihood that parasites in body fluids or biopsy specimens will be examined carefully by the most capable individuals.

INTESTINAL PARASITES

Most helminths and protozoa exit the body in the fecal stream. The patient should be instructed to collect feces in a clean waxed or cardboard container and to record the time of collection on the container. Contamination with water (which could contain free-living protozoa) or with urine (which can damage trophozoites) should be avoided. Fecal samples should be collected before ingestion of barium or other contrast agents for radiologic procedures and before treatment with antidiarrheal agents and antacids, because these substances change the consistency of the feces and interfere with microscopic detection of parasites. Because of the cyclic shedding of most parasites in the feces, a minimum of three samples collected on alternate days should be examined. Examination of a single sample can be up to 50% less sensitive. When delays in transport to the laboratory are unavoidable, fecal samples should be kept in polyvinyl alcohol or another fixative to preserve protozoal trophozoites. New collection kits with instructions for the patient to transfer portions of the sample directly into fixative and bacterial carrier medium may enhance the recovery of trophozoites. Refrigeration will also preserve trophozoites for a few hours and protozoal cysts and helminthic ova for several days.

Analysis of fecal samples entails both macroscopic and microscopic examination. Watery or loose stools are more likely to contain protozoal trophozoites, but protozoal cysts and all stages of helminths may be found in formed feces. If adult worms or tapeworm segments are observed, they should be transported promptly to the laboratory or washed and preserved in fixative for later examination. The only tapeworm with motile segments is *Taenia saginata*, the beef tapeworm, which patients sometimes bring to the physician. Because the ova of *T. saginata* are morphologically indistinguishable from those of *Taenia solium* (the cause of cysticercosis), motility is an important distinguishing characteristic.

Microscopic examination of feces is not complete until direct wet mounts have been evaluated and concentration techniques as well as permanent stains have been applied. Before accepting a report of negativity for ova and parasites as final, the physician should insist that the laboratory undertake each of these procedures. Some intestinal parasites are more readily detected in

TABLE 115-1

FLATWORM INFECTIONS

PARASITE	GEOGRAPHIC DISTRIBUTION	LIFE-CYCLE HOSTS: INTERMEDIATE (TRANSMISSION)	LIFE-CYCLE HOSTS: DEFINITIVE	DIAGNOSIS: PARASITE STAGE	DIAGNOSIS: BODY FLUID OR TISSUE	DIAGNOSIS: SEROLOGIC TESTS	DIAGNOSIS: OTHER
Tapeworms (Cestodes)							
Intestinal tapeworms							
Taenia saginata (beef tapeworm)	Worldwide	Beef	Humans	Ova, segments	Feces	—	Motile segments
Hymenolepis nana (dwarf tapeworm)	Worldwide	Grain beetles	Humans, mice[a]	Ova	Feces	—	—
Diphyllobothrium latum (fish tapeworm)	Worldwide	Copepods–fish[b]	Humans, other mammals	Ova, segments	Feces	—	Megaloblastic anemia in 1%
T. solium[c] (pork tapeworm)	Worldwide	Swine	Humans	Ova, segments	Feces	WB	Especially Mexico, Central and South America, Africa
Somatic tapeworms							
Echinococcus granulosus (hydatid disease)	Sheep-raising and hunting areas	Sheep, camels, humans, others	Dogs	Hydatid	Lung, liver	WB, EIA	Chest radiography, CT, MRI
E. multilocularis (hydatid disease)	Subarctic areas	Rodents, humans	Foxes, dogs, cats	Hydatid	Liver	—	May resemble cholangiocellular carcinoma
T. solium[c] (pork tapeworm)	Worldwide	Swine, humans	Humans	Cysticercus	Muscles, CNS	WB	CT, MRI, radiography
Flukes (Trematodes)							
Intestinal flukes							
Fasciolopsis buski	China, India	Snails–water chestnuts	Humans	Ova	Feces	—	—
Heterophyes heterophyes	Far East, India	Snails–fish	Humans	Ova	Feces	—	—
Metagonimus yokogawai	Far East, Balkans, North Africa	Snails–fish	Humans	Ova	Feces	—	—
Liver flukes							
Clonorchis sinensis	China, Southeast Asia	Snails–fish	Humans	Ova	Feces, bile	—	Recurrent bacterial cholangitis
Fasciola hepatica	Sheep-raising areas	Snails–watercress	Humans, sheep	Ova	Feces,[d] bile	EIA	Cirrhosis, portal hypertension
Lung flukes							
Paragonimus spp.	Orient, Africa, the Americas	Snails–crabs/crayfish	Humans, other mammals	Adults, ova	Lung, sputum, feces	WB, EIA	Chest radiography, CT, MRI

(*continued*)

TABLE 115-1

FLATWORM INFECTIONS (*CONTINUED*)

PARASITE	GEOGRAPHIC DISTRIBUTION	LIFE-CYCLE HOSTS: INTERMEDIATE (TRANSMISSION)	LIFE-CYCLE HOSTS: DEFINITIVE	DIAGNOSIS: PARASITE STAGE	DIAGNOSIS: BODY FLUID OR TISSUE	DIAGNOSIS: SEROLOGIC TESTS	DIAGNOSIS: OTHER
Flukes (Trematodes) (*continued*)							
Blood flukes							
Schistosoma mansoni	Africa, Central and South America, West Indies	Snails	Humans	Ova, adults	Feces	EIA, WB	Rectal snips, liver biopsy
S. haematobium	Africa	Snails	Humans	Ova, adults	Urine	WB	Liver, urine, or bladder biopsy
S. japonicum	Far East	Snails	Humans	Ova, adults	Feces	WB	Liver biopsy

[a]Larvae also can mature in intestinal villi of humans and mice.
[b]When there are two intermediate hosts, the first is separated from the second by a dash. Definitive hosts are infected by the second intermediate host.
[c]*T. solium* can cause either intestinal infections or cysticercosis. Its ova are identical to those of *T. saginata*; scolices and segments of the two species differ.
[d]Ova seldom reach the fecal stream during acute disease.
Note: CNS, central nervous system; EIA, enzyme immunoassay; WB, western blot. Serologic tests listed in Tables 115-1, 115-2, and 115-3 are available commercially or from the Centers for Disease Control and Prevention, Atlanta, GA.

TABLE 115-2

ROUNDWORM INFECTIONS

PARASITE	GEOGRAPHIC DISTRIBUTION	LIFE-CYCLE HOSTS: INTERMEDIATE (TRANSMISSION)	LIFE-CYCLE HOSTS: DEFINITIVE	DIAGNOSIS: PARASITE STAGE	DIAGNOSIS: BODY FLUID OR TISSUE	DIAGNOSIS: SEROLOGIC TESTS	DIAGNOSIS: OTHER
Intestinal Roundworms							
Enterobius vermicularis (pinworm)	Temperate and tropical zones	Fecal-oral	Humans	Ova	Perianal skin	—	"Cellophane tape" test
Trichuris trichiura (whipworm)	Temperate and tropical zones	Soil, fecal-oral	Humans	Ova	Feces	—	Rectal prolapse
Ascaris lumbricoides (roundworm of humans)	Temperate and tropical zones	Soil, fecal-oral	Humans	Ova	Feces	—	Sx of pulmonary migration
Ancylostoma duodenale (Old World hookworm)	Eurasia, Africa, Pacific	Soil to skin	Humans	Ova/larvae	Feces	—	Sx of pulmonary migration, anemia
Necator americanus (New World hookworm)	U.S., Africa, worldwide	Soil to skin	Humans	Ova/larvae	Feces	—	Sx of pulmonary migration, anemia
Strongyloides stercoralis (strongyloidiasis)	Moist tropics and subtropics	Soil to skin	Humans	Larvae	Feces, sputum, duodenal fluid	EIA	Dissemination in immunodeficiency
Capillaria philippinensis	Southeast Asia, Taiwan, Egypt	Raw fish	Birds	Ova, larvae, adults	Feces	—	Malabsorption/autoinfection, biopsy
Tissue Roundworms							
Trichinella spiralis (trichinellosis)	Worldwide	Swine/humans	Swine/humans	Larvae	Muscle	EIA	Muscle biopsy
Wuchereria bancrofti (filariasis)	Coastal areas in tropics and subtropics	Mosquitoes	Humans	Microfilariae	Blood, lymph nodes	EIA, RAPID	Nocturnal periodicity[a]

(*continued*)

TABLE 115-2

ROUNDWORM INFECTIONS (*CONTINUED*)

PARASITE	GEOGRAPHIC DISTRIBUTION	LIFE-CYCLE HOSTS: INTERMEDIATE (TRANSMISSION)	LIFE-CYCLE HOSTS: DEFINITIVE	DIAGNOSIS: PARASITE STAGE	DIAGNOSIS: BODY FLUID OR TISSUE	DIAGNOSIS: SEROLOGIC TESTS	DIAGNOSIS: OTHER
Tissue Roundworms (*continued*)							
Brugia malayi (filariasis)	Asia, Indian subcontinent	Mosquitoes	Humans	Microfilariae	Blood	EIA, RAPID	Nocturnal
Loa loa (African eye worm)	West and Central Africa	Mango flies (*Chrysops*)	Humans	Microfilariae	Blood	RAPID	May be visible in eye, diurnal
Onchocerca volvulus (river blindness)	Africa, Mexico, Central and South America	Blackflies	Humans	Adults/larvae	Skin/eye	—	Examine nodules or skin snips
Dracunculus medinensis (guinea worm)	Africa	*Cyclops*	Humans	Adults/larvae	Skin	—	May be visible in lesion
Angiostrongylus cantonensis	Southeast Asia, Pacific, Caribbean	Snails/slugs, shrimp/fish	Rats	Larvae	CSF (rarely found)	—	Eosinophilic meningitis
Larva Migrans Syndromes							
Ancylostoma braziliense (creeping eruption)	Tropical and temperate zones	Soil to skin	Dogs/cats, humans	Larvae	Skin	—	Dog and cat hookworm
Toxocara canis and *cati* (visceral larva migrans)	Tropical and temperate zones	Soil, fecal-oral	Dogs/cats, humans	Larvae	Viscera, CNS, eye	EIA	Also caused by roundworms of other species

[a]Except for infection acquired in the South Pacific, blood should be drawn at midnight.
Note: CNS, central nervous system; CSF, cerebrospinal fluid; EIA, enzyme immunoassay; RAPID, rapid immunographic assay (available at the National Institutes of Health: 301-496-5398); Sx, signs/symptoms.

TABLE 115-3

PROTOZOAL INFECTIONS

PARASITE	GEOGRAPHIC DISTRIBUTION	LIFE-CYCLE HOSTS: INTERMEDIATE (TRANSMISSION)	LIFE-CYCLE HOSTS: DEFINITIVE	DIAGNOSIS: PARASITE STAGE	DIAGNOSIS: BODY FLUID OR TISSUE	DIAGNOSIS: SEROLOGIC TESTS	DIAGNOSIS: OTHER
Intestinal Protozoans							
Entamoeba histolytica (amebiasis)	Worldwide, especially tropics	Fecal-oral	Humans	Troph, cyst	Feces, liver	EIA, antigen detection	Ultrasound, liver CT, PCR
Giardia lamblia (giardiasis)	Worldwide	Fecal-oral	Humans	Troph, cyst	Feces	Antigen detection	String test, DFA, PCR
Isospora belli	Worldwide	Fecal-oral	Humans	Oocyst	Feces	—	Acid-fast[a]
Cryptosporidium	Worldwide	Fecal-oral	Humans, other animals	Oocyst	Feces	Antigen detection	Acid-fast,[a] DFA, biopsy, PCR
Cyclospora cayetanensis	Worldwide?	Fecal-oral	Humans, other animals?	Oocyst	Feces	—	Acid-fast,[a] modified safranin, autofluorescence, biopsy, PCR

(*continued*)

TABLE 115-3

PROTOZOAL INFECTIONS (*CONTINUED*)

		LIFE-CYCLE HOSTS		DIAGNOSIS			
PARASITE	GEOGRAPHIC DISTRIBUTION	INTERMEDIATE (TRANSMISSION)	DEFINITIVE	PARASITE STAGE	BODY FLUID OR TISSUE	SEROLOGIC TESTS	OTHER
Intestinal Protozoans (*continued*)							
Microsporidia (*Enterocytozoon bieneusi, Encephalitozoon* spp.) (microsporidiosis)	Worldwide?	?	Animals, humans	Spore	Feces	—	Modified trichrome, biopsy, PCR
Free-Living Amebas							
Naegleria	Worldwide	Warm water	Humans	Troph, cyst	CNS, nares	DFA	Biopsy, nasal swab, culture
Acanthamoeba	Worldwide	Soil, water	Humans	Troph, cyst	CNS, skin, cornea	DFA	Biopsy, scrapings, culture
Balamuthia	The Americas	Soil?	Humans, other animals	Troph, cyst	Brain	DFA	Biopsy
Blood and Tissue Protozoans							
Plasmodium spp. (malaria)	Subtropics and tropics	Mosquitoes	Humans	Asexual	Blood	Limited use	PCR
Babesia microti (babesiosis)	U.S., especially New England	Ticks	Rodents, humans	Asexual	Blood	IIF	Animal spp. in asplenia, PCR
Trypanosoma rhodesiense (African sleeping sickness)	Sub-Saharan East Africa	Tsetse flies	Humans, herbivores	Tryp	Blood, CSF	IIF[b]	Also chancre, lymph nodes
T. gambiense (African sleeping sickness)	Sub-Saharan West Africa	Tsetse flies	Humans, swine	Tryp	Blood, CSF	Card agglutination,[c] IIF[b]	Also chancre, lymph nodes
T. cruzi (Chagas' disease)	Mexico to South America	Reduviid bugs (triatomes)	Humans, dogs, wild animals	Amastigote, tryp	Multiple organs/blood	IIF, EIA	Reactivation in immunosuppression
Leishmania tropica, etc.	Widespread in tropics and subtropics	Sandflies *(Phlebotomus)*	Humans, dogs, rodents	Amastigote	Skin	IFA, EIA[d]	Biopsy, scrapings, culture
L. braziliensis (mucocutaneous)	Mexico to South America	Sandflies *(Lutzomyia)*	Humans, dogs, rodents	Amastigote	Skin, mucous membranes	IFA[b], EIA	Biopsy, scrapings, culture
L. donovani (kala-azar)	Widespread in tropics and subtropics	Sandflies *(Phlebotomus)*	Humans, dogs, wild animals	Amastigote	RE system	IFA[b], EIA	Biopsy, culture, PCR
Toxoplasma gondii (toxoplasmosis)	Worldwide	Humans, other mammals	Cats	Cyst, troph	CNS, eye, muscles, other	EIA, IIF	PCR

[a]Acid-fastness is best demonstrated by auramine fluorescence or modified acid-fast stain.
[b]Contact the CDC at 770-488-7760.
[c]Card agglutination is provided to endemic countries by the World Health Organization.
[d]Limited specificity; most sensitive for *L. donovani.*
Abbreviations: CNS, central nervous system; CSF, cerebrospinal fluid; DFA, direct fluorescent antibody; EIA, enzyme immunoassay; IFA, indirect fluorescent antibody; IIF, indirect immunofluorescence; PCR, polymerase chain reaction; RE, reticuloendothelial; troph, trophozoite; tryp, trypomastigote form.

material other than feces. For example, examination of duodenal contents is sometimes necessary to detect *Giardia lamblia*, *Cryptosporidium*, and *Strongyloides* larvae. Use of the "cellophane tape" technique to detect pinworm ova on the perianal skin sometimes also reveals ova of *T. saginata* deposited perianally when the motile segments disintegrate **(Table 115-4)**.

Two routine solutions are used to make wet mounts for identification of the various life stages of helminths and protozoa: physiologic saline for trophozoites, cysts, ova, and larvae and dilute iodine solution for protozoal cysts and ova. Iodine solution must never be used to examine specimens for trophozoites because it kills the parasites and thus eliminates their characteristic motility.

The two most common concentration procedures for detecting small numbers of cysts and ova are formalin-ether sedimentation and zinc sulfate flotation. The formalin-ether technique is preferable because all parasites sediment but not all float. Slides permanently stained for trophozoites should be prepared before concentration. Additional slides stained for cysts and ova may be made from the concentrate.

In many instances, especially in the differentiation of *Entamoeba histolytica* from other amebas, identification of parasites from wet mounts or concentrates must be considered tentative. Permanently stained smears allow study of the cellular detail necessary for definitive identification. The iron-hematoxylin stain is excellent for critical work, but trichrome staining, which can be completed in 1 h, is a satisfactory alternative that also reveals parasites in specimens preserved in polyvinyl alcohol fixative. Modified acid-fast staining and fluorescent auramine microscopy are useful adjuncts for detection and identification of several intestinal protozoa, including *Cryptosporidium* and *Cyclospora*. Microsporidia, which cause chronic diarrhea in HIV-infected patients, may be missed unless a special modified trichrome stain is requested (Table 115-3).

BLOOD AND TISSUE PARASITES

Invasion of tissue by protozoa and helminths renders the choice of diagnostic techniques more difficult. For example, physicians must understand that aspiration of an amebic liver abscess rarely reveals *E. histolytica* because the trophozoites are located primarily in the abscess wall. They must remember that the urine sediment offers the best opportunity to detect *Schistosoma haematobium* in the young Ethiopian immigrant or the American traveler who returns from Africa with hematuria. Tables 115-1, 115-2, and 115-3, which offer a quick guide to the geographic distribution and anatomic locations of the major tissue parasites, should help the physician to select the appropriate body fluid or biopsy site for microscopic examination. **Tables 115-5** and **115-6** provide additional information about the identification of parasites in

TABLE 115-4

ALTERNATIVE PROCEDURES FOR LABORATORY DIAGNOSIS OF PARASITES FOUND IN FECES[a]

PARASITES AND FECAL STAGES	ALTERNATIVE DIAGNOSTIC PROCEDURES
Tapeworms (Cestodes)	
Taenia saginata ova and segments	Perianal "cellophane tape" test for ova
T. solium ova and segments	Serology; brain biopsy for neurocysticercosis
Flukes (Trematodes)	
Clonorchis (Opisthorchis) sinensis ova	Examination of bile for ova and adults in cholangitis
Fasciola hepatica ova	Examination of bile for ova and adults in cholangitis
Paragonimus ova	Serology; sputum; biopsy of lung or brain for larvae
Schistosoma ova	Serology for all; rectal snips (especially for *S. mansoni*), urine (*S. haematobium*), liver biopsy and liver ultrasound
Roundworms	
Enterobius vermicularis ova and adults	Perianal "cellophane tape" test for ova and adults
Trichuris trichiura ova	None
Ascaris lumbricoides ova and adults	Examination of sputum for larvae in lung disease
Hookworm ova and occasional larvae	Examination of sputum for larvae in lung disease
Strongyloides larvae	Duodenal aspirate or jejunal biopsy; serology; sputum or lung biopsy for filariform larvae in disseminated disease
Protozoans	
Entamoeba histolytica trophozoites and cysts	Serology; liver biopsy for trophozoites
Giardia lamblia trophozoites and cysts	Duodenal aspirate or jejunal biopsy[b]
Isospora belli oocysts	Duodenal aspirate or jejunal biopsy[b]
Cryptosporidium oocysts	Duodenal aspirate or jejunal biopsy[b]
Microsporidial spores	Duodenal aspirate or jejunal biopsy[b]

[a]Stains and concentration techniques are discussed in the text.
[b]Commercial string test is satisfactory; *Isospora* and *Cryptosporidium* are acid-fast.

TABLE 115-5

IDENTIFICATION OF PARASITES IN BLOOD AND OTHER BODY FLUIDS

BODY FLUID, PARASITE	ENRICHMENT/STAIN	CULTURE TECHNIQUE
Blood		
Plasmodium spp.	Thick and thin smears/Giemsa or Wright's	Not useful for diagnosis
Leishmania spp.	Buffy coat/Giemsa	Media available from CDC
African trypanosomes[a]	Buffy coat, anion column/wet mount and Giemsa	Mouse or rat inoculation[b]
Trypanosoma cruzi[c]	As for African species	As above and xenodiagnosis
Toxoplasma gondii	Buffy coat/Giemsa	Fibroblast cell lines
Microfilariae[d]	Filtration/wet mount and Giemsa	None
Urine		
Schistosoma haematobium	Centrifugation/wet mount	None
Microfilariae (in chyluria)	As for blood	None
Spinal Fluid		
African trypanosomes	Centrifugation, anion column/wet mount and Giemsa	As for blood
Naegleria fowleri	Centrifugation/wet mount and Giemsa or trichrome	Nonnutrient agar overlaid with *Escherichia coli*

[a]*Trypanosoma rhodesiense* and *T. gambiense*.
[b]Inject mice intraperitoneally with 0.2 mL of whole heparinized blood (0.5 mL for rats). After 5 days, check tail blood daily for trypanosomes as described above. Call the CDC (770-488-7775) for information on diagnosis and treatment.
[c]Detectable in blood by conventional techniques only during acute disease. Xenodiagnosis is successful in ~50% of patients with chronic Chagas' disease.
[d]Daytime (1000–1400 h) and nighttime (2200–0200 h) blood samples should be drawn to maximize the chance of detecting *Wuchereria* (nocturnal except for Pacific strains), *Brugia* (nocturnal), and *Loa loa* (diurnal).

samples from specific anatomic locations. The laboratory procedures for detection of parasites in other body fluids are similar to those used in the examination of feces. The physician should insist on wet mounts, concentration techniques, and permanent stains for all body fluids. The trichrome or iron-hematoxylin stain is satisfactory for all tissue helminths in body fluids other than blood, but microfilarial worms and blood protozoa are more easily visualized with Giemsa or Wright's staining.

The most common parasites detected in Giemsa-stained blood smears are the plasmodia, microfilariae, and African trypanosomes (Table 115-5). Most patients with Chagas' disease present in the chronic phase, when *Trypanosoma cruzi* is no longer microscopically detectable in blood smears. Wet mounts are sometimes more sensitive than stained smears for the detection of microfilariae and African trypanosomes because these active parasites cause noticeable movement of the erythrocytes in the microscopic field. Filtration of blood through a polycarbonate filter (pore size, 3–5 mm) facilitates the detection of microfilariae. The intracellular amastigote forms of *Leishmania* spp. and *T. cruzi* can sometimes be visualized in stained smears of peripheral blood, but aspirates of the bone marrow, liver, and spleen are the best sources for microscopic detection and culture of *Leishmania* in kala-azar and of *T. cruzi* in chronic Chagas' disease. The diagnosis of malaria and the critical distinction among the various *Plasmodium* species are made by microscopic examination of stained thick and thin blood films (Chap. 119). Detection of subpatent infection and identification of *Plasmodium* species can be confirmed by PCR. Recently, *P. knowlesi,* a simian parasite, has been identified as the cause of an increasing number of infections in Malaysian Borneo and other areas of Southeast Asia. PCR or another molecular method is required to differentiate *P. knowlesi* from *P. malariae*.

Although most tissue parasites stain with the traditional hematoxylin and eosin, surgical biopsy specimens should also be stained with appropriate special stains. The surgical pathologist who is accustomed to applying silver stains for *Pneumocystis* to induced sputum and transbronchial biopsies may need to be reminded to examine wet mounts and iron-hematoxylin–stained preparations of pulmonary specimens for helminthic ova and *E. histolytica*. The clinician should also be able to advise the surgeon and pathologist about optimal techniques for the identification of parasites in specimens obtained by certain specialized minor procedures (Table 115-6). For example, the excision of skin snips for the diagnosis of onchocerciasis, the collection of rectal snips for the diagnosis of schistosomiasis, and punch biopsy of skin lesions for the identification and culture of cutaneous and mucocutaneous species of *Leishmania* are simple procedures, but the diagnosis can be missed if the specimens are improperly obtained or processed.

TABLE 115-6

MINOR PROCEDURES FOR DIAGNOSIS OF PARASITIC INFECTIONS

PARASITE(S) AND STAGE	PROCEDURE
Onchocerca volvulus and *Mansonella streptocerca* microfilariae	*Skin snips:* Lift skin with a needle and excise ~1 mg to a depth of 0.5 mm from several sites. Weigh each sample, place it in 0.5 mL of saline for 4 h, and examine wet mounts and Giemsa stains of the saline either directly or after filtration. Count microfilariae.[a]
Loa loa adults and *O. volvulus* adults and microfilariae	*Biopsies of subcutaneous nodules:* Stain routine histopathologic sections and impression smears with Giemsa.
Trichinella spiralis larvae (and perhaps *Taenia solium* cysticerci)	*Muscle biopsies:* Excise ~1.0 g of deltoid or gastrocnemius muscle and squash between two glass slides for direct microscopic examination.
Schistosoma ova of all species, but especially *S. mansoni*	*Rectal snips:* From four areas of mucosa, take 2-mg snips, tease onto a glass slide, and flatten with a second slide before examining directly at 10×. Preparations may be fixed in alcohol or stained.
Trypanosoma gambiense and *T. rhodesiense* trypomastigotes	*Aspirate of chancre or lymph node:*[b] Aspirate center with an 18-gauge needle, place a drop on a slide, and examine for motile forms. An otherwise insufficient volume of material may be stained with Giemsa.
Acanthamoeba spp. trophozoites or cysts	*Corneal scrapings:* Have an ophthalmologist obtain a sample for immediate Giemsa staining and culture on nutrient agar overlaid with *Escherichia coli*.
Cutaneous and mucocutaneous *Leishmania* spp.	*Swabs, aspirates, or punch biopsies of skin lesions:* Obtain a specimen from the margin of a lesion for Giemsa staining of impression smears; section and culture on special media from the CDC.

[a]Counts of >100/mg are associated with a significant risk of complications.
[b]Lymph node aspiration is contraindicated in some infections and should be used judiciously.

NONSPECIFIC TESTS

Eosinophilia (>500/μL) commonly accompanies infections with most of the tissue helminths; absolute numbers of eosinophils may be high in trichinellosis and the migratory phases of filariasis **(Table 115-7)**. Intestinal helminths provoke eosinophilia only during pulmonary migration of the larval stages. Eosinophilia is not a manifestation of protozoal infections. Parasitic causes of eosinophilia in cerebrospinal fluid include nematodes (e.g., *Angiostrongylus*, *Gnathostoma*, *Toxocara*, and *Baylisascaris* species) as well as flatworms (e.g., *Taenia solium* and *Schistosoma* species).

Like the hypochromic microcytic anemia of heavy hookworm infections, other nonspecific laboratory abnormalities may suggest parasitic infection in patients with appropriate geographic and/or environmental exposures. Biochemical evidence of cirrhosis or an abnormal urine sediment in an African immigrant certainly raises the possibility of schistosomiasis, and anemia and thrombocytopenia in a febrile traveler or immigrant are among the hallmarks of malaria. CT and MRI also contribute to the diagnosis of infections with many tissue parasites and have become invaluable adjuncts in the diagnosis of neurocysticercosis and cerebral toxoplasmosis.

ANTIBODY AND ANTIGEN DETECTION

Useful antibody assays for many of the important tissue parasites are available; most of those listed in **Table 115-8** can be obtained from the Centers for Disease Control and Prevention (CDC) in Atlanta. The results of serologic tests not listed in the tables should be interpreted with caution.

The value of antibody assays is limited by several factors. For example, the preparation of thick and thin blood smears remains the procedure of choice for the diagnosis of malaria in individual patients because diagnostic titers to plasmodia develop slowly and do not differentiate species—a critical step in patient management. Filarial antigens cross-react with those from other nematodes; as in assays for antibody to most parasites, the presence of antibody in the filarial assay fails to distinguish between past and current infection. Despite these specific limitations, the restricted geographic distribution of many tropical parasites increases the diagnostic usefulness of both the presence and the absence of antibody in travelers from industrialized countries. In contrast, a large proportion of the world's population has been exposed to *Toxoplasma gondii*, and the presence of IgG antibody to *T. gondii* does not constitute proof of active disease.

TABLE 115-7

PARASITES FREQUENTLY ASSOCIATED WITH EOSINOPHILIA[a]

PARASITE	COMMENT
Tapeworms (Cestodes)	
Echinococcus granulosus	When hydatid cyst leaks
Taenia solium	During muscle encystation and in cerebrospinal fluid with neurocysticercosis
Flukes (Trematodes)	
Paragonimus spp.	Uniformly high in acute stage
Fasciola hepatica	May be high in acute stage
Clonorchis (Opisthorchis) sinensis	Variable
Schistosoma mansoni	50% of infected travelers
S. haematobium	25% of infected travelers
S. japonicum	Up to 6000/μL in acute infection
Roundworms	
Ascaris lumbricoides	During larval migration
Hookworm species	During larval migration
Strongyloides stercoralis	Profound during migration and early years of infection
Trichinella spiralis	Up to 7000/μL
Filarial species[b]	Varies but can reach 5000–8000/μL
Toxocara spp.	>3000/μL
Ancylostoma braziliense	With extensive cutaneous eruption
Gnathostoma spinigerum	In visceral larva migrans and eosinophilic meningitis
Angiostrongylus cantonensis	In eosinophilic meningitis
A. costaricensis	During larval migration in mesenteric vessels

[a]Virtually every helminth has been associated with eosinophilia. This table includes both common and uncommon parasites that frequently elicit eosinophilia during infection.
[b]*Wuchereria bancrofti, Brugia* spp., *Loa loa*, and *Onchocerca volvulus*.

TABLE 115-8

SEROLOGIC AND MOLECULAR TESTS FOR PARASITIC INFECTIONS[a]

PARASITE, INFECTION	ANTIBODY	ANTIGEN OR DNA/RNA
Tapeworms		
Echinococcosis	WB, EIA	
Cysticercosis	WB	
Flukes		
Paragonimiasis	WB, EIA[b]	
Schistosomiasis	EIA, WB	
Fascioliasis	EIA[b]	
Roundworms		
Strongyloidiasis	EIA	
Trichinellosis	EIA	
Toxocariasis	EIA	
Filariasis	EIA[c]	RAPID[c]
Protozoans		
Amebiasis	EIA	EIA,[b] RAPID,[b] PCR
Giardiasis		EIA,[b] RAPID,[b] DFA, PCR
Cryptosporidiosis		EIA,[b] DFA, RAPID,[b] PCR
Malaria (all species)	IIF[d]	RAPID, PCR
Babesiosis	IIF	PCR
Chagas' disease	IIF, EIA	PCR
Leishmaniasis	IIF, EIA	PCR[b]
Toxoplasmosis	IIF, EIA (IgM)[e]	PCR[b]
Microsporidiosis		PCR
Cyclosporiasis		PCR
Acanthamebiasis		DFA, PCR
Naegleriasis		DFA, PCR
Balmuthiasis		DFA

[a]Unless otherwise noted, all tests are available at the CDC.
[b]Research or commercial laboratories only.
[c]Available at the NIH (301-496-5398) and commercially.
[d]Of limited use for management of acute disease.
[e]Determination of infection within the last 3 months may require additional tests by a research laboratory.
Note: DFA, direct fluorescent antibody; EIA, enzyme immunoassay; IIF, indirect immunofluorescence; PCR, polymerase chain reaction; RAPID, rapid immunographic assay; WB, western blot. Most antigen and antibody parasite detection kits are available commercially. Most PCRs listed are now available at the CDC and in commercial or research laboratories. Contact Dr. Alexandre da Silva at the CDC (770-488-4072).

Fewer antibody assays are available for the diagnosis of infection with intestinal parasites. *E. histolytica* is the major exception. Sensitive, specific serologic tests are invaluable in the diagnosis of amebiasis. Commercial kits for the detection of antigen by enzyme-linked immunosorbent assay or of whole organisms by fluorescent antibody assay are now available for several protozoan parasites. A rapid test (approved by the U.S. Food and Drug Administration) for the detection of *P. falciparum* in blood is less sensitive than thick smears read by an experienced microscopist, but its use is increasing in developing countries because of its simplicity (Table 115-8).

MOLECULAR TECHNIQUES

DNA hybridization with probes that are repeated many times in the genome of a specific parasite and amplification of a specific DNA fragment by the polymerase chain reaction (PCR) have now been established as useful techniques for the diagnosis of several protozoan infections (Table 115-8). Although PCR is very sensitive, it is an adjunct to conventional techniques for parasite detection and should be requested only when microscopic and immunodiagnostic procedures fail to establish the probable diagnosis. For example, only multiple negative blood smears or the failure to identify the infecting species justifies PCR for the diagnosis or proper management of malaria. In addition to PCR of anticoagulated blood, the CDC (contact Dr. Alexandre da Silva, 770-488-4072, for details) and several commercial laboratories now perform PCRs for detection of certain specific parasites in stool samples, biopsy specimens, and bronchoalveolar lavage fluid (Table 115-8). Although PCRs are now used primarily for the detection of protozoans, active research efforts are likely to establish their feasibility for the detection of several helminths.

CHAPTER 116

AGENTS USED TO TREAT PARASITIC INFECTIONS

Thomas A. Moore

Parasitic infections afflict more than half of the world's population and impose a substantial health burden, particularly in underdeveloped nations, where they are most prevalent. The reach of some parasitic diseases, including malaria, has expanded over the past few decades as a result of factors such as deforestation, population shifts, global warming, and other climatic events. Despite major efforts at vaccine development and vector control, chemotherapy remains the single most effective means of controlling parasitic infections. Efforts to combat the spread of some diseases are hindered by the development and spread of drug resistance, the limited introduction of new antiparasitic agents, and the proliferation of counterfeit medications. However, there are good reasons to be optimistic. The past 10 years have witnessed the launch of ambitious global initiatives aimed at controlling or eliminating threats such as AIDS, tuberculosis, and malaria. Recognition of the substantial burden imposed by the "neglected" tropical diseases has generated multinational partnerships to develop and deploy effective antiparasitic agents. Vaccines against several tropical diseases are being developed, and clinical trials have begun for vaccines against schistosomiasis, hookworm, and leishmaniasis.

This chapter deals exclusively with the agents used to treat infections due to parasites. Specific treatment recommendations for the parasitic diseases of humans are listed in subsequent chapters. The pharmacology of the antiparasitic agents is discussed in great detail in Chap. 117.

Table 116-1 presents a brief overview of each agent (including some drugs that are covered in other chapters), along with its major toxicities, spectrum of activity, and safety for use during pregnancy and lactation. Many of the agents are approved by the U.S. Food and Drug Administration but are considered investigational for the treatment of certain infections; these drugs are marked accordingly in the table. In addition, drugs available only through the Centers for Disease Control and Prevention (CDC) Drug Service (telephone: 404-639-3670 or 404-639-2888; *www.cdc.gov/laboratory/drugservice/*) or only through their manufacturers (whose contact information may be available from the CDC) are specified by footnotes in the table.

TABLE 116-1

OVERVIEW OF AGENTS USED FOR THE TREATMENT OF PARASITIC INFECTIONS

DRUGS BY CLASS	PARASITIC INFECTION(S)	ADVERSE EFFECTS	MAJOR DRUG-DRUG INTERACTIONS	PREGNANCY CLASS[a]	BREAST MILK
4-Aminoquinolines					
Amodiaquine	Malaria[b]	Agranulocytosis, hepatotoxicity	No information	Not assigned	No information
Chloroquine	Malaria[b]	*Occasional:* pruritus, nausea, vomiting, headache, hair depigmentation, exfoliative dermatitis, reversible corneal opacity. *Rare:* irreversible retinal injury, nail discoloration, blood dyscrasias	Antacids and kaolin: reduced absorption of chloroquine Ampicillin: bioavailability reduced by chloroquine Cimetidine: increased serum levels of chloroquine Cyclosporine: serum levels increased by chloroquine	Not assigned[c]	Yes
8-Aminoquinolines					
Primaquine	Malaria[b]	*Frequent:* hemolysis in patients with G6PD deficiency. *Occasional*: methemoglobinemia, GI disturbances. *Rare*: CNS symptoms	Quinacrine: potentiated toxicity of primaquine	Contraindicated	No information
Tafenoquine	Malaria[b]	*Frequent:* hemolysis in patients with G6PD deficiency, mild GI upset. *Occasional*: methemoglobinemia, headaches	No information	Not assigned	No information
Aminoalcohols					
Halofantrine	Malaria[b]	*Frequent*: abdominal pain, diarrhea. *Occasional*: ECG disturbances (dose-related prolongation of QTc and PR interval), nausea, pruritus. Contraindicated in persons who have cardiac disease or who have taken mefloquine in the preceding 3 weeks	Concomitant use of agents that prolong QTc interval contraindicated	C	No information
Lumefantrine	Malaria[b]	*Occasional*: nausea, vomiting, diarrhea, abdominal pain, anorexia, headache, dizziness	No major interactions	Not assigned	No information
Aminoglycosides					
Paromomycin	Amebiasis,[b] infection with *Dientamoeba fragilis*, giardiasis, cryptosporidiosis, leishmaniasis	*Frequent*: GI disturbances (oral dosing only). *Occasional*: nephrotoxicity, ototoxicity, vestibular toxicity (parenteral dosing only)	No major interactions	Not assigned[c]	No information

(*continued*)

TABLE 116-1

OVERVIEW OF AGENTS USED FOR THE TREATMENT OF PARASITIC INFECTIONS (*CONTINUED*)

DRUGS BY CLASS	PARASITIC INFECTION(S)	ADVERSE EFFECTS	MAJOR DRUG-DRUG INTERACTIONS	PREGNANCY CLASS[a]	BREAST MILK
Amphotericin B Amphotericin B deoxycholate Amphotec (InterMune)	Leishmaniasis,[d] amebic meningoencephalitis	*Frequent*: fever, chills, hypokalemia, hypomagnesemia, nephrotoxicity. *Occasional*: vomiting, dyspnea, hypotension	Antineoplastic agents: renal toxicity, bronchospasm, hypotension Glucocorticoids, ACTH, digitalis: hypokalemia	B	No information
Amphotericin B lipid complex, ABLC (Abelcet) Amphotericin B, liposomal (AmBisome)			Zidovudine: increased myelo- and nephrotoxicity		
Antimonials	Leishmaniasis				
Pentavalent antimony[e]		*Frequent:* arthralgias/myalgias, pancreatitis, ECG changes (QT prolongation, T wave flattening or inversion)	No major interactions	Not assigned	Yes
Meglumine antimoniate		*Frequent:* arthralgias/myalgias, pancreatitis, ECG changes (QT prolongation, T wave flattening or inversion)	Antiarrhythmics and tricyclic antidepressants: increased risk of cardiotoxicity	Not assigned	No information
Artemisinin and derivatives	Malaria[f]	*Occasional:* neurotoxicity (ataxia, convulsions), nausea, vomiting, anorexia, contact dermatitis			
Arteether			No information	Not assigned	Yes[g]
Artemether			No clinically significant interactions	C	Yes[g]
Artesunate[e]			Mefloquine: levels decreased and clearance accelerated by artesunate	C	Yes[g]
Dihydroartemisinin			Mefloquine: increased absorption	Not assigned	Yes[g]
Atovaquone	Malaria,[b] babesiosis	*Frequent:* nausea, vomiting. *Occasional*: abdominal pain, headache	Plasma levels decreased by rifampin, tetracycline; bioavailability decreased by metoclopramide	C	No information

(*continued*)

TABLE 116-1

OVERVIEW OF AGENTS USED FOR THE TREATMENT OF PARASITIC INFECTIONS (*CONTINUED*)

DRUGS BY CLASS	PARASITIC INFECTION(S)	ADVERSE EFFECTS	MAJOR DRUG-DRUG INTERACTIONS	PREGNANCY CLASS[a]	BREAST MILK
Azoles Fluconazole Itraconazole Ketoconazole	Leishmaniasis	*Serious*: hepatotoxicity. *Rare*: exfoliative skin disorders, anaphylaxis	Warfarin, oral hypoglycemics, phenytoin, cyclosporine, theophylline, digoxin, dofetilide, quinidine, carbamazepine, rifabutin, busulfan, docetaxel, vinca alkaloids, pimozide, alprazolam, diazepam, midazolam, triazolam, verapamil, atorvastatin, cerivastatin, lovastatin, simvastatin, tacrolimus, sirolimus, indinavir, ritonavir, saquinavir, alfentanil, buspirone, methylprednisolone, trimetrexate: plasma levels increased by azoles Carbamazepine, phenobarbital, phenytoin, isoniazid, rifabutin, rifampin, antacids, H2-receptor antagonists, proton pump inhibitors, nevirapine: decreased plasma levels of azoles Clarithromycin, erythromycin, indinavir, ritonavir: increased plasma levels of azoles	C	Yes
Benzimidazoles Albendazole	Ascariasis, capillariasis, clonorchiasis, cutaneous larva migrans, cysticercosis,[b] echinococcosis,[b] enterobiasis, eosinophilic enterocolitis, gnathostomiasis, hookworm, lymphatic filariasis, microsporidiosis, strongyloidiasis, trichinellosis, trichostrongyliasis, trichuriasis, visceral larva migrans	*Occasional*: nausea, vomiting, abdominal pain, headache, reversible alopecia, elevated aminotransferases. *Rare*: leukopenia, rash	Dexamethasone, praziquantel: plasma level of albendazole sulfoxide increased by ~50%	C	Yes[g]

(*continued*)

TABLE 116-1

OVERVIEW OF AGENTS USED FOR THE TREATMENT OF PARASITIC INFECTIONS (*CONTINUED*)

DRUGS BY CLASS	PARASITIC INFECTION(S)	ADVERSE EFFECTS	MAJOR DRUG-DRUG INTERACTIONS	PREGNANCY CLASS[a]	BREAST MILK
Mebendazole	Ascariasis,[b] capillariasis, eosinophilic enterocolitis, enterobiasis,[b] hookworm,[b] trichinellosis, trichostrongyliasis, trichuriasis,[b] visceral larva migrans	*Occasional*: diarrhea, abdominal pain, elevated aminotransferases. *Rare*: agranulocytosis, thrombocytopenia, alopecia	Cimetidine: inhibited mebendazole metabolism	C	No information
Thiabendazole	Strongyloidiasis,[b] cutaneous larva migrans,[b] visceral larva migrans[b]	*Frequent*: anorexia, nausea, vomiting, diarrhea, headache, dizziness, asparagus-like urine odor. *Occasional*: drowsiness, giddiness, crystalluria, elevated aminotransferases, psychosis. *Rare*: hepatitis, seizures, angioneurotic edema, Stevens-Johnson syndrome, tinnitus	Theophylline: serum levels increased by thiabendazole	C	No information
Triclabendazole	Fascioliasis, paragonimiasis	*Occasional*: abdominal cramps, diarrhea, biliary colic, transient headache	No information	Not assigned	Yes
Benznidazole	Chagas' disease	*Frequent*: rash, pruritus, nausea, leukopenia, paresthesias	No major interactions	Not assigned	No information
Bithionol[e]	Fascioliasis, paragonimiasis	Diarrhea, abdominal cramps (usually mild and transient)	?	?	?
Clindamycin	Babesiosis, malaria, toxoplasmosis	*Occasional*: pseudomembranous colitis, abdominal pain, diarrhea, nausea/vomiting. *Rare*: pruritus, skin rashes	No major interactions	B	Yes[g]
Diloxanide furoate	Amebiasis	*Frequent*: flatulence. *Occasional*: nausea, vomiting, diarrhea. *Rare*: pruritus	None reported	Contraindicated	No information
Eflornithine[h] (difluoromethylornithine, DFMO)	Trypanosomiasis	*Frequent*: pancytopenia. *Occasional*: diarrhea, seizures. *Rare*: transient hearing loss	No major interactions	Contraindicated	No information
Emetine and dehydroemetine[e]	Amebiasis, fascioliasis	*Severe*: cardiotoxicity. Frequent: pain at injection site. *Occasional*: dizziness, headache, GI symptoms	None reported	X	No information

(*continued*)

TABLE 116-1

OVERVIEW OF AGENTS USED FOR THE TREATMENT OF PARASITIC INFECTIONS (*CONTINUED*)

DRUGS BY CLASS	PARASITIC INFECTION(S)	ADVERSE EFFECTS	MAJOR DRUG-DRUG INTERACTIONS	PREGNANCY CLASS[a]	BREAST MILK
Folate antagonists					
Dihydrofolate reductase inhibitors					
Pyrimethamine	Malaria,[b] isosporiasis, toxoplasmosis[b]	*Occasional*: folate deficiency. *Rare*: rash, seizures, severe skin reactions (toxic epidermal necrolysis, erythema multiforme, Stevens-Johnson syndrome)	Sulfonamides, proguanil, zidovudine: increased risk of bone marrow suppression when used concomitantly	C	Yes
Proguanil and chlorproguanil	Malaria	*Occasional*: urticaria. *Rare*: hematuria, GI disturbances	No major interactions	C	Yes
Trimethoprim	Cyclosporiasis, isosporiasis	Hyperkalemia, GI upset, mild stomatitis	Methotrexate: reduced clearance Warfarin: effect prolonged Phenytoin: hepatic metabolism increased	C	Yes
Dihydropteroate synthetase inhibitors: sulfonamides Sulfadiazine Sulfamethoxazole Sulfadoxine	Malaria,[b] toxoplasmosis[b]	*Frequent:* GI disturbances, allergic skin reactions, crystalluria. *Rare*: severe skin reactions (toxic epidermal necrolysis, erythema multiforme, Stevens-Johnson syndrome), agranulocytosis, aplastic anemia, hypersensitivity of the respiratory tract, hepatitis, interstitial nephritis, hypoglycemia, aseptic meningitis	Thiazide diuretics: increased risk of thrombocytopenia in elderly patients Warfarin: effect prolonged by sulfonamides Methotrexate: levels increased by sulfonamides Phenytoin: metabolism impaired by sulfonamides Sulfonylureas: effect prolonged by sulfonamides	B	Yes
Dihydropteroate synthetase inhibitors: sulfones					
Dapsone	Leishmaniasis, malaria, toxoplasmosis	*Frequent*: rash, anorexia. *Occasional*: hemolysis, methemoglobinemia, neuropathy, allergic dermatitis, anorexia, nausea, vomiting, tachycardia, headache, insomnia, psychosis, hepatitis. *Rare*: agranulocytosis	Rifampin: lowered plasma levels of dapsone	C	Yes

(*continued*)

TABLE 116-1

OVERVIEW OF AGENTS USED FOR THE TREATMENT OF PARASITIC INFECTIONS (*CONTINUED*)

DRUGS BY CLASS	PARASITIC INFECTION(S)	ADVERSE EFFECTS	MAJOR DRUG-DRUG INTERACTIONS	PREGNANCY CLASS[a]	BREAST MILK
Fumagillin	Microsporidiosis	*Rare*: neutropenia, thrombocytopenia	None reported	No information	No information
Furazolidone	Giardiasis	*Frequent*: nausea/vomiting, brown urine. *Occasional*: rectal itching, headache. *Rare*: hemolytic anemia, disulfiram-like reactions, MAO-inhibitor interactions	Risk of hypertensive crisis when administered for >5 days with MAO inhibitors	C	No information
Iodoquinol	Amebiasis,[b] balantidiasis, *D. fragilis* infection	*Occasional*: headache, rash, pruritus, thyrotoxicosis, nausea, vomiting, abdominal pain, diarrhea. *Rare*: optic neuritis, peripheral neuropathy, seizures, encephalopathy	No major interactions	C	No information
Ivermectin	Ascariasis, cutaneous larva migrans, gnathostomiasis, loiasis, lymphatic filariasis, onchocerciasis,[b] scabies, strongyloidiasis,[b] trichuriasis	*Occasional*: fever, pruritus, headache, myalgias. *Rare*: hypotension	No major interactions	C	Yes[g]
Levamisole	Ascariasis, hookworm	*Frequent*: GI disturbances, dizziness, headache. *Rare*: agranulocytosis, peripheral neuropathy	Alcohol: disulfiram-like effect Warfarin: prolonged prothrombin time	C	No information
Macrolides					
Azithromycin	Babesiosis	*Occasional*: nausea, vomiting, diarrhea, abdominal pain. *Rare*: angioedema, cholestatic jaundice	Cyclosporine and digoxin: levels increased by azithromycin Nelfinavir: increased levels of azithromycin	B	Yes
Spiramycin[h]	Toxoplasmosis	*Occasional*: GI disturbances, transient skin eruptions. *Rare*: thrombocytopenia, QT prolongation in an infant, cholestatic hepatitis	No major interactions	Not assigned[c]	Yes[g]
Mefloquine	Malaria[b]	*Frequent*: lightheadedness, nausea, headache. *Occasional*: confusion; nightmares; insomnia; visual disturbance; transient and clinically silent ECG abnormalities, including sinus bradycardia, sinus arrhythmia, first-degree AV block, prolongation of QTc interval, and abnormal T waves. *Rare*: psychosis, convulsions, hypotension	Administration of halofantrine <3 weeks after mefloquine use may produce fatal QTc prolongation. Mefloquine may lower plasma levels of anticonvulsants. Levels decreased and clearance accelerated by artesunate	C	Yes

(*continued*)

TABLE 116-1

OVERVIEW OF AGENTS USED FOR THE TREATMENT OF PARASITIC INFECTIONS (*CONTINUED*)

DRUGS BY CLASS	PARASITIC INFECTION(S)	ADVERSE EFFECTS	MAJOR DRUG-DRUG INTERACTIONS	PREGNANCY CLASS[a]	BREAST MILK
Melarsoprol[e]	Trypanosomiasis	*Frequent*: myocardial injury, encephalopathy, peripheral neuropathy, hypertension. *Occasional*: G6PD-induced hemolysis, erythema nodosum leprosum. *Rare*: hypotension	No major interactions	Not assigned	No information
Metrifonate	Schistosomiasis	*Frequent*: abdominal pain, nausea, vomiting, diarrhea, headache, vertigo, bronchospasm. *Rare*: cholinergic symptoms	No major interactions	B	No
Miltefosine	Leishmaniasis	*Frequent*: mild and transient (1–2 days) GI disturbances within first 2 weeks of therapy (resolve after treatment completion); motion sickness. *Occasional*: reversible elevations of creatinine and aminotransferases	No major interactions	Not assigned	No information
Niclosamide	Intestinal cestodes[b]	*Occasional*: nausea, vomiting, dizziness, pruritus	No major interactions	B	No information
Nifurtimox[e]	Chagas' disease	*Frequent*: nausea, vomiting, abdominal pain, insomnia, paresthesias, weakness, tremors. *Rare*: seizures (all are reversible and dose-related)	No major interactions	Not assigned	No information
Nitazoxanide	Cryptosporidiosis,[b] giardiasis[b]	*Occasional*: abdominal pain, diarrhea. *Rare*: vomiting, headache	No major interactions	B	No information
Nitroimidazoles					
Metronidazole	Amebiasis,[b] balantidiasis, dracunculiasis, giardiasis, trichomoniasis,[b] *D. fragilis* infection	*Frequent*: nausea, headache, anorexia, metallic aftertaste. *Occasional*: vomiting, insomnia, vertigo, paresthesias, disulfiram-like effects. *Rare*: seizures, peripheral neuropathy	Warfarin: effect enhanced by metronidazole Disulfiram: psychotic reaction Phenobarbital, phenytoin: accelerate elimination of metronidazole Lithium: serum levels elevated by metronidazole Cimetidine: prolonged half-life of metronidazole	B	Yes
Tinidazole	Amebiasis,[b] giardiasis, trichomoniasis	*Occasional*: nausea, vomiting, metallic taste	See metronidazole	C	Yes

(*continued*)

TABLE 116-1

OVERVIEW OF AGENTS USED FOR THE TREATMENT OF PARASITIC INFECTIONS (*CONTINUED*)

DRUGS BY CLASS	PARASITIC INFECTION(S)	ADVERSE EFFECTS	MAJOR DRUG-DRUG INTERACTIONS	PREGNANCY CLASS[a]	BREAST MILK
Oxamniquine	Schistosomiasis	*Occasional*: dizziness, drowsiness, headache, orange urine, elevated aminotransferases. *Rare*: seizures	No major interactions	C	No information
Paromomycin	Amebiasis,[b] *D. fragilis* infection, giardiasis, cryptosporidiosis, leishmaniasis	*Frequent*: GI disturbances (oral dosing only). *Occasional*: nephrotoxicity, ototoxicity, vestibular toxicity (parenteral dosing only)	No major interactions	Oral: B Parenteral: not assigned[c]	No information
Pentamidine isethionate	Leishmaniasis, trypanosomiasis	*Frequent*: hypotension, hypoglycemia, pancreatitis, sterile abscesses at IM injection sites, GI disturbances, reversible renal failure. *Occasional*: hepatotoxicity, cardiotoxicity, delirium. *Rare*: anaphylaxis	No major interactions	C	No information
Piperazine and derivatives					
Piperazine	Ascariasis, enterobiasis	*Occasional*: nausea, vomiting, diarrhea, abdominal pain, headache. *Rare*: neurotoxicity, seizures	None reported	C	No information
Diethylcarbamazine[e]	Lymphatic filariasis, loiasis, tropical pulmonary eosinophilia	*Frequent*: dose-related nausea, vomiting. *Rare*: fever, chills, arthralgias, headaches	None reported	Not assigned[c]	No information
Praziquantel	Clonorchiasis,[b] cysticercosis, diphyllobothriasis, hymenolepiasis, taeniasis, opisthorchiasis, intestinal trematodes, paragonimiasis, schistosomiasis[b]	*Frequent*: abdominal pain, diarrhea, dizziness, headache, malaise. *Occasional*: fever, nausea. *Rare*: pruritus, singultus	No major interactions	B	Yes
Pyrantel pamoate	Ascariasis, eosinophilic enterocolitis, enterobiasis,[b] hookworm, trichostrongyliasis	*Occasional*: GI disturbances, headache, dizziness, elevated aminotransferases	No major interactions	C	No information

(*continued*)

TABLE 116-1

OVERVIEW OF AGENTS USED FOR THE TREATMENT OF PARASITIC INFECTIONS (*CONTINUED*)

DRUGS BY CLASS	PARASITIC INFECTION(S)	ADVERSE EFFECTS	MAJOR DRUG-DRUG INTERACTIONS	PREGNANCY CLASS[a]	BREAST MILK
Quinacrine[h]	Giardiasis[b]	*Frequent*: headache, nausea, vomiting, bitter taste. *Occasional*: yellow-orange discoloration of skin, sclerae, urine; begins after 1 week of treatment and lasts up to 4 months after drug discontinuation. *Rare*: psychosis, exfoliative dermatitis, retinopathy, G6PD-induced hemolysis, exacerbation of psoriasis, disulfiram-like effects	Primaquine: toxicity potentiated by quinacrine	C	No information
Quinine and quinidine	Malaria, babesiosis	*Frequent*: cinchonism (tinnitus, high-tone deafness, headache, dysphoria, nausea, vomiting, abdominal pain, visual disturbances, postural hypotension), hyperinsulinemia resulting in life-threatening hypoglycemia. *Occasional*: deafness, hemolytic anemia, arrhythmias, hypotension due to rapid IV infusion	Carbonic-anhydrase inhibitors, thiazide diuretics: reduced renal elimination of quinidine Amiodarone, cimetidine: increased quinidine levels Nifedipine: decreased quinidine levels; quinidine slows metabolism of nifedipine Phenobarbital, phenytoin, rifampin: accelerated hepatic elimination of quinidine Verapamil: reduced hepatic clearance of quinidine Diltiazem: decreased clearance of quinidine	X	Yes[g]
Quinolones Ciprofloxacin	Cyclosporiasis, isosporiasis	*Occasional*: nausea, diarrhea, vomiting, abdominal pain/discomfort, headache, restlessness, rash. *Rare*: myalgias/arthralgias, tendon rupture, CNS symptoms (nervousness, agitation, insomnia, anxiety, nightmares or paranoia); convulsions	Probenecid: increased serum levels of ciprofloxacin Theophylline, warfarin: serum levels increased by ciprofloxacin	C	Yes

(*continued*)

TABLE 116-1

OVERVIEW OF AGENTS USED FOR THE TREATMENT OF PARASITIC INFECTIONS (*CONTINUED*)

DRUGS BY CLASS	PARASITIC INFECTION(S)	ADVERSE EFFECTS	MAJOR DRUG-DRUG INTERACTIONS	PREGNANCY CLASS[a]	BREAST MILK
Suramin[e]	Trypanosomiasis	*Frequent*: immediate: fever, urticaria, nausea, vomiting, hypotension; delayed (up to 24 h): exfoliative dermatitis, stomatitis, paresthesias, photophobia, renal dysfunction. *Occasional*: nephrotoxicity, adrenal toxicity, optic atrophy, anaphylaxis	No major interactions	Not assigned	No information
Tetracyclines	Balantidiasis, *D. fragilis* infection, malaria; lymphatic filariasis (doxycycline)	*Frequent*: GI disturbances. *Occasional*: photosensitivity dermatitis. *Rare*: exfoliative dermatitis, esophagitis, hepatotoxicity	Warfarin: effect prolonged by tetracyclines	D	Yes

[a]Based on U.S. Food and Drug Administration pregnancy categories of A–D, X.
[b]Approved by the FDA for this indication.
[c]Use in pregnancy is recommended by international organizations outside the United States.
[d]Only AmBisome has been approved by the FDA for this indication.
[e]Available through the CDC.
[f]Only artemether (in combination with lumefantrine) and artesunate have been approved by the FDA for this indication.
[g]Not believed to be harmful.
[h]Available through the manufacturer.
Abbreviations: ACTH, adrenocorticotropic hormone; AV, atrioventricular; CNS, central nervous system; ECG, electrocardiogram; G6PD, glucose 6-phosphate dehydrogenase; MAO, monoamine oxidase.

CHAPTER 117

PHARMACOLOGY OF AGENTS USED TO TREAT PARASITIC INFECTIONS

Thomas A. Moore

This chapter deals exclusively with the pharmacologic properties of the agents used to treat infections due to parasites. Specific treatment recommendations for the parasitic diseases of humans are listed in the chapters on those diseases. Information on these agents' major toxicities, spectrum of activity, and safety for use during pregnancy and lactation is presented in Chap. 116. Many of the agents discussed herein are approved by the U.S. Food and Drug Administration (FDA) but are considered investigational for the treatment of certain infections (see Table 116-1). Drugs marked in the text with an asterisk (*) are available only through the Centers for Disease Control and Prevention (CDC) Drug Service (telephone: 404-639-3670 or 404-639-2888; *www.cdc.gov/ncpdcid/dsr/*). Drugs marked with a dagger (†) are available only through their manufacturers; contact information for these manufacturers may be available from the CDC.

Albendazole

Like all benzimidazoles, albendazole acts by selectively binding to free β-tubulin in nematodes, inhibiting the polymerization of tubulin and the microtubule-dependent uptake of glucose. Irreversible damage occurs in gastrointestinal (GI) cells of the nematodes, resulting in starvation, death, and expulsion by the host. While highly injurious to nematodes, this fundamental disruption of cellular metabolism also offers treatment for a wide range of parasitic diseases.

Albendazole is poorly absorbed from the GI tract. Administration with a fatty meal increases its absorption by two- to sixfold. Poor absorption may be advantageous for the treatment of intestinal helminths, but successful treatment of tissue helminth infections (e.g., hydatid disease and neurocysticercosis) requires that a sufficient amount of active drug reach the site of infection. The metabolite albendazole sulfoxide is responsible for the drug's therapeutic effect outside the gut lumen. Albendazole sulfoxide crosses the blood-brain barrier, reaching a level significantly higher than that achieved in plasma. The high concentrations of albendazole sulfoxide attained in cerebrospinal fluid (CSF) probably explain the efficacy of albendazole in the treatment of neurocysticercosis.

Albendazole is extensively metabolized in the liver, but there are few data regarding the drug's use in patients with hepatic disease. Single-dose albendazole therapy in humans is largely without side effects (overall frequency, ≤1%). More prolonged courses (e.g., as administered for cystic and alveolar echinococcal disease) have been associated with liver function abnormalities and bone marrow toxicity. Thus, when prolonged use is anticipated, the drug should be administered in treatment cycles of 28 days interrupted by 14 days off therapy. Prolonged therapy with full-dose albendazole (800 mg/d) should be approached cautiously in patients also receiving drugs with known effects on the cytochrome P450 system.

Amodiaquine

Amodiaquine has been widely used in the treatment of malaria for >40 years. Like chloroquine (the other major 4-aminoquinoline), amodiaquine is now of limited use because of the spread of resistance. Amodiaquine interferes with hemozoin formation through complexation with heme. Although rapidly absorbed, amodiaquine behaves as a prodrug after oral administration, with the principal plasma metabolite monodesethylamodiaquine as the predominant antimalarial agent. Amodiaquine and its metabolites are all excreted in urine, but there are no recommendations concerning dosage adjustment in patients with impaired renal function. Severe adverse events can occur, albeit rarely (1 case in 2000 treatment courses), with amodiaquine administration. Agranulocytosis and hepatotoxicity can develop with repeated use; therefore, this drug should not be used for prophylaxis. Despite widespread resistance, amodiaquine has been shown to be effective in some areas when combined with other antimalarial drugs. Its use with artesunate in a fixed-dose combination with a soluble formulation creates an antimalarial specifically designed for children. Amodiaquine is not available in the United States.

Amphotericin B

See Table 116-1 and Chap. 105.

Antimonials*

Despite associated adverse reactions and the need for prolonged parenteral treatment, the pentavalent antimonial compounds (designated Sb^v) have remained the first-line therapy for all forms of leishmaniasis throughout the world, primarily because they are affordable, are effective, and have survived the test of time. Although they have been used for almost 100 years, their mechanism of action against *Leishmania* species has only recently come to light. Pentavalent antimonials are active only after bioreduction to the trivalent Sb(III) form. This form inhibits trypanothione reductase, a critical enzyme involved in the oxidative stress management of *Leishmania* species. The fact that *Leishmania* species use trypanothione rather than glutathione (which is used by mammalian cells) may explain the parasite-specific activity of antimonials. The drugs are taken up by the reticuloendothelial system, and their activity against *Leishmania* species may be enhanced by this localization. Sodium stibogluconate is the only pentavalent antimonial available in the United States; meglumine antimoniate is principally used in francophone countries.

Resistance is a major problem in some areas. Although low-level unresponsiveness to Sb^v was identified in India in the 1970s, incremental increases in both the recommended daily dosage (to 20 mg/kg) and the duration of treatment (to 28 days) satisfactorily compensated for the growing resistance until around 1990. There has since been a steady erosion in the capacity of Sb^v to induce long-term cure in patients with kala-azar who live in eastern India. Foremost among the many factors that have probably contributed to this failure is the provision of suboptimal treatment for years, which led to the development of drug resistance among parasites. Coinfection with HIV impairs the treatment response.

Sodium stibogluconate is available in aqueous solution and is administered parenterally. Antimony appears to have two elimination phases. When administered IV, the mean half-life of the first phase is <2 h; the mean half-life of the terminal elimination phase is nearly 36 h. This slower phase may be due to conversion of pentavalent antimony to a trivalent form that is the likely cause of the side effects often seen with prolonged therapy.

Artemisinin derivatives*

Artesunate, artemether, arteether, and the parent compound artemisinin are sesquiterpene lactones derived

from the wormwood plant *Artemisia annua*. These agents are at least tenfold more potent in vivo than other antimalarial drugs and presently show no cross-resistance with known antimalarial drugs; thus, they have become first-line agents for the treatment of severe falciparum malaria. The artemisinin compounds are rapidly effective against the asexual blood forms of *Plasmodium* species but are not active against intrahepatic forms. Artemisinin and its derivatives are highly lipid soluble and readily cross both host and parasite cell membranes. One factor that explains the drugs' highly selective toxicity against malaria is that parasitized erythrocytes concentrate artemisinin and its derivatives to concentrations one hundredfold higher than those in uninfected erythrocytes. The antimalarial effect of these agents results primarily from dihydroartemisinin, a compound to which artemether and artesunate are both converted. In the presence of heme or molecular iron, the endoperoxide moiety of dihydroartemisinin decomposes, generating free radicals and other metabolites that damage parasite proteins. The compounds are available for oral, rectal, IV, or IM administration, depending on the derivative. In the United States, IV artesunate is available for the treatment of severe, quinidine-unresponsive malaria through the CDC malaria hotline (770-488-7788, M-F, 0800-1630 EST; 770-488-7100 after hours). Artemisinin and its derivatives are cleared rapidly from the circulation. Their short half-lives limit their value for prophylaxis and monotherapy. These agents should be used only in combination with another, longer-acting agent (e.g., artesunate-mefloquine, dihydroartemisinin-piperaquine). A combined formulation of artemether and lumefantrine is now available for the treatment of acute uncomplicated falciparum malaria acquired in areas where *Plasmodium falciparum* is resistant to chloroquine and antifolates.

Atovaquone

Atovaquone is a hydroxynaphthoquinone that exerts broad-spectrum antiprotozoal activity via selective inhibition of parasite mitochondrial electron transport. This agent exhibits potent activity against toxoplasmosis and babesiosis when used with pyrimethamine and azithromycin, respectively. Atovaquone possesses a novel mode of action against *Plasmodium* species, inhibiting the electron transport system at the level of the cytochrome bc1 complex. The drug is active against both the erythrocytic and the exoerythrocytic stages of *Plasmodium* species; however, because it does not eradicate hypnozoites from the liver, patients with *Plasmodium vivax* or *Plasmodium ovale* infections must be given radical prophylaxis.

Malarone is a fixed-dose combination of atovaquone and proguanil used for malaria prophylaxis as well as for the treatment of acute, uncomplicated *P. falciparum* malaria. Malarone has been shown to be effective in regions with multidrug-resistant *P. falciparum*. Resistance to atovaquone has yet to be reported.

The bioavailability of atovaquone varies considerably. Absorption after a single oral dose is slow, increases two- to threefold with a fatty meal, and is dose-limited above 750 mg. The elimination half-life is increased in patients with moderate hepatic impairment. Because of the potential for drug accumulation, the use of atovaquone is generally contraindicated in persons with a creatinine clearance rate <30 mL/min. No dosage adjustments are needed in patients with mild to moderate renal impairment.

Azithromycin

See Table 116-1 and Chap. 36.

Azoles

See Table 116-1 and Chap. 105.

Benznidazole

This oral nitroimidazole derivative is used to treat Chagas' disease, with cure rates of 80–90% recorded in acute infections. Benznidazole is believed to exert its trypanocidal effects by generating oxygen radicals to which the parasites are more sensitive than mammalian cells because of a relative deficiency in antioxidant enzymes. Benznidazole also appears to alter the balance between pro- and anti-inflammatory mediators by downregulating the synthesis of nitrite, interleukin (IL) 6, and IL-10 in macrophages. Benznidazole is highly lipophilic and readily absorbed. The drug is extensively metabolized; only 5% of the dose is excreted unchanged in the urine. Benznidazole is well tolerated; adverse effects are rare and usually manifest as gastrointestinal upset or pruritic rash.

Bithionol*

Bithionol is a chlorinated bisphenol with activity against trematodes. *Fasciola hepatica* uses fumarate reduction coupled to rhodoquinone for anaerobic energy metabolism. Bithionol competitively inhibits electron transfer to fumarate by rhodoquinone; the result is impaired anaerobic energy metabolism and trematode death. Bithionol is parasite specific for two reasons: (1) fumarate reductase catalyzes the reverse of the reaction of mammalian succinic dehydrogenase in the Krebs cycle, and (2) the rhodoquinone respiratory chain link is unique to the parasite. In the mammalian respiratory chain, the quinone electron carrier is ubiquinone. Bithionol is readily absorbed from the GI tract. It is no longer produced, but limited supplies are available from the CDC.

Chloroquine

This 4-aminoquinoline has marked, rapid schizonticidal and gametocidal activity against blood forms of *P. ovale* and *Plasmodium malariae* and against susceptible strains of *P. vivax* and *P. falciparum*. It is not active against intrahepatic forms (*P. vivax* and *P. ovale*). Parasitized erythrocytes accumulate chloroquine in significantly greater concentrations than do normal erythrocytes. Chloroquine, a weak

base, concentrates in the food vacuoles of intraerythrocytic parasites because of a relative pH gradient between the extracellular space and the acidic food vacuole. Once it enters the acidic food vacuole, chloroquine is rapidly converted to a membrane-impermeable protonated form and is trapped. Continued accumulation of chloroquine in the parasite's acidic food vacuoles results in drug levels that are 600-fold higher at this site than in plasma. The high accumulation of chloroquine results in an increase in pH within the food vacuole to a level above that required for the acid proteases' optimal activity, inhibiting parasite heme polymerase; as a result, the parasite is effectively killed with its own metabolic waste. Compared with susceptible strains, chloroquine-resistant plasmodia transport chloroquine out of intraparasitic compartments more rapidly and maintain lower chloroquine concentrations in their acid vesicles. Hydroxychloroquine, a congener of chloroquine, is equivalent to chloroquine in its antimalarial efficacy but is preferred to chloroquine for the treatment of autoimmune disorders because it produces less ocular toxicity when used in high doses.

Chloroquine is well absorbed. However, because it exhibits extensive tissue binding, a loading dose is required to yield effective plasma concentrations. A therapeutic drug level in plasma is reached 2–3 h after oral administration (the preferred route). Chloroquine can be administered IV, but excessively rapid parenteral administration can result in seizures and death from cardiovascular collapse. The mean half-life of chloroquine is 4 days, but the rate of excretion decreases as plasma levels decline, making once-weekly administration possible for prophylaxis in areas with sensitive strains. About one-half of the parent drug is excreted in urine, but the dose should not be reduced for persons with acute malaria and renal insufficiency.

Ciprofloxacin

See Table 116-1 and Chap. 36.

Clindamycin

See Table 116-1 and Chap. 36.

Dapsone

See Table 116-1 and Chap. 73.

Dehydroemetine

Emetine is an alkaloid derived from ipecac; dehydroemetine is synthetically derived from emetine and is considered less toxic. Both agents are active against *Entamoeba histolytica* and appear to work by blocking peptide elongation and thus inhibiting protein synthesis. Emetine is rapidly absorbed after parenteral administration, rapidly distributed throughout the body, and slowly excreted in the urine in unchanged form. Both agents are contraindicated in patients with renal disease.

Diethylcarbamazine*

A derivative of the antihelminthic agent piperazine with a long history of successful use, diethylcarbamazine (DEC) remains the treatment of choice for lymphatic filariasis and loiasis and has also been used for visceral larva migrans. While piperazine itself has no antifilarial activity, the piperazine ring of DEC is essential for the drug's activity. DEC's mechanism of action remains to be fully defined. Proposed mechanisms include immobilization due to inhibition of parasite cholinergic muscle receptors, disruption of microtubule formation, and alteration of helminthic surface membranes resulting in enhanced killing by the host's immune system. DEC enhances adherence properties of eosinophils. The development of resistance under drug pressure (i.e., a progressive decrease in efficacy when the drug is used widely in human populations) has not been observed, although DEC has variable effects when administered to persons with filariasis. Monthly administration provides effective prophylaxis against both bancroftian filariasis and loiasis.

DEC is well absorbed after oral administration, with peak plasma concentrations reached within 1–2 h. No parenteral form is available. The drug is eliminated largely by renal excretion, with <5% found in feces. If more than one dose is to be administered to an individual with renal dysfunction, the dose should be reduced commensurate with the reduction in creatinine clearance rate. Alkalinization of the urine prevents renal excretion and increases the half-life of DEC. Use in patients with onchocerciasis can precipitate a Mazzotti reaction, with pruritus, fever, and arthralgias. Like other piperazines, DEC is active against *Ascaris* species. Patients co-infected with this nematode may expel live worms after treatment.

Diloxanide furoate

Diloxanide furoate, a substituted acetanilide, is a luminally active agent used to eradicate the cysts of *E. histolytica*. After ingestion, diloxanide furoate is hydrolyzed by enzymes in the lumen or mucosa of the intestine, releasing furoic acid and the ester diloxanide; the latter acts directly as an amebicide.

Diloxanide furoate is given alone to asymptomatic cyst passers. For patients with active amebic infections, diloxanide is generally administered in combination with a 5-nitroimidazole such as metronidazole or tinidazole. Diloxanide furoate is rapidly absorbed after oral administration. When coadministered with a 5-nitroimidazole, only diloxanide appears in the systemic circulation; levels peak within 1 h and disappear within 6 h. About 90% of an oral dose is excreted in the urine within 48 h, chiefly as the glucuronide metabolite. Diloxanide furoate is contraindicated in pregnant and breast-feeding women and in children <2 years of age.

Eflornithine†

Eflornithine (difluoromethylornithine, or DFMO) is a fluorinated analogue of the amino acid ornithine.

Although originally designed as an antineoplastic agent, eflornithine has proven effective against some trypanosomatids. At one point, the production of this effective agent ceased despite the increasing incidence of human African trypanosomiasis; however, production resumed after eflornithine was discovered to be an effective cosmetic depilatory agent.

Eflornithine has specific activity against all stages of infection with *Trypanosoma brucei gambiense*; however, it is inactive against *T. b. rhodesiense*. The drug acts as an irreversible suicide inhibitor of ornithine decarboxylase, the first enzyme in the biosynthesis of the polyamines putrescine and spermidine. Polyamines are essential for the synthesis of trypanothione, an enzyme required for the maintenance of intracellular thiols in the correct redox state and for the removal of reactive oxygen metabolites. However, polyamines are also essential for cell division in eukaryotes, and ornithine decarboxylase is similar in trypanosomes and mammals. The selective antiparasitic activity of eflornithine is partly explained by the structure of the trypanosomal enzyme, which lacks a 36-amino-acid C-terminal sequence found on mammalian ornithine decarboxylase. This difference results in a lower turnover of ornithine decarboxylase and a more rapid decrease of polyamines in trypanosomes than in the mammalian host. The diminished effectiveness of eflornithine against *T. b. rhodesiense* appears to be due to the parasite's ability to replace the inhibited enzyme more rapidly than *T. b. gambiense*.

Eflornithine is less toxic but more costly than conventional therapy. It can be administered IV or PO. The dose should be reduced in renal failure. Eflornithine readily crosses the blood-brain barrier; CSF levels are highest in persons with the most severe central nervous system (CNS) involvement.

Fumagillin†

Fumagillin is a water-insoluble antibiotic that is derived from the fungus *Aspergillus fumigatus* and is active against microsporidia. This drug is effective when used topically to treat ocular infections due to *Encephalitozoon* species. When given systemically, fumagillin was effective but caused thrombocytopenia in all recipients in the second week of treatment; this side effect was readily reversed when administration of the drug was stopped. The mechanisms by which fumagillin inhibits microsporidial replication are poorly understood, although the drug may inhibit methionine aminopeptidase 2 by irreversibly blocking the active site.

Furazolidone

This nitrofuran derivative is an effective alternative agent for the treatment of giardiasis and also exhibits activity against *Isospora belli*. Since it is the only agent active against *Giardia* that is available in liquid form, it is often used to treat young children. Furazolidone undergoes reductive activation in *Giardia lamblia* trophozoites—an event that, unlike the reductive activation of metronidazole, involves an NADH oxidase. The killing effect correlates with the toxicity of reduced products, which damage important cellular components, including DNA. Although furazolidone had been thought to be largely unabsorbed when administered orally, the occurrence of systemic adverse reactions indicates that this is not the case. More than 65% of the drug dose can be recovered from the urine as colored metabolites. Omeprazole reduces the oral bioavailability of furazolidone.

Furazolidone is a monoamine oxidase (MAO) inhibitor; thus caution should be used in its concomitant administration with other drugs (especially indirectly acting sympathomimetic amines) and in the consumption of food and drink containing tyramine during treatment. However, hypertensive crises have not been reported in patients receiving furazolidone, and it has been suggested that—since furazolidone inhibits MAOs gradually over several days—the risks are small if treatment is limited to a 5-day course. Because hemolytic anemia can occur in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency and glutathione instability, furazolidone treatment is contraindicated in mothers who are breast-feeding and in neonates.

Halofantrine

This 9-phenanthrenemethanol is one of three classes of arylaminoalcohols first identified as potential antimalarial agents by the World War II Malaria Chemotherapy Program. Its activity is believed to be similar to that of chloroquine, although it is an oral alternative for the treatment of malaria due to chloroquine-resistant *P. falciparum*. Although the mechanism of action is poorly understood, halofantrine is thought to share mechanism(s) with the 4-aminoquinolines, forming a complex with ferriprotoporphyrin IX and interfering with the degradation of hemoglobin.

Halofantrine exhibits erratic bioavailability, but its absorption is significantly enhanced when it is taken with a fatty meal. The elimination half-life of halofantrine is 1–2 days; it is excreted mainly in feces. Halofantrine is metabolized into *N*-debutyl-halofantrine by the cytochrome P450 enzyme CYP3A4. Grapefruit juice should be avoided during treatment because it increases both halofantrine's bioavailability and halofantrine-induced QT interval prolongation by inhibiting CYP3A4 at the enterocyte level.

Iodoquinol

Iodoquinol (diiodohydroxyquin), a hydroxyquinoline, is an effective luminal agent for the treatment of amebiasis, balantidiasis, and infection with *Dientamoeba fragilis*. Its mechanism of action is unknown. It is poorly absorbed. Because the drug contains 64% organically bound iodine, it should be used with caution in patients with thyroid disease. Iodine dermatitis occurs occasionally during iodoquinol treatment. Protein-bound serum iodine levels may be increased during treatment and can interfere with certain tests of thyroid function. These effects may persist for as long as

6 months after discontinuation of therapy. Iodoquinol is contraindicated in patients with liver disease. Most serious are the reactions related to prolonged high-dose therapy (optic neuritis, peripheral neuropathy), which should not occur if the recommended dosage regimens are followed.

Ivermectin

Ivermectin (22,23-dihydroavermectin) is a derivative of the macrocyclic lactone avermectin produced by the soil-dwelling actinomycete *Streptomyces avermitilis*. Ivermectin is active at low doses against a wide range of helminths and ectoparasites. It is the drug of choice for the treatment of onchocerciasis, strongyloidiasis, cutaneous larva migrans, and scabies. Ivermectin is highly active against microfilariae of the lymphatic filariases but has no macrofilaricidal activity. When ivermectin is used in combination with other agents such as DEC or albendazole for treatment of lymphatic filariasis, synergistic activity is seen. While active against the intestinal helminths *Ascaris lumbricoides* and *Enterobius vermicularis*, ivermectin is only variably effective in trichuriasis and is ineffective against hookworms. Widespread use of ivermectin for treatment of intestinal nematode infections in sheep and goats has led to the emergence of drug resistance in veterinary practice; this development may portend problems in human medical use.

Data suggest that ivermectin acts by opening the neuromuscular membrane-associated, glutamate-dependent chloride channels. The influx of chloride ions results in hyperpolarization and muscle paralysis—particularly of the nematode pharynx, with consequent blockage of the oral ingestion of nutrients. Because these chloride channels are present only in invertebrates, the paralysis is seen only in the parasite.

Ivermectin is available for administration to humans only as an oral formulation. The drug is highly protein bound; it is almost completely excreted in feces. Both food and beer increase the bioavailability of ivermectin significantly. Ivermectin is distributed widely throughout the body; animal studies indicate that it accumulates at the highest concentration in adipose tissue and liver, with little accumulation in the brain. Few data exist to guide therapy in hosts with conditions that may influence drug pharmacokinetics.

Ivermectin is generally administered as a single dose of 150–200 μg/kg. In the absence of parasitic infection, the adverse effects of ivermectin in therapeutic doses are minimal. Adverse effects in patients with filarial infections include fever, myalgia, malaise, lightheadedness, and (occasionally) postural hypotension. The severity of such side effects is related to the intensity of parasite infection, with more symptoms in individuals with a heavy parasite burden. In onchocerciasis, skin edema, pruritus, and mild eye irritation may also occur. The adverse effects are generally self-limiting and only occasionally require symptom-based treatment with antipyretics or antihistamines. More severe complications of ivermectin therapy for onchocerciasis include encephalopathy in patients heavily infected with *Loa loa*.

Lumefantrine

Lumefantrine (benflumetol), a fluorene arylaminoalcohol derivative synthesized in the 1970s by the Chinese Academy of Military Medical Sciences (Beijing), has marked blood schizonticidal activity against a wide range of plasmodia. This agent conforms structurally and in mode of action to other arylaminoalcohols (quinine, mefloquine, and halofantrine). Lumefantrine exerts its antimalarial effect as a consequence of its interaction with heme, a degradation product of hemoglobin metabolism. Although its antimalarial activity is slower than that of the artemisinin-based drugs, the recrudescence rate with the recommended lumefantrine regimen is lower. The pharmacokinetic properties of lumefantrine are reminiscent of those of halofantrine, with variable oral bioavailability, considerable augmentation of oral bioavailability by concomitant fat intake, and a terminal elimination half-life of ~4–5 days in patients with malaria.

Artemether and lumefantrine have synergistic activity, and clinical studies of several hundred patients in China show the combination to be safe and well tolerated. The combined formulation of artemether and lumefantrine has been developed for the treatment of falciparum malaria in areas where *P. falciparum* is resistant to chloroquine and antifolates. This combination has now been approved by the FDA.

Mebendazole

This benzimidazole is a broad-spectrum antiparasitic agent widely used to treat intestinal helminthiases. Its mechanism of action is similar to that of albendazole; however, it is a more potent inhibitor of parasite malic dehydrogenase and exhibits a more specific and selective effect against intestinal nematodes than the other benzimidazoles.

Mebendazole is available only in oral form but is poorly absorbed from the GI tract; only 5–10% of a standard dose is measurable in plasma. The proportion absorbed from the GI tract is extensively metabolized in the liver. Metabolites appear in the urine and bile; impaired liver or biliary function results in higher plasma mebendazole levels in treated patients. No dose reduction is warranted in patients with renal function impairment. Because mebendazole is poorly absorbed, its incidence of side effects is low. Transient abdominal pain and diarrhea sometimes occur, usually in persons with massive parasite burdens.

Mefloquine

Mefloquine is the preferred drug for prophylaxis of chloroquine-resistant malaria; high doses can be used for treatment. Despite the development of drug-resistant strains of *P. falciparum* in parts of Africa and Southeast Asia, mefloquine is an effective drug throughout most of the world. Cross-resistance of mefloquine with halofantrine and with quinine has been documented in limited areas. Like quinine and chloroquine, this quinoline is active only against the asexual erythrocytic stages of

malarial parasites. Unlike quinine, however, mefloquine has a relatively poor affinity for DNA and, as a result, does not inhibit the synthesis of parasitic nucleic acids and proteins. Although both mefloquine and chloroquine inhibit hemozoin formation and heme degradation, mefloquine differs in that it forms a complex with heme that may be toxic to the parasite.

Mefloquine HCl is poorly water soluble and intensely irritating when given parenterally; thus it is available only in tablet form. Its absorption is adversely affected by vomiting and diarrhea but is significantly enhanced when the drug is administered with or after food. About 98% of the drug binds to protein. Mefloquine is excreted mainly in the bile and feces; therefore, no dose adjustment is needed in persons with renal insufficiency. The drug and its main metabolite are not appreciably removed by hemodialysis. No special chemoprophylactic dosage adjustments are indicated for the achievement of plasma concentrations in dialysis patients that are similar to those in healthy persons. Pharmacokinetic differences have been detected among various ethnic populations. In practice, however, these distinctions are of minor importance compared with host immune status and parasite sensitivity. In patients with impaired liver function, the elimination of mefloquine may be prolonged, leading to higher plasma levels.

Mefloquine should be used with caution by individuals participating in activities requiring alertness and fine-motor coordination. If the drug is to be administered for a prolonged period, periodic evaluations are recommended, including liver function tests and ophthalmic examinations. Sleep abnormalities (insomnia, abnormal dreams) have occasionally been reported. Psychosis and seizures occur rarely; mefloquine should not be prescribed to patients with neuropsychiatric conditions, including depression, generalized anxiety disorder, psychosis, schizophrenia, and seizure disorder. If acute anxiety, depression, restlessness, or confusion develops during prophylaxis, these psychiatric symptoms may be considered prodromal to a more serious event, and the drug should be discontinued.

Concomitant use of quinine, quinidine, or drugs producing β-adrenergic blockade may cause significant electrocardiographic abnormalities or cardiac arrest. Halofantrine must not be given simultaneously with or <3 weeks after mefloquine because a potentially fatal prolongation of the QTc interval on electrocardiography may occur. No data exist on mefloquine use after halofantrine use. Administration of mefloquine with quinine or chloroquine may increase the risk of convulsions. Mefloquine may lower plasma levels of anticonvulsants. Caution should be exercised with regard to concomitant antiretroviral therapy, since mefloquine has been shown to exert variable effects on ritonavir pharmacokinetics that are not explained by hepatic CYP3A4 activity or ritonavir protein binding. Vaccinations with attenuated live bacteria should be completed at least 3 days before the first dose of mefloquine.

Women of childbearing age who are traveling to areas where malaria is endemic should be warned against becoming pregnant and encouraged to practice contraception during malaria prophylaxis with mefloquine and for up to 3 months thereafter. However, in the case of unplanned pregnancy, use of mefloquine is not considered an indication for pregnancy termination.

*Melarsoprol**

Melarsoprol has been used since 1949 for the treatment of human African trypanosomiasis. This trivalent arsenical compound is indicated for the treatment of African trypanosomiasis with neurologic involvement and for the treatment of early disease that is resistant to suramin or pentamidine. Melarsoprol, like other drugs containing heavy metals, interacts with thiol groups of several different proteins; however, its antiparasitic effects appear to be more specific. Trypanothione reductase is a key enzyme involved in the oxidative stress management of both *Trypanosoma* and *Leishmania* species, helping to maintain an intracellular reducing environment by reduction of disulfide trypanothione to its dithiol derivative dihydrotrypanothione. Melarsoprol sequesters dihydrotrypanothione, depriving the parasite of its main sulfhydryl antioxidant, and inhibits trypanothione reductase, depriving the parasite of the essential enzyme system that is responsible for keeping trypanothione reduced. These effects are synergistic. The selectivity of arsenical action against trypanosomes is due at least in part to the greater melarsoprol affinity of reduced trypanothione than of other monothiols (e.g., cysteine) on which the mammalian host depends for maintenance of high thiol levels. Melarsoprol enters the parasite via an adenosine transporter; drug-resistant strains lack this transport system.

Melarsoprol is always administered IV. A small but therapeutically significant amount of the drug enters the CSF. The compound is excreted rapidly, with ~80% of the arsenic found in feces.

Melarsoprol is highly toxic. The most serious adverse reaction is reactive encephalopathy, which affects 6% of treated individuals and usually develops within 4 days of the start of therapy, with an average case-fatality rate of 50%. Glucocorticoids are administered with melarsoprol to prevent this development. Because melarsoprol is intensely irritating, care must be taken to avoid infiltration of the drug.

Metrifonate

Metrifonate has selective activity against *Schistosoma haematobium*. This organophosphorous compound is a prodrug that is converted nonenzymatically to dichlorvos (2,2-dichlorovinyl dimethylphosphate, DDVP), a highly active chemical that irreversibly inhibits the acetylcholinesterase enzyme. Schistosomal cholinesterase is more susceptible to dichlorvos than is the corresponding human enzyme. The exact mechanism of action of metrifonate is uncertain, but the drug is believed to inhibit tegumental acetylcholine receptors that mediate glucose transport.

Metrifonate is administered in a series of three doses at 2-week intervals. After a single oral dose, metrifonate produces a 95% decrease in plasma cholinesterase activity within 6 h, with a fairly rapid return to normal. However, 2.5 months are required for erythrocyte cholinesterase levels to return to normal. Treated persons should not be exposed to neuromuscular blocking agents or organophosphate insecticides for at least 48 h after treatment.

Metronidazole and other nitroimidazoles

See Table 116-1 and Chap. 36.

Miltefosine

In the early 1990s, miltefosine (hexadecylphosphocholine), originally developed as an antineoplastic agent, was discovered to have significant antiproliferative activity against *Leishmania* species, *Trypanosoma cruzi*, and *T. brucei* parasites in vitro and in experimental animal models. Miltefosine is the first oral drug that has proved to be highly effective and comparable to amphotericin B against visceral leishmaniasis in India, where antimonial-resistant cases are prevalent. Miltefosine is also effective in previously untreated visceral infections. Cure rates in cutaneous leishmaniasis are comparable to those obtained with antimony.

The activity of miltefosine is attributed to interaction with cell signal transduction pathways and inhibition of phospholipid and sterol biosynthesis. Resistance to miltefosine has not been observed clinically. The drug is readily absorbed from the GI tract, is widely distributed, and accumulates in several tissues. The efficacy of a 28-day treatment course in Indian visceral leishmaniasis is equivalent to that of amphotericin B therapy; however, it appears that a shortened course of 21 days may be equally efficacious.

General recommendations for the use of miltefosine are limited by the exclusion of specific groups from the published clinical trials: persons <12 or >65 years of age, persons with the most advanced disease, breast-feeding women, HIV-infected patients, and individuals with significant renal or hepatic insufficiency.

Niclosamide

Niclosamide is active against a wide variety of adult tapeworms but not against tissue cestodes. It is also a molluscicide and is used in snail-control programs. The drug uncouples oxidative phosphorylation in parasite mitochondria, thereby blocking the uptake of glucose by the intestinal tapeworm and resulting in the parasite's death. Niclosamide rapidly causes spastic paralysis of intestinal cestodes in vitro. Its use is limited by its side effects, the necessarily long duration of therapy, the recommended use of purgatives, and—most important—limited availability (i.e., on a named-patient basis from the manufacturer).

Niclosamide is poorly absorbed. Tablets are given on an empty stomach in the morning after a liquid meal the night before, and this dose is followed by another 1 h later. For treatment of hymenolepiasis, the drug is administered for 7 days. A second course is often prescribed. The scolex and proximal segments of the tapeworms are killed on contact with niclosamide and may be digested in the gut. However, disintegration of the adult tapeworm results in the release of viable ova, which theoretically can result in autoinfection. Although fears of the development of cysticercosis in patients with *Taenia solium* infections have proved unfounded, it is still recommended that a brisk purgative be given 2 h after the first dose.

Nifurtimox*

This nitrofuran compound is an inexpensive and effective oral agent for the treatment of acute Chagas' disease. Trypanosomes lack catalase and have very low levels of peroxidase; as a result, they are very vulnerable to by-products of oxygen reduction. When nifurtimox is reduced in the trypanosome, a nitro anion radical is formed and undergoes autooxidation, resulting in the generation of the superoxide anion O_2^-, hydrogen peroxide (H_2O_2), hydroperoxyl radical (HO_2), and other highly reactive and cytotoxic molecules. Despite the abundance of catalases, peroxidases, and superoxide dismutases that neutralize these destructive radicals in mammalian cells, nifurtimox has a poor therapeutic index. Prolonged use is required, but the course may have to be interrupted because of drug toxicity, which develops in 40–70% of recipients. Nifurtimox is well absorbed and undergoes rapid and extensive biotransformation; <0.5% of the original drug is excreted in urine.

Nitazoxanide

Nitazoxanide is a 5-nitrothiazole compound used for the treatment of cryptosporidiosis and giardiasis; it is active against other intestinal protozoa as well. The drug is approved for use in children 1–11 years of age.

The antiprotozoal activity of nitazoxanide is believed to be due to interference with the pyruvate-ferredoxin oxidoreductase (PFOR) enzyme–dependent electron transfer reaction that is essential to anaerobic energy metabolism. Studies have shown that the PFOR enzyme from *G. lamblia* directly reduces nitazoxanide by transfer of electrons in the absence of ferredoxin. The DNA-derived PFOR protein sequence of *Cryptosporidium parvum* appears to be similar to that of *G. lamblia*. Interference with the PFOR enzyme–dependent electron transfer reaction may not be the only pathway by which nitazoxanide exerts antiprotozoal activity.

After oral administration, nitazoxanide is rapidly hydrolyzed to an active metabolite, tizoxanide (desacetyl-nitazoxanide). Tizoxanide then undergoes conjugation, primarily by glucuronidation. It is recommended that nitazoxanide be taken with food; however, no studies have been conducted to determine whether the

pharmacokinetics of tizoxanide and tizoxanide glucuronide differ in fasted versus fed subjects. Tizoxanide is excreted in urine, bile, and feces, and tizoxanide glucuronide is excreted in urine and bile. The pharmacokinetics of nitazoxanide in patients with impaired hepatic and/or renal function have not been studied. Tizoxanide is highly bound to plasma protein (>99.9%). Therefore, caution should be used when administering this agent concurrently with other highly plasma protein–bound drugs with narrow therapeutic indices, as competition for binding sites may occur.

Oxamniquine

This tetrahydroquinoline derivative is an effective alternative agent for the treatment of *Schistosoma mansoni*, although susceptibility to this drug exhibits regional variation. Oxamniquine exhibits anticholinergic properties, but its primary mode of action seems to rely on ATP-dependent enzymatic drug activation generating an intermediate that alkylates essential macromolecules, including DNA. In treated adult schistosomes, oxamniquine produces marked tegumental alterations that are similar to those seen with praziquantel but that develop less rapidly, becoming evident 4–8 days after treatment.

Oxamniquine is administered orally as a single dose and is well absorbed. Food retards absorption and reduces bioavailability. About 70% of an administered dose is excreted in urine as a mixture of pharmacologically inactive metabolites. Patients should be warned that their urine might have an intense orange-red color. Side effects are uncommon and usually mild, although hallucinations and seizures have been reported.

Paromomycin (aminosidine)

First isolated in 1956, this aminoglycoside is an effective oral agent for the treatment of infections due to intestinal protozoa. Parenteral paromomycin appears to be effective against visceral leishmaniasis in India.

Paromomycin inhibits protozoan protein synthesis by binding to the 30S ribosomal RNA in the aminoacyl-tRNA site, causing misreading of mRNA codons. Paromomycin is less active against *G. lamblia* than standard agents; however, like other aminoglycosides, paromomycin is poorly absorbed from the intestinal lumen, and the high levels of drug in the gut compensate for this relatively weak activity. If absorbed or administered systemically, paromomycin can cause ototoxicity and nephrotoxicity. However, systemic absorption is very limited, and toxicity should not be a concern in persons with normal kidneys. Topical formulations are not generally available.

Pentamidine isethionate

This diamidine is an effective alternative agent for some forms of leishmaniasis and trypanosomiasis. It is available for parenteral and aerosolized administration. While its mechanism of action remains undefined, it is known to exert a wide range of effects, including interaction with trypanosomal kinetoplast DNA; interference with polyamine synthesis by a decrease in the activity of ornithine decarboxylase; and inhibition of RNA polymerase, ribosomal function, and the synthesis of nucleic acids and proteins.

Pentamidine isethionate is well absorbed, is highly tissue bound, and is excreted slowly over several weeks, with an elimination half-life of 12 days. No steady-state plasma concentration is attained in persons given daily injections; the result is extensive accumulation of pentamidine in tissues, primarily the liver, kidney, adrenal, and spleen. Pentamidine does not penetrate well into the CNS. Pulmonary concentrations of pentamidine are increased when the drug is delivered in aerosolized form.

Piperazine

The antihelminthic activity of piperazine is confined to ascariasis and enterobiasis. Piperazine acts as an agonist at extrasynaptic γ-aminobutyric acid (GABA) receptors, causing an influx of chloride ions in the nematode somatic musculature. Although the initial result is hyperpolarization of the muscle fibers, the ultimate effect is flaccid paralysis leading to the expulsion of live worms. Patients should be warned, as this occurrence can be unsettling.

Praziquantel

This heterocyclic pyrazinoisoquinoline derivative is highly active against a broad spectrum of trematodes and cestodes. It is the mainstay of treatment for schistosomiasis and is a critical part of community-based control programs.

All of the effects of praziquantel can be attributed either directly or indirectly to an alteration of intracellular calcium concentrations. Although the exact mechanism of action remains unclear, the major mechanism is disruption of the parasite tegument, causing tetanic contractures with loss of adherence to host tissues and, ultimately, disintegration or expulsion. Praziquantel induces changes in the antigenicity of the parasite by causing the exposure of concealed antigens. Praziquantel also produces alterations in schistosomal glucose metabolism, including decreases in glucose uptake, lactate release, glycogen content, and ATP levels.

Praziquantel exerts its parasitic effects directly and does not need to be metabolized to be effective. It is well absorbed but undergoes extensive first-pass hepatic clearance. Levels of the drug are increased when it is taken with food, particularly carbohydrates, or with cimetidine. Serum levels are reduced by glucocorticoids, chloroquine, carbamazepine, and phenytoin. Praziquantel is completely metabolized in humans, with 80% of the dose recovered as metabolites in urine within 4 days. It is not known to what extent praziquantel crosses the

placenta, but retrospective studies suggest that it is safe in pregnancy.

Patients with schistosomiasis who have heavy parasite burdens may develop abdominal discomfort, nausea, headache, dizziness, and drowsiness. Symptoms begin 30 min after ingestion, may require spasmolytics for relief, and usually disappear spontaneously after a few hours.

Primaquine phosphate

Primaquine, an 8-aminoquinoline, has a broad spectrum of activity against all stages of plasmodial development in humans but has been used most effectively for eradication of the hepatic stage of these parasites. Despite its toxicity, it remains the drug of choice for radical cure of *P. vivax* infections. Primaquine must be metabolized by the host to be effective. It is, in fact, rapidly metabolized; only a small fraction of the dose of the parent drug is excreted unchanged. Although the parasiticidal activity of the three oxidative metabolites remains unclear, they are believed to affect both pyrimidine synthesis and the mitochondrial electron transport chain. The metabolites appear to have significantly less antimalarial activity than primaquine; however, their hemolytic activity is greater than that of the parent drug.

Primaquine causes marked hypotension after parenteral administration and therefore is given only by the oral route. It is rapidly and almost completely absorbed from the GI tract.

Patients should be tested for G6PD deficiency before they receive primaquine. The drug may induce the oxidation of hemoglobin into methemoglobin, irrespective of the G6PD status of the patient. Primaquine is otherwise well tolerated.

Proguanil (chloroguanide)

Proguanil inhibits plasmodial dihydrofolate reductase and is used with atovaquone for oral treatment of uncomplicated malaria or with chloroquine for malaria prophylaxis in parts of Africa without widespread chloroquine-resistant *P. falciparum*.

Proguanil exerts its effect primarily by means of the metabolite cycloguanil, whose inhibition of dihydrofolate reductase in the parasite disrupts deoxythymidylate synthesis, thus interfering with a key pathway involved in the biosynthesis of pyrimidines required for nucleic acid replication. There are no clinical data indicating that folate supplementation diminishes drug efficacy; women of childbearing age for whom atovaquone/proguanil is prescribed should continue taking folate supplements to prevent neural tube birth defects.

Proguanil is extensively absorbed regardless of food intake. The drug is 75% protein bound. The main routes of elimination are hepatic biotransformation and renal excretion; 40–60% of the proguanil dose is excreted by the kidneys. Drug levels are increased and elimination is impaired in patients with hepatic insufficiency.

Pyrantel pamoate

Pyrantel is a tetrahydropyrimidine formulated as pamoate. This safe, well-tolerated, inexpensive drug is used to treat a variety of intestinal nematode infections but is ineffective in trichuriasis. Pyrantel pamoate is usually effective in a single dose. Its target is the nicotinic acetylcholine receptor on the surface of nematode somatic muscle. Pyrantel depolarizes the neuromuscular junction of the nematode, resulting in its irreversible paralysis and allowing the natural expulsion of the worm.

Pyrantel pamoate is poorly absorbed from the intestine; >85% of the dose is passed unaltered in feces. The absorbed portion is metabolized and excreted in urine. Piperazine is antagonistic to pyrantel pamoate and should not be used concomitantly.

Pyrantel pamoate has minimal toxicity at the oral doses used to treat intestinal helminthic infection. It is not recommended for pregnant women or for children <12 months old.

Pyrimethamine

When combined with short-acting sulfonamides, this diaminopyrimidine is effective in malaria, toxoplasmosis, and isosporiasis. Unlike mammalian cells, the parasites that cause these infections cannot utilize preformed pyrimidines obtained through salvage pathways but rather rely completely on de novo pyrimidine synthesis, for which folate derivatives are essential cofactors. The efficacy of pyrimethamine is increasingly limited by the development of resistant strains of *P. falciparum* and *P. vivax*. Single amino acid substitutions to parasite dihydrofolate reductase confer resistance to pyrimethamine by decreasing the enzyme's binding affinity for the drug.

Pyrimethamine is well absorbed; the drug is 87% bound to human plasma proteins. In healthy volunteers, drug concentrations remain at therapeutic levels for up to 2 weeks; drug levels are lower in patients with malaria.

At the usual dosage, pyrimethamine alone causes little toxicity except for occasional skin rashes and, more rarely, blood dyscrasias. Bone marrow suppression sometimes occurs at the higher doses used for toxoplasmosis; at these doses, the drug should be administered with folinic acid.

Quinacrine*

Quinacrine is the only drug approved by the FDA for the treatment of giardiasis. Although its production was discontinued in 1992, quinacrine can be obtained from alternative sources through the CDC Drug Service. The antiprotozoal mechanism of quinacrine has not been fully elucidated. The drug inhibits NADH oxidase—the same enzyme that activates furazolidone. The differing relative quinacrine uptake rate between human cells and *G. lamblia* may explain the selective toxicity of the drug. Resistance correlates with decreased drug uptake.

Quinacrine is rapidly absorbed from the intestinal tract and is widely distributed in body tissues. Alcohol is best avoided due to a disulfiram-like effect.

Quinine and quinidine

When combined with another agent, the cinchona alkaloid quinine is effective for the oral treatment of both uncomplicated, chloroquine-resistant malaria and babesiosis. Quinine acts rapidly against the asexual blood stages of all forms of human malaria. For severe malaria, only quinidine (the dextroisomer of quinine) is available in the United States. Quinine concentrates in the acidic food vacuoles of *Plasmodium* species. The drug inhibits the nonenzymatic polymerization of the highly reactive, toxic heme molecule into the nontoxic polymer pigment hemozoin.

Quinine is readily absorbed when given orally. In patients with malaria, the elimination half-life of quinine increases according to the severity of the infection. However, toxicity is avoided by an increase in the concentration of plasma glycoproteins. The cinchona alkaloids are extensively metabolized, particularly by CYP3A4; only 20% of the dose is excreted unchanged in urine. The drug's metabolites are also excreted in urine and may be responsible for toxicity in patients with renal failure. Renal excretion of quinine is decreased when cimetidine is taken and increased when the urine is acidic. The drug readily crosses the placenta.

Quinidine is both more potent as an antimalarial and more toxic than quinine. Its use requires cardiac monitoring. Dose reduction is necessary in persons with severe renal impairment.

Spiramycin†

This macrolide is used to treat acute toxoplasmosis in pregnancy and congenital toxoplasmosis. While the mechanism of action is similar to that of other macrolides, the efficacy of spiramycin in toxoplasmosis appears to stem from its rapid and extensive intracellular penetration, which results in macrophage drug concentrations 10–20 times greater than serum concentrations.

Spiramycin is rapidly and widely distributed throughout the body and reaches concentrations in the placenta up to five times those in serum. This agent is excreted mainly in bile. Indeed, in humans, the urinary excretion of active compounds represents only 20% of the administered dose.

Serious reactions to spiramycin are rare. Of the available macrolides, spiramycin appears to have the lowest risk of drug interactions. Complications of treatment are rare but, in neonates, can include life-threatening ventricular arrhythmias that disappear with drug discontinuation.

Sulfonamides

See Table 116-1 and Chap. 36.

Suramin*

This derivative of urea is the drug of choice for the early stage of African trypanosomiasis. The drug is polyanionic and acts by forming stable complexes with proteins, thus inhibiting multiple enzymes essential to parasite energy metabolism. Suramin appears to inhibit all trypanosome glycolytic enzymes more effectively than it inhibits the corresponding host enzymes.

Suramin is parenterally administered. It binds to plasma proteins and persists at low levels for several weeks after infusion. Its metabolism is negligible. This drug does not penetrate the CNS.

Tafenoquine

Tafenoquine is an 8-aminoquinoline with causal prophylactic activity. Its prolonged half-life (2–3 weeks) allows longer dosing intervals when the drug is used for prophylaxis. Tafenoquine has been well tolerated in clinical trials. When tafenoquine is taken with food, its absorption is increased by 50% and the most commonly reported adverse event—mild GI upset—is diminished. Like primaquine, tafenoquine is a potent oxidizing agent, causing hemolysis in patients with G6PD deficiency as well as methemoglobinemia.

Tetracyclines

See Table 116-1 and Chap. 36.

Thiabendazole

Discovered in 1961, thiabendazole remains one of the most potent of the numerous benzimidazole derivatives. However, its use has declined significantly because of a higher frequency of adverse effects than is seen with other, equally effective agents.

Thiabendazole is active against most intestinal nematodes that infect humans. Although the exact mechanism of its antihelminthic activity has not been fully elucidated, it is likely to be similar to that of other benzimidazole drugs: namely, inhibition of polymerization of parasite β-tubulin. The drug also inhibits the helminth-specific enzyme fumarate reductase. In animals, thiabendazole has anti-inflammatory, antipyretic, and analgesic effects, which may explain its usefulness in dracunculiasis and trichinosis. Thiabendazole also suppresses egg and/or larval production by some nematodes and may inhibit the subsequent development of eggs or larvae passed in feces. Despite the emergence and global spread of thiabendazole-resistant trichostrongyliasis among sheep, there have been no reports of drug resistance in humans.

Thiabendazole is available in tablet form and as an oral suspension. The drug is rapidly absorbed from the GI tract but can also be absorbed through the skin. Thiabendazole should be taken after meals. This agent is extensively metabolized in the liver before ultimately being excreted; most of the dose is excreted within the first 24 h. The usual dose of thiabendazole is determined by the patient's weight, but some treatment regimens are parasite specific. No particular adjustments are recommended in patients with renal or hepatic failure; only cautious use is advised.

Coadministration of thiabendazole in patients taking theophylline can result in an increase in theophylline levels by >50%. Therefore, serum levels of theophylline should be monitored closely in this situation.

Tinidazole

This nitroimidazole is effective for the treatment of amebiasis, giardiasis, and trichomoniasis. Like metronidazole, tinidazole must undergo reductive activation by the parasite's metabolic system before it can act on protozoal targets. Tinidazole inhibits the synthesis of new DNA in the parasite and causes degradation of existing DNA. The reduced free-radical derivatives alkylate DNA, with consequent cytotoxic damage to the parasite. This damage appears to be produced by short-lived reduction intermediates, resulting in helix destabilization and strain breakage of DNA. The mechanism of action and side effects of tinidazole are similar to those of metronidazole, but adverse events appear to be less frequent and severe with tinidazole. In addition, the significantly longer half-life of tinidazole (>12 h) offers potential cure with a single dose.

Triclabendazole

While most benzimidazoles have broad-spectrum antihelminthic activity, they exhibit minimal or no activity against *F. hepatica*. In contrast, the antihelminthic activity of triclabendazole is highly specific for *Fasciola* and *Paragonimus* species, with little activity against nematodes, cestodes, and other trematodes. Triclabendazole is effective against all stages of *Fasciola* species. The active sulfoxide metabolite of triclabendazole binds to fluke tubulin by assuming a unique nonplanar configuration and disrupts microtubule-based processes. Resistance to triclabendazole in veterinary use has been reported in Australia and Europe; however, no resistance has been documented in humans.

Triclabendazole is rapidly absorbed after oral ingestion; administration with food enhances its absorption and shortens the elimination half-life of the active metabolite. Both the sulfoxide and the sulfone metabolites are highly protein bound (>99%). Treatment with triclabendazole is typically given in one or two doses. No clinical data are available regarding dose adjustment in renal or hepatic insufficiency; however, given the short course of therapy and extensive hepatic metabolism of triclabendazole, dose adjustment is unlikely to be necessary. No information exists on drug interactions.

Trimethoprim-sulfamethoxazole

See Table 116-1 and Chap. 36.

CHAPTER 118

AMEBIASIS AND INFECTION WITH FREE-LIVING AMEBAS

Samuel L. Stanley, Jr.

AMEBIASIS

DEFINITION

Amebiasis is infection with the parasitic intestinal protozoan *Entamoeba histolytica* (the "tissue-lysing ameba"). Most infections are probably asymptomatic, but *E. histolytica* can cause disease ranging from dysentery to extraintestinal infections, including liver abscesses.

LIFE CYCLE AND TRANSMISSION

E. histolytica exists in two stages: a hardy multinucleate cyst form **(Fig. 118-1)** and the motile trophozoite stage **(Fig. 118-2)**. Infection (of which humans are the natural hosts) is acquired by ingestion of cysts contained in fecally contaminated food or water or, more rarely, through oral-anal sexual contact. Cysts survive stomach acidity and excyst within the small intestine to form the

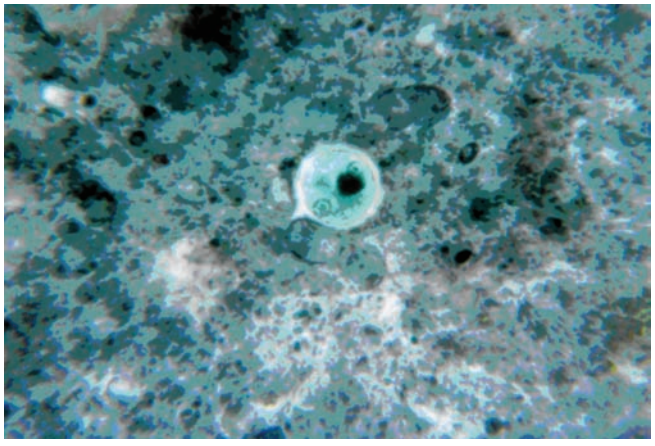


FIGURE 118-1
***Entamoeba* cyst.** Three of the four nuclei are clearly visible. (*Courtesy of Dr. George Healy, Centers for Disease Control and Prevention.*)

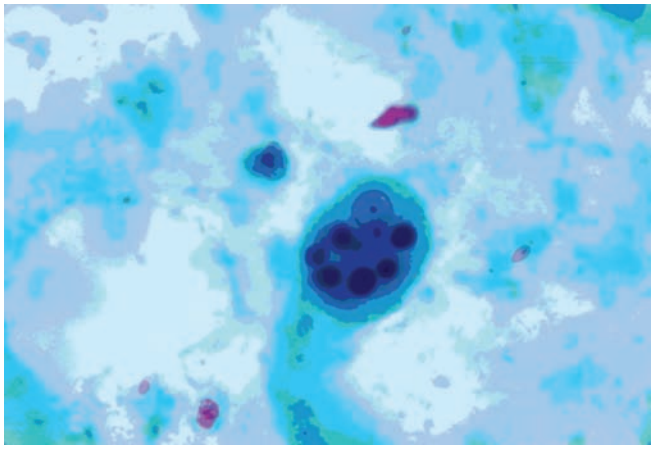


FIGURE 118-2
***E. histolytica* trophozoite with ingested red blood cells.** Note the single nucleus with central nucleolus. (*Courtesy of the Centers for Disease Control and Prevention.*)

20- to 50-μm trophozoite stage. Trophozoites can live within the large-bowel lumen without causing disease or can invade the intestinal mucosa, causing amebic colitis. In some cases, *E. histolytica* trophozoites invade through the mucosa and into the bloodstream, traveling through the portal circulation to reach the liver and causing amebic liver abscesses. Motile trophozoites may be excreted into the stool—a diagnostically important event—but are rapidly killed upon exposure to air or stomach acid and therefore are not infectious. Trophozoite cysts within the large bowel are excreted in the stool, continuing the life cycle.

EPIDEMIOLOGY

Molecular diagnostics continue to clarify what was once a confusing picture of the true incidence and prevalence of *E. histolytica* infection and disease. It was a staple of most textbooks that 10% of the world's population was infected with *E. histolytica*. We now know that most asymptomatic individuals harboring amebic trophozoites or cysts in their stools are infected with a noninvasive species: *Entamoeba dispar* or *Entamoeba moshkovskii*. *E. dispar* appears not to cause disease, even in the most profoundly immunosuppressed individuals; furthermore, at this time, there is little evidence to suggest that *E. moshkovskii* causes disease, although epidemiologic studies of this species are in their infancy. In contrast, *E. histolytica* infection can cause disease, although not all patients develop symptoms. It remains unclear how frequently people infected with *E. histolytica* do develop symptoms; in one study in a highly endemic area, only 10% of infected patients developed symptoms over a 1-year observation period. A remarkable feature of amebiasis is its more common occurrence in men than in women, although the prevalence of infection with *E. histolytica* does not appear to differ between the sexes. This pattern is particularly pronounced for amebic liver abscess, whose prevalence is ~7 times higher among men than among women. The explanation for this difference remains unknown, but less efficient complement-mediated killing of amebic trophozoites by serum from men than by serum from women has been reported.

E. histolytica infections are most common in areas of the world where poor sanitation and crowding compromise the barriers to contamination of food and drinking water with human feces. Endemic areas include parts of Mexico, India, and nations in the tropical regions of Africa, South and Central America, and Asia. *E. histolytica* was present in ~2.1% of individuals presenting with diarrhea in a large series from Bangladesh and in 1.4% of the asymptomatic control group. In 2007, amebiasis was listed as the sixth most common cause of disease in Mexico, with an incidence of ~544 cases per 100,000 population. In the United States and other developed countries, disease is unusual and is found almost exclusively in travelers or immigrants from endemic areas. Rarely, outbreaks take place in institutionalized populations, and infections have been documented with increased frequency among men who have sex with men; however, most of the latter cases have been asymptomatic and probably represent *E. dispar* infections.

PATHOGENESIS AND PATHOLOGY

E. histolytica trophozoites possess a potent repertoire of adhesins, proteinases, pore-forming proteins, and other effector molecules that enable them to lyse cells and tissue, induce both cellular necrosis and apoptosis, and resist both innate and adaptive immune defenses. Disease begins when *E. histolytica* trophozoites adhere to colonic mucosal epithelial cells. Disruption of the colonic mucin barrier is seen in pathologic sections from the diseased colon, but it is not clear whether this disruption is caused by the parasite, facilitating its adherence to mucosal cells, or occurs as a consequence of the adhesion event, with subsequent mucosal damage. Adherence is mediated primarily by a family of surface lectin molecules capable of binding to galactose and

N-acetylgalactosamine residues. *E. histolytica* can lyse host cells upon contact through a family of amphipathic peptides called *amoebapores* that form barrel-stave pores in target cell membranes. Both cellular necrosis and apoptosis can occur after *E. histolytica* comes into contact with host cells, and which outcome predominates may relate to inherent characteristics of the target cell or the tissue environment. One consistent and unequivocal finding is the important role played by amebic cysteine proteinases in the disease process. *E. histolytica* possesses a large family of cysteine proteinases that are capable of lysing the extracellular matrix between host cells (thus detaching cells and facilitating invasion) and cleaving host defense molecules (including complement components and antibodies). Studies in animal models, including chimeric mice with human intestinal xenografts, have shown that inhibition of *E. histolytica* cysteine proteinase activity, via either direct gene targeting or chemical inhibitors, significantly reduces disease. The ultimate effect of all these amebic virulence factors on the human colon is the production of small ulcers that have heaped borders and contain focal areas of epithelial cell loss, a modest inflammatory response, and mucosal hemorrhage. The intervening mucosa is usually normal, but diffuse hyperemia is sometimes seen. *E. histolytica* trophozoites can then invade laterally through the submucosal layer, creating the classic flask-shaped ulcers that appear on pathologic examination as narrow-necked lesions, broadening in the submucosal region, with *E. histolytica* trophozoites at the margins between dead and live tissues **(Fig. 118-3)**. Ulcers tend to stop at the muscularis layer, and full-thickness lesions and colonic perforation are unusual. Amebomas, a rare complication of intestinal disease, are granulomatous mass lesions protruding into the bowel lumen, with a thickened edematous and hemorrhagic bowel wall that can cause obstructive symptoms.

In some individuals with *E. histolytica* colonic infection, trophozoites invade the portal venous system and reach the liver, where they cause amebic liver abscesses. *E. histolytica* trophozoites must resist lysis by serum complement to survive in the bloodstream. Amebic liver abscesses have a characteristic appearance on pathologic examination: the roughly circular abscesses contain a large necrotic center resembling anchovy paste that is surrounded by a narrow ring of a few inflammatory cells, fibrosis, and occasionally a few amebic trophozoites. The adjacent liver parenchyma is usually completely normal. Results in experimental rodent models of amebic liver abscess suggest that initial lesions may have more inflammatory cells and that lysis of neutrophils by *E. histolytica* trophozoites may contribute to tissue damage. In murine models of disease, apoptosis is a prominent component of hepatocyte death and the blockade of caspase activity can significantly reduce liver abscess formation, but whether any of these factors is applicable to human disease is unclear.

The role of innate and adaptive immunity in preventing *E. histolytica* infection or controlling disease needs further clarification. Studies of children in a highly endemic area have suggested that prior *E. histolytica* intestinal infection may stimulate mucosal IgA antibodies to amebic antigens, thereby reducing the likelihood of subsequent infections; this protection is relatively short lived. In contrast, among individuals in an area of Vietnam with a high prevalence of amebic liver abscess, a prior episode of disease did not reduce the risk of a second case, despite the presence of serum antibodies. Studies of animal models suggest that cell-mediated immunity may play a role in host defense, and glucocorticoid use has been associated with worse outcomes in patients with amebic colitis. However, individuals with HIV/AIDS do not appear to be at increased risk for infection with *E. histolytica*, and there is no evidence that they develop more severe disease than do immunocompetent hosts.

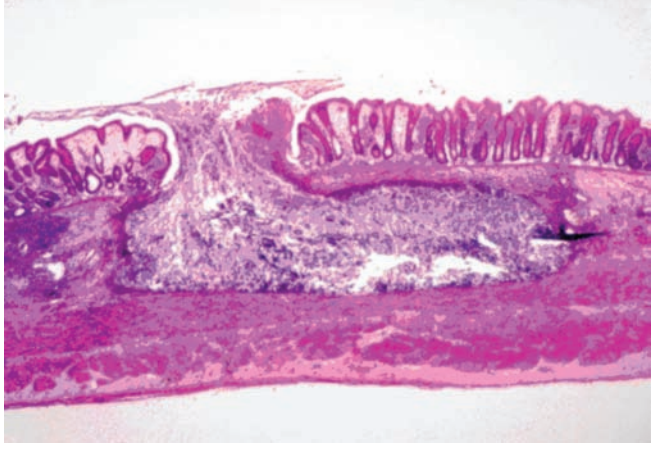


FIGURE 118-3
***E. histolytica* flask-shaped intestinal ulceration** from a kitten. (*Courtesy of Dr. Mae Melvin, Centers for Disease Control and Prevention.*)

CLINICAL SYNDROMES

Intestinal amebiasis

Most patients harboring *Entamoeba* species are asymptomatic, but individuals with *E. histolytica* infection can develop disease. Symptoms of amebic colitis generally appear 2–6 weeks after ingestion of the cyst form of the parasite. Diarrhea (classically heme-positive) and lower abdominal pain are the most common symptoms. Malaise and weight loss may be noted as disease progresses. Severe dysentery, with 10–12 small-volume, blood- and mucus-containing stools daily, may develop, but only ~40% of patients are febrile. Fulminant amebic colitis, with even more profuse diarrhea, severe abdominal pain (including peritoneal signs), fever, and pronounced leukocytosis are rare, disproportionately affecting young children, pregnant women, individuals being treated with glucocorticoids, and possibly individuals with diabetes or alcoholism. Paralytic ileus and colonic mucosal sloughing may be seen; intestinal perforation occurs in >75% of patients with this fulminant form of disease. Mortality rates from fulminant amebic colitis exceed 40% in some series. Recognized complications

of amebic colitis also include toxic megacolon (documented in ~0.5% of patients with colitis), with severe bowel dilation and intramural air, and the aforementioned ameboma, which presents as an abdominal mass that may be confused with colon cancer.

Amebic liver abscess

Just a century ago, amebic liver abscess—the most common extraintestinal manifestation of amebiasis—was almost always fatal; however, with current rapid diagnostic methods and effective medical treatment, mortality rates are now 1–3%. Disease begins when *E. histolytica* trophozoites penetrate through the colonic mucosa, travel through the portal circulation, and reach the liver. Most individuals with amebic liver abscess do not have concurrent signs or symptoms of colitis, and most do not have *E. histolytica* trophozoites in their stools. The exceptions are individuals with fulminant amebic colitis, in which concurrent amebic liver abscess is not uncommon. Disease can arise from months to years after travel to or residence in an endemic area; therefore, a careful travel history is key in making the diagnosis. The classic presentations of amebic liver abscess are right-upper-quadrant pain, fever, and hepatic tenderness. The pace of disease is usually acute, with symptoms lasting <10 days. However, a more chronic presentation, with weight loss and anorexia as prominent accompanying features, does occur. Jaundice is unusual, but dullness and rales at the right lung base (secondary to pleural effusion) are common. The most common laboratory findings are leukocytosis (without eosinophilia), an elevated alkaline phosphatase level, mild anemia, and an elevated erythrocyte sedimentation rate.

Other extraintestinal complications of amebiasis

Right-sided pleural effusions and atelectasis are common in cases of amebic liver abscess and generally require no treatment. However, the abscess ruptures through the diaphragm in ~10% of patients, causing pleuropulmonary amebiasis. Suggestive symptoms are sudden-onset cough, pleuritic chest pain, and shortness of breath. In some patients, pleuropulmonary amebiasis is the presenting manifestation of amebic liver abscess and may be confused with bacterial pneumonia and empyema. A dramatic complication is the development of a hepatobronchial fistula, in which patients can cough up the contents of the liver abscess—copious amounts of brown sputum that may contain *E. histolytica* trophozoites. In ~1–3% of cases, the amebic liver abscess ruptures into the peritoneum, and peritoneal signs and shock develop. Even rarer is rupture of an amebic liver abscess into the pericardium; the signs and symptoms are those commonly seen with pericarditis (chest pain, pericardial rub, dyspnea, tachypnea, or cardiac tamponade), and nearly 30% of cases end in death. Cerebral abscesses complicate <0.1% of cases of amebic liver abscess and are associated with the sudden onset of headache, vomiting, seizures, and mental status changes and a high mortality rate. Cutaneous amebiasis (which usually involves the anal and perianal regions), genital disease (including rectovaginal fistulas), and urinary tract lesions are rare but reported complications of amebiasis.

DIAGNOSTIC TESTS

The diagnosis of amebic colitis has traditionally been based on the demonstration of *E. histolytica* trophozoites or cysts in the stool or colonic mucosa of patients with diarrhea. However, the inability of microscopy to differentiate between *E. histolytica* and other *Entamoeba* species, such as *E. dispar* and *E. moshkovskii*, limits its effectiveness as a sole diagnostic method. Examination of three stool samples improves sensitivity for the detection of *Entamoeba* species, and it has been argued that the presence of amebic trophozoites containing red blood cells in a diarrheal stool is highly suggestive of *E. histolytica* infection. However, because trophozoites containing red blood cells are not found in most patients with *E. histolytica* infection, the applicability of this finding is limited.

Despite these inherent limitations, microscopy, often combined with serologic testing, remains the standard diagnostic approach in many hospitals and clinics worldwide. Culture of stools for *E. histolytica* trophozoites serves as a research tool but is generally not available for clinical use. PCR assay for DNA in stool samples is currently the most sensitive and specific method for identifying *E. histolytica* infection and has become a valuable epidemiologic and research tool; probes can be configured to detect *E. dispar* and *E. moshkovskii* as well. While significant advances are being made in reducing the costs of PCR-based diagnostics, this method still is not feasible for clinical diagnosis in most endemic areas. Commercially available tests that use enzyme-linked immunosorbent assays (ELISAs) or immunochromatographic techniques to detect *Entamoeba* antigens are less expensive and more easily performed and are being used with increasing frequency. Greater sensitivity than microscopy and the ability to detect *E. histolytica* specifically are claimed by some of the leading kits, representing significant advantages over microscopy. Unfortunately, not all clinical studies have supported these claims, concerns have been raised about the specificity of the tests in nonendemic areas, and the ELISAs are less sensitive and specific than are PCR-based diagnostics. At this point, antigen detection–based ELISAs that can specifically identify *E. histolytica* in stool probably represent the best choice in endemic areas; however, the results of any of these diagnostic tests need to be interpreted in light of clinical presentation, and a second confirmatory test (e.g., microscopy and/or amebic serology) may be prudent. In instances in which amebiasis is suspected on clinical grounds in a patient with acute colitis but initial stool samples are negative, colonoscopy with examination of brushings or mucosal biopsies for *E. histolytica* trophozoites may be helpful in making the diagnosis or in identifying other diseases, such as inflammatory bowel disease or pseudomembranous colitis.

The diagnosis of amebic liver abscess is based on the detection (generally by ultrasound or CT; Fig. 118-4) of one or more space-occupying lesions in the liver and a positive serologic test for antibodies to *E. histolytica* antigens. As has been noted, amebiasis can present months or years after travel to or residence in an endemic area, and so a careful travel history is mandatory when anyone presents with a liver abscess. Amebic liver abscesses are classically described as single, large, and located in the right lobe of the liver, but sensitive imaging techniques have shown that multiple abscesses are more common than previously suspected. When a patient has a space-occupying lesion of the liver, a positive amebic serology is highly sensitive (>94%) and highly specific (>95%) for the diagnosis of amebic liver abscess. False-negative serologic tests have been reported when serum samples were obtained very early in the course of abscess (within 7–10 days of onset), but repeat tests are almost always positive.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of amebic colitis includes bacterial dysentery (e.g., *Shigella* and *Campylobacter* infections), schistosomiasis, *Balantidium coli* infection, pseudomembranous colitis, inflammatory bowel disease, and ischemic colitis. Stool cultures for bacterial pathogens, microscopic examination of stools, and amebic serology help differentiate amebic colitis from these other entities. Amebomas may be confused with colonic carcinoma; several case reports describe instances in which amebomas and associated liver abscesses were initially considered to be colon cancer with liver metastases. Amebic liver abscess must be distinguished from pyogenic liver abscess, echinococcal cysts, and primary or metastatic liver tumors. It is difficult to differentiate pyogenic from amebic liver abscesses on purely clinical grounds, but amebic serology is usually the key test in excluding or diagnosing amebic liver abscess. Abscesses that rupture into the pleural space may be accompanied by cough, sputum production, and dyspnea and may initially be diagnosed as bronchopneumonia.

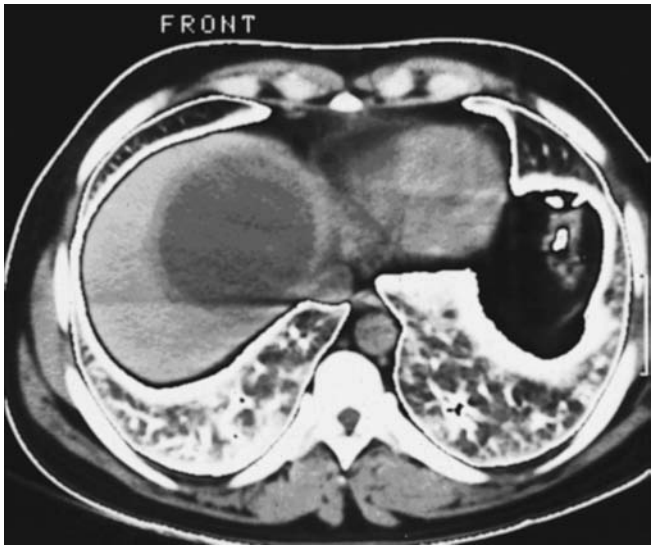


FIGURE 118-4
Large amebic abscess in the right lobe of the liver visualized by CT. (*Courtesy of Dr. M. M. Reeder, International Registry of Tropical Imaging.*)

TREATMENT Amebiasis

The nitroimidazole compounds tinidazole and metronidazole are the drugs of choice for the treatment of amebic colitis and amebic liver abscess (Table 118-1). To date, *E. histolytica* has not demonstrated resistance to any of the commonly used agents—a situation that greatly simplifies treatment. Tinidazole appears to be better tolerated and slightly more effective than metronidazole for amebic colitis and amebic liver abscess. Metronidazole is available as a parenteral formulation for patients who cannot take oral medications. Whenever possible, fulminant amebic colitis is managed conservatively, even in the presence of perforation, with the addition of antibiotics to treat gut bacteria and percutaneous catheter drainage of fluid collections if needed.

Remarkably, given the large size of amebic liver abscesses, treatment with tinidazole or metronidazole in the same doses used for amebic colitis is almost always successful. More than 90% of patients respond with a decrease in abdominal pain and fever within 72 h of the initiation of therapy. Drainage of amebic liver abscesses is rarely needed; in one large series, neither time to becoming afebrile nor length of hospitalization was significantly different for patients who underwent percutaneous radiography-guided aspiration of the abscess accompanied by medical therapy than for those who received medical therapy alone. Aspiration should be reserved for individuals in whom pyogenic abscess or a bacterial superinfection is suspected but whose diagnosis is uncertain, for patients failing to respond to tinidazole or metronidazole (i.e., those who have persistent fever or abdominal pain after 4 days of treatment), for individuals with large liver abscesses in the left lobe (because of the risk of rupture into the pericardium), and for patients whose large abscesses and accelerated clinical course raise concerns about imminent

TABLE 118-1
RECOMMENDED THERAPEUTIC DOSAGES OF ANTIAMEBIC DRUGS

DRUG	DOSAGE	DURATION, DAYS
Amebic Colitis or Amebic Liver Abscess		
Tinidazole	2 g/d PO with food	3
Metronidazole	750 mg tid PO or IV	5–10
***Entamoeba histolytica* Luminal Infection**		
Paromomycin	30 mg/kg qd PO in 3 divided doses	5–10
Iodoquinol	650 mg PO tid	20

rupture. In contrast, aspiration and/or percutaneous catheter drainage improves outcomes in patients with pleuropulmonary amebiasis and empyema (where amebic liver abscesses have ruptured into the pleural space), and percutaneous catheter or surgical drainage is absolutely indicated for cases of amebic pericarditis. Rupture of an amebic liver abscess into the peritoneum is generally managed conservatively, with medical therapy and percutaneous catheter drainage of fluid collections as needed.

Neither metronidazole nor tinidazole reaches high levels in the gut lumen; therefore, patients with amebic colitis or amebic liver abscess should also receive treatment with a luminal agent (paromomycin or iodoquinol) to ensure eradication of the infection (Table 118-1). Paromomycin is the preferred agent. Asymptomatic individuals with documented *E. histolytica* infection should be treated because of the risks of developing amebic colitis or amebic liver abscess in the future and of transmitting the infection to others. Paromomycin or iodoquinol in the doses listed in the table should be used in these cases.

Nitazoxanide, a broad-spectrum antiparasitic drug, is efficacious against *E. histolytica* trophozoites in both tissue and gut lumen and may become an important addition to the therapeutic repertoire. However, clinical experience with nitazoxanide for the treatment of *E. histolytica* infection remains limited at this point.

PREVENTION

Avoidance of the ingestion of food and water contaminated with human feces is the only way to prevent *E. histolytica* infection. Travelers to endemic areas should exercise the same measures used to reduce the risk of travelers' diarrhea. Treatment of asymptomatic persons who pass *E. histolytica* cysts in the stool may help reduce opportunities for disease transmission. There is no evidence for any effective prophylaxis, and no vaccine is available.

INFECTION WITH FREE-LIVING AMEBAS

In contrast to the trophozoites of the parasitic *E. histolytica*, which can survive only in humans and some other primate hosts, free-living amebas of the genera *Naegleria*, *Acanthamoeba*, and *Balamuthia* live in brackish or freshwater habitats around the world (including lakes, tap water, swimming pools, and air conditioning and heating ducts) and are accidental and opportunistic agents of disease.

NAEGLERIA INFECTIONS

Naegleria (the "brain-eating ameba") is the causative agent of primary amebic meningoencephalitis (PAM). Nearly always fatal but quite rare, cases of PAM have been reported from 15 countries and from all continents except Antarctica; 35 cases were reported in the United States between 1998 and 2009. *Naegleria* prefers warm freshwater, and most cases occur in otherwise healthy children, who usually have swum in lakes or swimming pools during the previous 2 weeks. *Naegleria* enters the central nervous system via water inhaled or splashed into the nose, with trophozoites disrupting the olfactory mucosa, invading through the cribriform plate, and ascending via the olfactory nerves into the brain. The earliest manifestations are anosmia (usually perceived as alterations in taste), headache, fever, photophobia, nausea, and vomiting. Cranial nerve palsies, especially of the third, fourth, and sixth nerves, are documented and rapid progression of disease, with seizures, coma, and death within 7–10 days of the onset of symptoms, are common. Pathologic examination reveals hemorrhagic necrosis of brain tissue (often most prominent in the olfactory bulbs), evidence of increased intracranial pressure, scant purulent material that may contain a few amebas, and marked leptomeningitis **(Fig. 118-5)**.

The diagnosis of PAM is based on the finding of motile *Naegleria* trophozoites in wet mounts of freshly obtained cerebrospinal fluid (CSF). Laboratory findings in the CSF resemble those in bacterial meningitis, with high opening pressures, low glucose levels, high protein concentrations, and elevated polymorphonuclear cell–predominant white blood cell counts. PAM should be suspected in any patient who has an appropriate history and purulent meningoencephalitis with negative gram stains, negative antigen detection and PCR tests for other pathogens, and negative bacterial cultures. Unfortunately, the prognosis for PAM is dismal. The few survivors who have been reported were treated with high-dose amphotericin B and rifampin in combination.

ACANTHAMOEBA INFECTIONS

Acanthamoeba species are free-living amebas that cause two major clinical syndromes: granulomatous amebic encephalitis and keratitis. Granulomatous amebic encephalitis occurs in debilitated, chronically ill, and

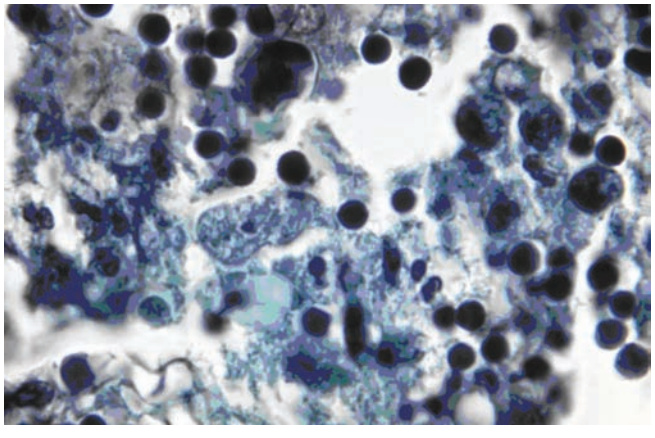


FIGURE 118-5
***Naegleria* in a section of human brain tissue** from a patient with primary amebic meningoencephalitis. (*Courtesy of Dr. George Healy, Centers for Disease Control and Prevention.*)

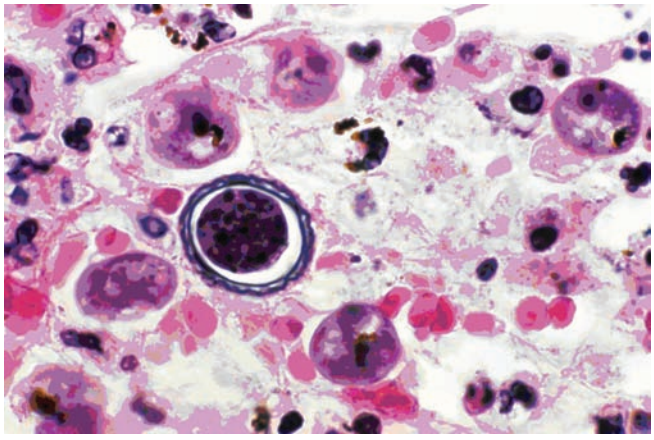


FIGURE 118-6
***Acanthamoeba* cyst in brain tissue** from a patient with granulomatous amebic encephalitis. (*Courtesy of Dr. George Healy, Centers for Disease Control and Prevention*.)

immunosuppressed individuals who may be undergoing chemotherapy, receiving glucocorticoids, or suffering from lymphoproliferative diseases, systemic lupus erythematosus, or AIDS. It is believed that *Acanthamoeba* reaches the central nervous system through the bloodstream, traveling from a primary site of infection in the nares, skin, sinuses, or lungs. The pace of infection is indolent compared with that of PAM. Granulomatous amebic encephalitis tends to present as a space-occupying lesion in the brain. Common symptoms include altered mental status, stiff neck, and headache along with focal findings including hemiparesis, ataxia, and cranial nerve palsies. Seizures and coma often precede death. Pathologic findings in the brain include cerebral edema and multiple areas of necrosis and hemorrhage. Amebic trophozoites and cysts are scattered throughout the tissue and are often located near blood vessels **(Fig. 118-6)**. Multinucleated giant cells forming granulomas give the syndrome its name but are seen less often in highly immunocompromised patients. The diagnosis is usually made by detection of *Acanthamoeba* trophozoites or cysts in biopsy specimens; a fluorescein-labeled antiserum is available from the Centers for Disease Control and Prevention (CDC) to help identify *Acanthamoeba* in microscopic sections. *Acanthamoeba* trophozoites and cysts are occasionally seen in CSF, but samples from most patients with granulomatous amebic encephalitis show mild lymphocyte-predominant pleocytosis, slightly elevated protein levels, and normal or slightly depressed glucose concentrations without the presence of amebas. CT findings vary, with hypodense lesions that resemble infarcts in some patients and multiple enhancing lesions that resemble toxoplasmosis in others. Unfortunately, there are no therapies with proven efficacy against this disease, and almost all cases have ended in death. There have been case reports of survivors treated with multidrug combinations that included pentamidine, sulfadiazine, flucytosine, rifampin, and fluconazole.

Acanthamoeba keratitis is associated with corneal injuries complicated by exposure to water or soil and with the wearing of contact lenses. In contact lens–associated infection, extended wear, breaches in hygiene and disinfection procedures, swimming with contact lenses in place, and the use of homemade saline solutions contaminated with *Acanthamoeba* are important risk factors. The incidence of *Acanthamoeba* keratitis varies from 1.65–2.01 cases per million contact lens users in the United States to 17.53–19.5 cases per million users in the United Kingdom. Unilateral photophobia, excessive tearing, redness, and foreign-body sensation are the earliest signs and symptoms; disease is bilateral in some contact lens users. *Acanthamoeba* keratitis can progress rapidly; abscesses, hypopyon, scleritis, and corneal perforation with vision loss can develop within weeks. The disease may be diagnosed by identification of the polygonal cyst form in corneal scrapings or biopsy material, by culture of biopsy samples or contact lenses on *Escherichia coli*–seeded agar plates, by confocal microscopy, and by PCR. The differential diagnosis includes bacterial, fungal, mycobacterial, and viral (particularly herpetic) causes. Current therapy involves topical administration of a cationic antiseptic agent such as a biguanide or chlorhexidine, with or without a diamidine agent. The persistence of the cyst form of *Acanthamoeba* complicates treatment, and long durations of therapy (6 months to 1 year) are required. In severe cases, particularly when vision is threatened or already diminished, penetrating keratoplasty may be indicated.

BALAMUTHIA INFECTIONS

Balamuthia mandrillaris is a free-living ameba that causes meningoencephalitis in both immunosuppressed and immunocompetent hosts, particularly children and the elderly. The disease presents similarly to granulomatous amebic encephalitis caused by *Acanthamoeba*, and essentially all of the points made earlier with regard to the latter organism—in terms of clinical presentation, pathologic findings, and lack of proven therapies—apply to *Balamuthia* infections as well. Most cases are identified post mortem; the few cases identified before death have been found during histologic examination of brain biopsy specimens. A specific antiserum is available from the CDC to aid in identifying *B. mandrillaris* in clinical specimens.

CHAPTER 119

MALARIA

Nicholas J. White ■ Joel G. Breman

Humanity has but three great enemies: Fever, famine and war; of these by far the greatest, by far the most terrible, is fever.

William Osler

Malaria is a protozoan disease transmitted by the bite of infected *Anopheles* mosquitoes. The most important of the parasitic diseases of humans, it is transmitted in 108 countries containing 3 billion people and causes nearly 1 million deaths each year. Malaria has been eliminated from the United States, Canada, Europe, and Russia; in the late twentieth and early twenty-first centuries, however, its prevalence rose in many parts of the tropics. Despite enormous control efforts, increases in the drug resistance of the parasite, the insecticide resistance of its vectors, and human travel and migration have contributed to this resurgence. Occasional local transmission after importation of malaria has occurred in several southern and eastern areas of the United States and in Europe, indicating the continual danger to nonmalarious countries. Although there are many promising new control and research initiatives, malaria remains today, as it has been for centuries, a heavy burden on tropical communities, a threat to nonendemic countries, and a danger to travelers.

ETIOLOGY AND PATHOGENESIS

Five species of the genus *Plasmodium* cause nearly all malarial infections in humans. These are *P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae,* and—in Southeast Asia—the monkey malaria parasite *P. knowlesi*, which can be reliably identified only by molecular methods **(Table 119-1)**. Almost all deaths are caused by falciparum malaria. Human infection begins when a female anopheline mosquito inoculates plasmodial *sporozoites* from its salivary gland during a blood meal **(Fig. 119-1)**. These microscopic motile forms of the malarial parasite are carried rapidly via the bloodstream to the liver, where they invade hepatic parenchymal cells and begin a period of asexual reproduction. By this amplification process (known as *intrahepatic* or *preerythrocytic schizogony* or *merogony*), a single sporozoite eventually may produce from 10,000 to >30,000 daughter merozoites. The swollen infected liver cell eventually bursts, discharging motile *merozoites* into the bloodstream. These merozoites then invade the red blood cells (RBCs) and multiply six- to twentyfold every 48–72 h. When the parasites reach densities of ~50/μL of blood (~100 million parasites in the blood of an adult), the symptomatic stage of the infection begins. In *P. vivax* and *P. ovale* infections, a proportion of the intrahepatic forms do not divide immediately but remain dormant for a period ranging from 3 weeks to a year or longer before reproduction begins. These dormant forms, or *hypnozoites*, are the cause of the relapses that characterize infection with these two species.

After entry into the bloodstream, merozoites rapidly invade erythrocytes and become *trophozoites*. Attachment is mediated via a specific erythrocyte surface receptor. In the case of *P. vivax*, this receptor is related to the Duffy blood-group antigen Fy^a or Fy^b. Most West Africans and people with origins in that region carry the Duffy-negative FyFy phenotype and are therefore resistant to *P. vivax* malaria. During the early stage of intraerythrocytic development, the small "ring forms" of the different parasitic species appear similar under light microscopy. As the trophozoites enlarge, species-specific characteristics become evident, pigment becomes visible, and the parasite assumes an irregular or ameboid shape. By the end of the 48-h intraerythrocytic life cycle (24 h for *P. knowlesi*, 72 h for *P. malariae*), the parasite has consumed two-thirds of the RBC's hemoglobin and has grown to occupy most of the cell. It is now called a *schizont*. Multiple nuclear divisions have taken place (*schizogony* or *merogony*), and the RBC then ruptures to release 6–30 daughter merozoites, each potentially capable of invading a new RBC and repeating the cycle. The disease in human beings is caused by the direct effects of RBC invasion and destruction by the asexual parasite and the host's reaction. After a series of asexual cycles (*P. falciparum*) or immediately after release from the liver (*P. vivax*, *P. ovale*, *P. malariae*, *P. knowlesi*), some of the parasites develop into morphologically distinct, longer-lived sexual forms (*gametocytes*) that can transmit malaria.

TABLE 119-1

CHARACTERISTICS OF *PLASMODIUM* SPECIES INFECTING HUMANS

	FINDING FOR INDICATED SPECIES[a]			
CHARACTERISTIC	***P. FALCIPARUM***	***P. VIVAX***	***P. OVALE***	***P. MALARIAE***
Duration of intrahepatic phase (days)	5.5	8	9	15
Number of merozoites released per infected hepatocyte	30,000	10,000	15,000	15,000
Duration of erythrocytic cycle (hours)	48	48	50	72
Red cell preference	Younger cells (but can invade cells of all ages)	Reticulocytes and cells up to 2 weeks old	Reticulocytes	Older cells
Morphology	Usually only ring forms[b]; banana-shaped gametocytes	Irregularly shaped large rings and trophozoites; enlarged erythrocytes; Schüffner's dots	Infected erythrocytes, enlarged and oval with tufted ends; Schüffner's dots	Band or rectangular forms of trophozoites common
Pigment color	Black	Yellow-brown	Dark brown	Brown-black
Ability to cause relapses	No	Yes	Yes	No

[a]In Southeast Asia, the monkey malaria parasite *P. knowlesi* also causes disease in humans.
[b]Parasitemias of >2% are suggestive of *P. falciparum* infection.

After being ingested in the blood meal of a biting female anopheline mosquito, the male and female gametocytes form a zygote in the insect's midgut. This zygote matures into an ookinete, which penetrates and encysts in the mosquito's gut wall. The resulting oocyst expands by asexual division until it bursts to liberate myriad motile sporozoites, which then migrate in the hemolymph to the salivary gland of the mosquito to await inoculation into another human at the next feeding.

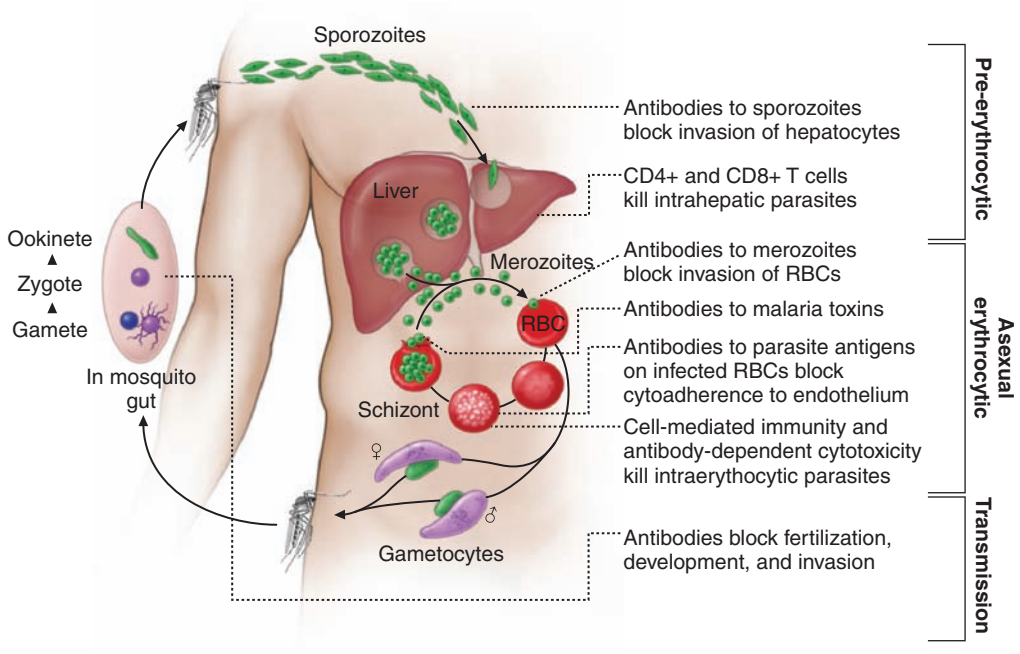


FIGURE 119-1
The malaria transmission cycle from mosquito to human. RBC, red blood cell.

EPIDEMIOLOGY

Malaria occurs throughout most of the tropical regions of the world **(Fig. 119-2)**. *P. falciparum* predominates in Africa, New Guinea, and Hispaniola (i.e., the Dominican Republic and Haiti); *P. vivax* is more common in Central America. The prevalence of these two species is approximately equal in South America, the Indian subcontinent, eastern Asia, and Oceania. *P. malariae* is found in most endemic areas, especially throughout sub-Saharan Africa, but is much less common. *P. ovale* is relatively unusual outside of Africa and, where it is found, comprises <1% of isolates. Patients infected with *P. knowlesi* have been identified on the island of Borneo and to a lesser extent elsewhere in Southeast Asia where the main hosts, long-tailed and pig-tailed macaques, are found.

FIGURE 119-2

Malaria-endemic countries in the Americas (***bottom***) and in Africa, the Middle East, Asia, and the South Pacific (***top***), 2007. CAR, Central African Republic; DROC, Democratic Republic of the Congo; UAE, United Arab Emirates.

The epidemiology of malaria is complex and may vary considerably even within relatively small geographic areas. Endemicity traditionally has been defined in terms of parasitemia rates or palpable-spleen rates in children 2–9 years of age as hypoendemic (<10%), mesoendemic (11–50%), hyperendemic (51–75%), and holoendemic (>75%); however, it is uncommon to use these indices for planning control programs because statistically valid national surveys are not done routinely in most endemic areas. In holo- and hyperendemic areas (e.g., certain regions of tropical Africa or coastal New Guinea) where there is intense *P. falciparum* transmission, people may sustain more than one infectious mosquito bite per day and are infected repeatedly throughout their lives. In such settings, rates of morbidity and mortality due to malaria are considerable during early childhood. Immunity against disease is hard won in these areas, and the burden of disease in young children is high; by adulthood, however, most malarial infections are asymptomatic. Constant, frequent, year-round infection is termed *stable transmission*. In areas where transmission is low, erratic, or focal, full protective immunity is not acquired, and symptomatic disease may occur at all ages. This situation usually exists in hypoendemic areas and is termed *unstable transmission*. Even in stable transmission areas, there is often an increased incidence of symptomatic malaria coinciding with increased mosquito breeding and transmission during the rainy season. Malaria can behave like an epidemic disease in some areas, particularly those with unstable malaria, such as northern India (the state of Rajasthan), Sri Lanka, Iraq, Turkey, the horn of Africa, Rwanda, Burundi, southern Africa, Madagascar, and central Asia. An epidemic can develop when there are changes in environmental, economic, or social conditions, such as heavy rains following drought or migrations (usually of refugees or workers) from a nonmalarious region to an area of high transmission; a breakdown in malaria control and prevention services can intensify epidemic conditions. This situation usually results in considerable mortality among all age groups.

The principal determinants of the epidemiology of malaria are the number (density), the human-biting habits, and the longevity of the anopheline mosquito vectors. Not all of the >400 anophelines can transmit malaria, and the ~40 species that do so vary considerably in their efficiency as malaria vectors. More specifically, the transmission of malaria is directly proportional to the density of the vector, the square of the number of human bites per day per mosquito, and the tenth power of the probability of the mosquito's surviving for 1 day. Mosquito longevity is particularly important because the portion of the parasite's life cycle that takes place within the mosquito—from gametocyte ingestion to subsequent inoculation (*sporogony*)—lasts 8–30 days, depending on ambient temperature; thus, to transmit malaria, the mosquito must survive for >7 days. Sporogony is not completed at cooler temperatures—i.e., <16°C for *P. vivax* and <21°C for *P. falciparum*; thus transmission does not occur below these temperatures, although malaria outbreaks and transmission have occurred in the highlands (>1500 m) of east Africa, which were previously free of vectors. The most effective mosquito vectors of malaria are those, such as *Anopheles gambiae* in Africa, which are long-lived, occur in high densities in tropical climates, breed readily, and bite humans in preference to other animals. The entomologic inoculation rate (EIR; the number of sporozoite-positive mosquito bites per person per year) is the most common measure of malaria transmission and varies from <1 in some parts of Latin America and Southeast Asia to >300 in parts of tropical Africa.

ERYTHROCYTE CHANGES IN MALARIA

After invading an erythrocyte, the growing malarial parasite progressively consumes and degrades intracellular proteins, principally hemoglobin. The potentially toxic heme is detoxified by lipid-mediated crystallization to biologically inert hemozoin (malaria pigment). The parasite also alters the RBC membrane by changing its transport properties, exposing cryptic surface antigens, and inserting new parasite-derived proteins. The RBC becomes more irregular in shape, more antigenic, and less deformable.

In *P. falciparum* infections, membrane protuberances appear on the erythrocyte's surface 12–15 h after the cell's invasion. These "knobs" extrude a high-molecular-weight, antigenically variant, strain-specific erythrocyte membrane adhesive protein (PfEMP1) that mediates attachment to receptors on venular and capillary endothelium—an event termed *cytoadherence*. Several vascular receptors have been identified, of which intercellular adhesion molecule 1 (ICAM-1) is probably the most important in the brain, chondroitin sulfate B in the placenta, and CD36 in most other organs. Thus, the infected erythrocytes stick inside and eventually block capillaries and venules. At the same stage, these *P. falciparum*–infected RBCs may also adhere to uninfected RBCs (to form rosettes) and to other parasitized erythrocytes (agglutination). The processes of cytoadherence, rosetting, and agglutination are central to the pathogenesis of falciparum malaria. They result in the sequestration of RBCs containing mature forms of the parasite in vital organs (particularly the brain), where they interfere with microcirculatory flow and metabolism. Sequestered parasites continue to develop out of reach of the principal host defense mechanism: splenic processing and filtration. As a consequence, only the younger ring forms of the asexual parasites are seen circulating in the peripheral blood in falciparum malaria, and the level of peripheral parasitemia underestimates the true number of parasites within the body. Severe malaria is also associated with reduced deformability of the uninfected erythrocytes, which compromises their passage through the partially obstructed capillaries and venules and shortens RBC survival.

In the other three ("benign") human malarias, sequestration does not occur, and all stages of the parasite's development are evident on peripheral-blood smears. Whereas *P. vivax*, *P. ovale*, and *P. malariae* show a marked predilection for either young RBCs (*P. vivax*, *P. ovale*) or old cells (*P. malariae*) and produce a level of parasitemia that

is seldom >2%, *P. falciparum* can invade erythrocytes of all ages and may be associated with very high levels of parasitemia.

HOST RESPONSE

Initially, the host responds to plasmodial infection by activating nonspecific defense mechanisms. Splenic immunologic and filtrative clearance functions are augmented in malaria, and the removal of both parasitized and uninfected erythrocytes is accelerated. The parasitized cells escaping splenic removal are destroyed when the schizont ruptures. The material released induces the activation of macrophages and the release of proinflammatory mononuclear cell–derived cytokines, which cause fever and exert other pathologic effects. Temperatures of ≥40°C damage mature parasites; in untreated infections, the effect of such temperatures is to further synchronize the parasitic cycle, with eventual production of the regular fever spikes and rigors that originally served to characterize the different malarias. These regular fever patterns (tertian, every 2 days; quartan, every 3 days) are seldom seen today in patients who receive prompt and effective antimalarial treatment.

The geographic distributions of sickle cell disease, hemoglobins C and E, hereditary ovalocytosis, the thalassemias, and glucose-6-phosphate dehydrogenase (G6PD) deficiency closely resemble that of falciparum malaria before the introduction of control measures. This similarity suggests that these genetic disorders confer protection against death from falciparum malaria. For example, HbA/S heterozygotes (sickle cell trait) have a sixfold reduction in the risk of dying from severe falciparum malaria. This decrease in risk appears to be related to impaired parasite growth at low oxygen tensions and reduced parasitized red cell cytoadherence. Parasite multiplication in HbA/E heterozygotes is reduced at high parasite densities. In Melanesia, children with α-thalassemia appear to have more frequent malaria (both vivax and falciparum) in the early years of life, and this pattern of infection appears to protect them against severe disease. In Melanesian ovalocytosis, rigid erythrocytes resist merozoite invasion, and the intraerythrocytic milieu is hostile.

Nonspecific host defense mechanisms stop the infection's expansion, and the subsequent strain-specific immune response then controls the infection. Eventually, exposure to sufficient strains confers protection from high-level parasitemia and disease but not from infection. As a result of this state of infection without illness (*premunition*), asymptomatic parasitemia is common among adults and older children living in regions with stable and intense transmission (i.e., holo- or hyperendemic areas). Immunity is mainly specific for both the species and the strain of infecting malarial parasite. Both humoral immunity and cellular immunity are necessary for protection, but the mechanisms of each are incompletely understood (Fig. 119-1). Immune individuals have a polyclonal increase in serum levels of IgM, IgG, and IgA, although much of this antibody is unrelated to protection. Antibodies to a variety of parasitic antigens presumably act in concert to limit in vivo replication of the parasite. In the case of falciparum malaria, the most important of these antigens is the surface adhesin—the variant protein PfEMP1 mentioned earlier. Passively transferred IgG from immune adults has been shown to reduce levels of parasitemia in children; although parasitemia in very young infants can occur, passive transfer of maternal antibody contributes to the relative (but not complete) protection of infants from severe malaria in the first months of life. This complex immunity to disease declines when a person lives outside an endemic area for several months or longer.

Several factors retard the development of cellular immunity to malaria. These factors include the absence of major histocompatibility antigens on the surface of infected RBCs, which precludes direct T cell recognition; malaria antigen–specific immune unresponsiveness; and the enormous strain diversity of malarial parasites, along with the ability of the parasites to express variant immunodominant antigens on the erythrocyte surface that change during the period of infection. Parasites may persist in the blood for months (or, in the case of *P. malariae*, for many years) if treatment is not given. The complexity of the immune response in malaria, the sophistication of the parasites' evasion mechanisms, and the lack of a good in vitro correlate with clinical immunity have all slowed progress toward an effective vaccine.

CLINICAL FEATURES

Malaria is a very common cause of fever in tropical countries. The first symptoms of malaria are nonspecific; the lack of a sense of well-being, headache, fatigue, abdominal discomfort, and muscle aches followed by fever are all similar to the symptoms of a minor viral illness. In some instances, a prominence of headache, chest pain, abdominal pain, arthralgia, myalgia, or diarrhea may suggest another diagnosis. Although headache may be severe in malaria, there is not neck stiffness or photophobia as occurs in meningitis. While myalgia may be prominent, it is not usually as severe as in dengue fever, and the muscles are not tender as in leptospirosis or typhus. Nausea, vomiting, and orthostatic hypotension are common. The classic malarial paroxysms, in which fever spikes, chills, and rigors occur at regular intervals, are relatively unusual and suggest infection with *P. vivax* or *P. ovale*. The fever is irregular at first (that of falciparum malaria may never become regular); the temperature of nonimmune individuals and children often rises above 40°C in conjunction with tachycardia and sometimes delirium. Although childhood febrile convulsions may occur with any of the malarias, generalized seizures are specifically associated with falciparum malaria and may herald the development of encephalopathy (cerebral malaria). Many clinical abnormalities have been described in acute malaria, but most patients with uncomplicated infections have few abnormal physical findings other than fever, malaise,

mild anemia, and (in some cases) a palpable spleen. Anemia is common among young children living in areas with stable transmission, particularly where resistance has compromised the efficacy of antimalarial drugs. In nonimmune individuals with acute malaria, the spleen takes several days to become palpable, but splenic enlargement is found in a high proportion of otherwise healthy individuals in malaria-endemic areas and reflects repeated infections. Slight enlargement of the liver is also common, particularly among young children. Mild jaundice is common among adults; it may develop in patients with otherwise uncomplicated malaria and usually resolves over 1–3 weeks. Malaria is not associated with a rash like those seen in meningococcal septicemia, typhus, enteric fever, viral exanthems, and drug reactions. Petechial hemorrhages in the skin or mucous membranes—features of viral hemorrhagic fevers and leptospirosis—develop only rarely in severe falciparum malaria.

SEVERE FALCIPARUM MALARIA

Appropriately and promptly treated, uncomplicated falciparum malaria (i.e., the patient can swallow medicines and food) carries a mortality rate of ~0.1%. However, once vital-organ dysfunction occurs or the total proportion of erythrocytes infected increases to >2% (a level corresponding to $>10^{12}$ parasites in an adult), mortality risk rises steeply. The major manifestations of severe falciparum malaria are shown in **Table 119-2**, and features indicating a poor prognosis are listed in **Table 119-3**.

Cerebral malaria

Coma is a characteristic and ominous feature of falciparum malaria and, despite treatment, is associated with death rates of ~20% among adults and 15% among children. Any obtundation, delirium, or abnormal behavior

TABLE 119-2

MANIFESTATIONS OF SEVERE FALCIPARUM MALARIA

SIGNS	MANIFESTATIONS
Major	
Unarousable coma/cerebral malaria	Failure to localize or respond appropriately to noxious stimuli; coma persisting for >30 min after generalized convulsion
Acidemia/acidosis	Arterial pH of <7.25 or plasma bicarbonate level of <15 mmol/L; venous lactate level of >5 mmol/L; manifests as labored deep breathing, often termed "respiratory distress"
Severe normochromic, normocytic anemia	Hematocrit of <15% or hemoglobin level of <50 g/L (<5 g/dL) with parasitemia level of >100,000/μL
Renal failure	Urine output (24 h) of <400 mL in adults or <12 mL/kg in children; no improvement with rehydration; serum creatinine level of >265 μmol/L (>3 mg/dL)
Pulmonary edema/adult respiratory distress syndrome	Noncardiogenic pulmonary edema, often aggravated by overhydration
Hypoglycemia	Plasma glucose level of <2.2 mmol/L (<40 mg/dL)
Hypotension/shock	Systolic blood pressure of <50 mmHg in children 1–5 years or <80 mmHg in adults; core/skin temperature difference of >10°C; capillary refill >2 s
Bleeding/disseminated intravascular coagulation	Significant bleeding and hemorrhage from the gums, nose, and gastrointestinal tract and/or evidence of disseminated intravascular coagulation
Convulsions	More than two generalized seizures in 24 h; signs of continued seizure activity sometimes subtle (e.g., tonic-clonic eye movements without limb or face movement)
Hemoglobinuria[a]	Macroscopic black, brown, or red urine; not associated with effects of oxidant drugs and red blood cell enzyme defects (such as G6PD deficiency)
Other	
Impaired consciousness/arousable	Unable to sit or stand without support
Extreme weakness	Prostration; inability to sit unaided[b]
Hyperparasitemia	Parasitemia level of >5% in nonimmune patients (>20% in any patient)
Jaundice	Serum bilirubin level of >50 mmol/L (>3 mg/dL) if combined with other evidence of vital-organ dysfunction

[a]Hemoglobinuria may occur in uncomplicated malaria.
[b]In a child who is normally able to sit.
Abbreviation: G6PD, glucose-6-phosphate dehydrogenase.

TABLE 119-3

FEATURES INDICATING A POOR PROGNOSIS IN SEVERE FALCIPARUM MALARIA
Clinical
Marked agitation
Hyperventilation (respiratory distress)
Hypothermia (<36.5°C)
Bleeding
Deep coma
Repeated convulsions
Anuria
Shock
Laboratory
Biochemistry
Hypoglycemia (<2.2 mmol/L)
Hyperlactatemia (>5 mmol/L)
Acidosis (arterial pH <7.3, serum HCO_3 <15 mmol/L)
Elevated serum creatinine (>265 μmol/L)
Elevated total bilirubin (>50 μmol/L)
Elevated liver enzymes (AST/ALT 3 times upper limit of normal)
Elevated muscle enzymes (CPK ↑, myoglobin ↑)
Elevated urate (>600 μmol/L)
Hematology
Leukocytosis (>12,000/μL)
Severe anemia (PCV <15%)
Coagulopathy
Decreased platelet count (<50,000/μL)
Prolonged prothrombin time (>3 s)
Prolonged partial thromboplastin time
Decreased fibrinogen (<200 mg/dL)
Parasitology
Hyperparasitemia
Increased mortality at >100,000/μL
High mortality at >500,000/μL
>20% of parasites identified as pigment-containing trophozoites and schizonts
>5% of neutrophils with visible pigment

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; PCV, packed cell volume.

should be taken very seriously. The onset may be gradual or sudden following a convulsion.

Cerebral malaria manifests as diffuse symmetric encephalopathy; focal neurologic signs are unusual. Although some passive resistance to head flexion may be detected, signs of meningeal irritation are absent. The eyes may be divergent and a pout reflex is common, but other primitive reflexes are usually absent. The corneal reflexes are preserved, except in deep coma. Muscle tone may be either increased or decreased. The tendon reflexes are variable, and the plantar reflexes may be flexor or extensor; the abdominal and cremasteric reflexes are absent. Flexor or extensor posturing may be seen. On routine funduscopy, ~15% of patients have retinal hemorrhages; with pupillary dilatation and indirect ophthalmoscopy, this figure increases to 30–40%. Other funduscopic abnormalities **(Fig. 119-3)** include discrete spots of retinal opacification (30–60%), papilledema (8%

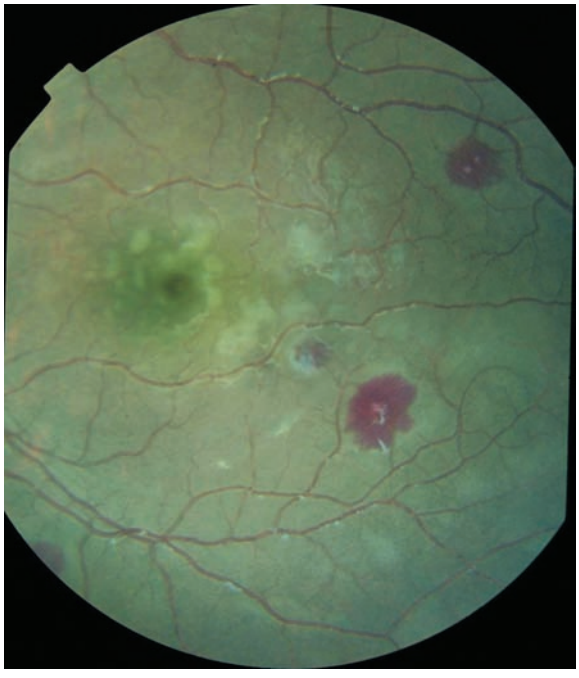


FIGURE 119-3
The eye in cerebral malaria: perimacular whitening and pale-centered retinal hemorrhages. (*Courtesy of N. Beare, T. Taylor, S. Harding, S. Lewallen, and M. Molyneux; with permission.*)

among children, rare among adults), cotton wool spots (<5%), and decolorization of a retinal vessel or segment of vessel (occasional cases). Convulsions, usually generalized and often repeated, occur in ~10% of adults and up to 50% of children with cerebral malaria. More covert seizure activity is also common, particularly among children, and may manifest as repetitive tonic-clonic eye movements or even hypersalivation. Whereas adults rarely (i.e., in <3% of cases) suffer neurologic sequelae, ~5% of children surviving cerebral malaria—especially those with hypoglycemia, severe anemia, repeated seizures, and deep coma—have residual neurologic deficits when they regain consciousness; hemiplegia, cerebral palsy, cortical blindness, deafness, and impaired cognition and learning (all of varying duration) have been reported. The majority of these deficits improve markedly or resolve completely within 6 months. Approximately 10% of children surviving cerebral malaria have a persistent language deficit. The incidence of epilepsy is increased and the life expectancy decreased among these children.

Hypoglycemia

Hypoglycemia, an important and common complication of severe malaria, is associated with a poor prognosis and is particularly problematic in children and pregnant women. Hypoglycemia in malaria results from a failure of hepatic gluconeogenesis and an increase in the consumption of glucose by both the host and, to a much lesser extent, the malaria parasites. To compound the situation, quinine (and quinidine), which is still widely used for the treatment of both severe and uncomplicated falciparum

malaria, is a powerful stimulant of pancreatic insulin secretion. Hyperinsulinemic hypoglycemia is especially troublesome in pregnant women receiving quinine treatment. In severe disease, the clinical diagnosis of hypoglycemia is difficult: the usual physical signs (sweating, gooseflesh, tachycardia) are absent, and the neurologic impairment caused by hypoglycemia cannot be distinguished from that caused by malaria.

Acidosis

Acidosis, an important cause of death from severe malaria, results from accumulation of organic acids. Hyperlactatemia commonly coexists with hypoglycemia. In adults, coexisting renal impairment often compounds the acidosis; in children, ketoacidosis may also contribute. Other still-unidentified organic acids are major contributors to acidosis. Acidotic breathing, sometimes called respiratory distress, is a sign of poor prognosis. It is often followed by circulatory failure refractory to volume expansion or inotropic drug treatment and ultimately by respiratory arrest. The plasma concentrations of bicarbonate or lactate are the best biochemical prognosticators in severe malaria. Lactic acidosis is caused by the combination of anaerobic glycolysis in tissues where sequestered parasites interfere with microcirculatory flow, hypovolemia, lactate production by the parasites, and a failure of hepatic and renal lactate clearance. The prognosis of severe acidosis is poor.

Noncardiogenic pulmonary edema

Adults with severe falciparum malaria may develop noncardiogenic pulmonary edema even after several days of antimalarial therapy. The pathogenesis of this variant of the adult respiratory distress syndrome is unclear. The mortality rate is >80%. This condition can be aggravated by overly vigorous administration of IV fluid. Noncardiogenic pulmonary edema can also develop in otherwise uncomplicated vivax malaria, where recovery is usual.

Renal impairment

Renal impairment is common among adults with severe falciparum malaria but rare among children. The pathogenesis of renal failure is unclear but may be related to erythrocyte sequestration and agglutination interfering with renal microcirculatory flow and metabolism. Clinically and pathologically, this syndrome manifests as acute tubular necrosis. Renal cortical necrosis never develops. Acute renal failure may occur simultaneously with other vital-organ dysfunction (in which case the mortality risk is high) or may progress as other disease manifestations resolve. In survivors, urine flow resumes in a median of 4 days, and serum creatinine levels return to normal in a mean of 17 days. Early dialysis or hemofiltration considerably enhances the likelihood of a patient's survival, particularly in acute hypercatabolic renal failure.

Hematologic abnormalities

Anemia results from accelerated RBC removal by the spleen, obligatory RBC destruction at parasite schizogony, and ineffective erythropoiesis. In severe malaria, both infected and uninfected RBCs show reduced deformability, which correlates with prognosis and development of anemia. Splenic clearance of all RBCs is increased. In nonimmune individuals and in areas with unstable transmission, anemia can develop rapidly and transfusion is often required. As a consequence of repeated malarial infections, children in many areas of Africa may develop severe anemia resulting from both shortened survival of uninfected RBCs and marked dyserythropoiesis. Anemia is a common consequence of antimalarial drug resistance, which results in repeated or continued infection.

Slight coagulation abnormalities are common in falciparum malaria, and mild thrombocytopenia is usual. Of patients with severe malaria, <5% have significant bleeding with evidence of disseminated intravascular coagulation. Hematemesis from stress ulceration or acute gastric erosions may also occur rarely.

Liver dysfunction

Mild hemolytic jaundice is common in malaria. Severe jaundice is associated with *P. falciparum* infections; is more common among adults than among children; and results from hemolysis, hepatocyte injury, and cholestasis. When accompanied by other vital-organ dysfunction (often renal impairment), liver dysfunction carries a poor prognosis. Hepatic dysfunction contributes to hypoglycemia, lactic acidosis, and impaired drug metabolism. Occasional patients with falciparum malaria may develop deep jaundice (with hemolytic, hepatic, and cholestatic components) without evidence of other vital-organ dysfunction.

Other complications

HIV/AIDS predisposes to more severe malaria in nonimmune individuals. Malaria anemia is worsened by concurrent infections with intestinal helminths, hookworm in particular. Septicemia may complicate severe malaria, particularly in children. Differentiating severe malaria from sepsis with incidental parasitemia in childhood is very difficult. In endemic areas, *Salmonella* bacteremia has been associated specifically with *P. falciparum* infections. Chest infections and catheter-induced urinary tract infections are common among patients who are unconscious for >3 days. Aspiration pneumonia may follow generalized convulsions. The frequency of complications of severe falciparum malaria is summarized in **Table 119-4**.

MALARIA IN PREGNANCY

In areas of high malaria transmission, falciparum malaria in primi- and secundigravid women is associated with low birth weight (average reduction, ~170 g)

TABLE 119-4

RELATIVE INCIDENCE OF SEVERE COMPLICATIONS OF FALCIPARUM MALARIA

COMPLICATION	NON-PREGNANT ADULTS	PREGNANT WOMEN	CHILDREN
Anemia	+	++	+++
Convulsions	+	+	+++
Hypoglycemia	+	+++	+++
Jaundice	+++	+++	+
Renal failure	+++	+++	–
Pulmonary edema	++	+++	+

Note: –, rare; +, infrequent; ++, frequent; +++, very frequent.

and consequently increased infant and childhood mortality rates. In general, infected mothers in areas of stable transmission remain asymptomatic despite intense accumulation of parasitized erythrocytes in the placental microcirculation. Maternal HIV infection predisposes pregnant women to malaria, predisposes their newborns to congenital malarial infection, and exacerbates the reduction in birth weight associated with malaria.

In areas with unstable transmission of malaria, pregnant women are prone to severe infections and are particularly vulnerable to high-level parasitemia with anemia, hypoglycemia, and acute pulmonary edema. Fetal distress, premature labor, and stillbirth or low birth weight are common results. Fetal death is usual in severe malaria. Congenital malaria occurs in <5% of newborns whose mothers are infected; its frequency and the level of parasitemia are related directly to the parasite density in maternal blood and in the placenta. *P. vivax* malaria in pregnancy is also associated with a reduction in birth weight (average, 110 g), but, in contrast to the situation in falciparum malaria, this effect is more pronounced in multigravid than in primigravid women. About 150,000 women die in childbirth yearly, with most deaths occurring in low-income countries; maternal death from hemorrhage at childbirth is correlated with malaria-induced anemia.

MALARIA IN CHILDREN

Most of the nearly 1 million persons who die of falciparum malaria each year are young African children. Convulsions, coma, hypoglycemia, metabolic acidosis, and severe anemia are relatively common among children with severe malaria, whereas deep jaundice, acute renal failure, and acute pulmonary edema are unusual. Severely anemic children may present with labored deep breathing, which in the past has been attributed incorrectly to "anemic congestive cardiac failure," but in fact is usually caused by metabolic acidosis, often compounded by hypovolemia. In general, children tolerate antimalarial drugs well and respond rapidly to treatment.

TRANSFUSION MALARIA

Malaria can be transmitted by blood transfusion, needlestick injury, sharing of needles by infected injection drug users, or organ transplantation. The incubation period in these settings is often short because there is no preerythrocytic stage of development. The clinical features and management of these cases are the same as for naturally acquired infections. Radical chemotherapy with primaquine is unnecessary for transfusion-transmitted *P. vivax* and *P. ovale* infections.

CHRONIC COMPLICATIONS OF MALARIA

TROPICAL SPLENOMEGALY (HYPERREACTIVE MALARIAL SPLENOMEGALY)

Chronic or repeated malarial infections produce hypergammaglobulinemia; normochromic, normocytic anemia; and, in certain situations, splenomegaly. Some residents of malaria-endemic areas in tropical Africa and Asia exhibit an abnormal immunologic response to repeated infections that is characterized by massive splenomegaly, hepatomegaly, marked elevations in serum titers of IgM and malarial antibody, hepatic sinusoidal lymphocytosis, and (in Africa) peripheral B cell lymphocytosis. This syndrome has been associated with the production of cytotoxic IgM antibodies to CD8+ T lymphocytes, antibodies to CD5+ T lymphocytes, and an increase in the ratio of CD4+ T cells to CD8+ T cells. These events may lead to uninhibited B cell production of IgM and the formation of cryoglobulins (IgM aggregates and immune complexes). This immunologic process stimulates reticuloendothelial hyperplasia and clearance activity and eventually produces splenomegaly. Patients with hyperreactive malarial splenomegaly (HMS) present with an abdominal mass or a dragging sensation in the abdomen and occasional sharp abdominal pains suggesting perisplenitis. Anemia and some degree of pancytopenia are usually evident, and in some cases malarial parasites cannot be found in peripheral-blood smears. Vulnerability to respiratory and skin infections is increased; many patients die of overwhelming sepsis. Persons with HMS who are living in endemic areas should receive antimalarial chemoprophylaxis; the results are usually good. In nonendemic areas, antimalarial treatment is advised. In some cases refractory to therapy, clonal lymphoproliferation may develop and then evolve into a malignant lymphoproliferative disorder.

QUARTAN MALARIAL NEPHROPATHY

Chronic or repeated infections with *P. malariae* (and possibly with other malarial species) may cause soluble immune-complex injury to the renal glomeruli, resulting in the nephrotic syndrome. Other unidentified factors must contribute to this process since only a very small proportion of infected patients develop renal disease. The histologic appearance is that of focal or segmental glomerulonephritis with splitting of the capillary basement membrane. Subendothelial dense deposits are seen on electron microscopy, and immunofluorescence reveals deposits of complement and immunoglobulins; in samples of renal tissue from children, *P. malariae* antigens are often visible. A coarse-granular pattern of basement membrane immunofluorescent deposits (predominantly IgG3) with selective proteinuria carries a better prognosis than a fine-granular, predominantly IgG2 pattern with nonselective proteinuria. Quartan nephropathy usually responds poorly to treatment with either antimalarial agents or glucocorticoids and cytotoxic drugs.

BURKITT'S LYMPHOMA AND EPSTEIN-BARR VIRUS INFECTION

It is possible that malaria-related immune dysregulation provokes infection with lymphoma viruses. Burkitt's lymphoma is strongly associated with Epstein-Barr virus. The prevalence of this childhood tumor is high in malarious areas of Africa.

DIAGNOSIS

DEMONSTRATION OF THE PARASITE

The diagnosis of malaria rests on the demonstration of asexual forms of the parasite in stained peripheral-blood smears. After a negative blood smear, repeat smears should be made if there is a high degree of suspicion. Of the Romanowsky stains, Giemsa at pH 7.2 is preferred; Field's, Wright's, or Leishman's stain can also be used. Both thin (**Figs. 119-4** and **119-5**; see also Figs. 121-3 and 121-4) and thick **(Figs. 119-6, 119-7, 119-8, and 119-9)** blood smears should be examined. The thin blood smear should be rapidly air-dried, fixed in anhydrous methanol, and stained; the RBCs in the tail of the film should then be examined under oil immersion (×1000 magnification). The level of parasitemia is expressed as the number of parasitized erythrocytes per 1000 RBCs. The thick blood film should be of uneven thickness. The smear should be dried thoroughly and stained without fixing. As many layers of erythrocytes overlie one another and are lysed during the staining procedure, the thick film has the

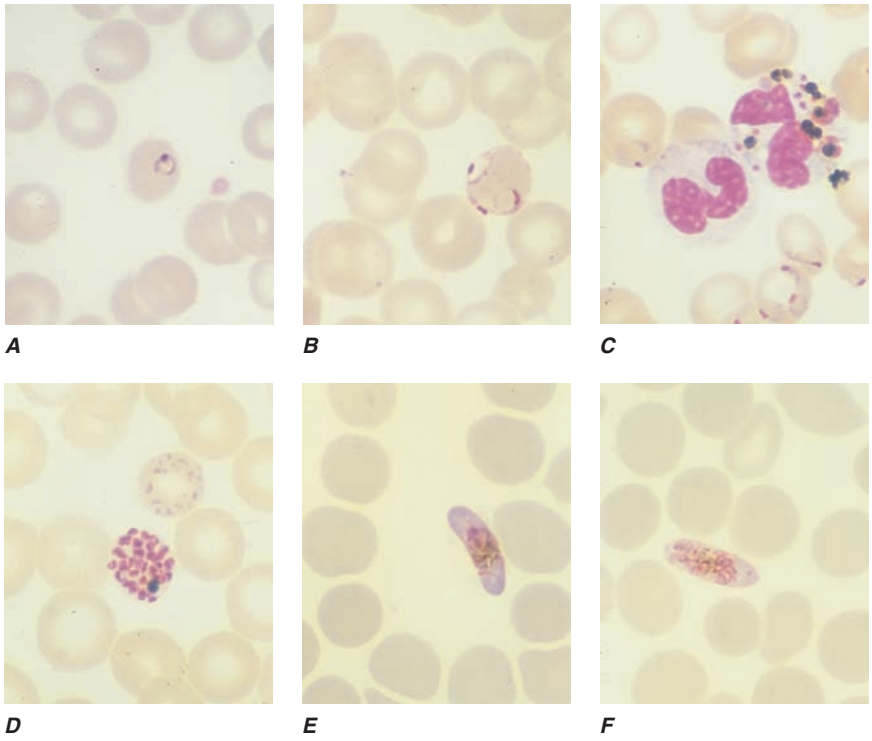


FIGURE 119-4
Thin blood films of *Plasmodium falciparum*. *A.* Young trophozoites. ***B.*** Old trophozoites. ***C.*** Pigment in polymorphonuclear cells and trophozoites. ***D.*** Mature schizonts. ***E.*** Female gametocytes. ***F.*** Male gametocytes. (*Reproduced from Bench Aids for the Diagnosis of Malaria Infections, 2nd ed, with the permission of the World Health Organization.*)

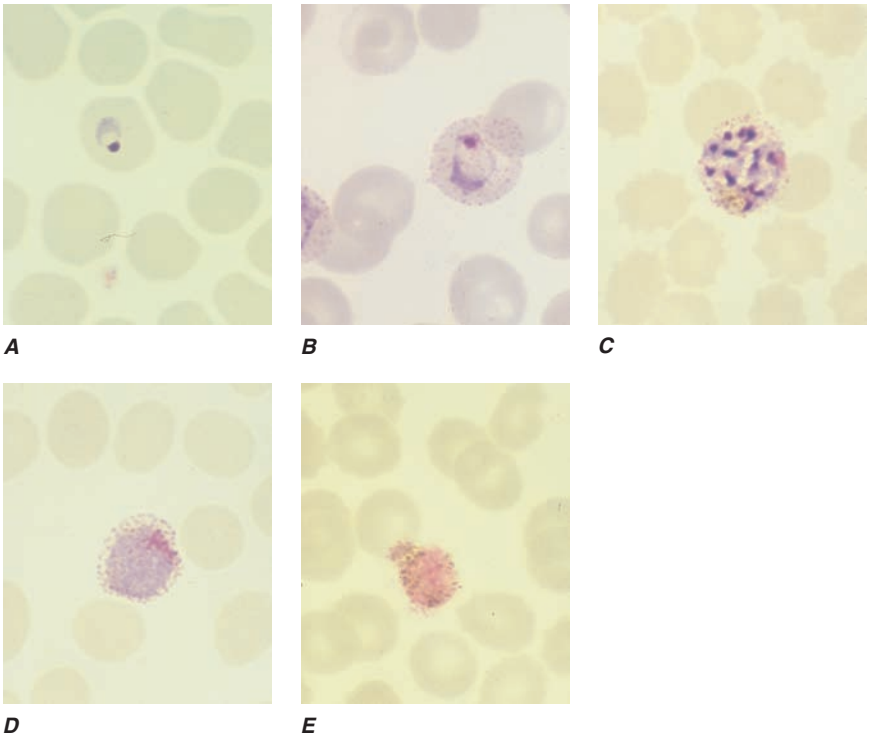


FIGURE 119-5
Thin blood films of *Plasmodium vivax*. *A.* Young trophozoites. ***B.*** Old trophozoites. ***C.*** Mature schizonts. ***D.*** Female gametocytes. ***E.*** Male gametocytes. (*Reproduced from Bench Aids for the Diagnosis of Malaria Infections, 2nd ed, with the permission of the World Health Organization.*)

advantage of concentrating the parasites (by 40- to 100-fold compared with a thin blood film) and thus increasing diagnostic sensitivity. Both parasites and white blood cells (WBCs) are counted, and the number of parasites per unit volume is calculated from the total leukocyte count. Alternatively, a WBC count of 8000/μL is assumed. This figure is converted to the number of parasitized erythrocytes per microliter. A minimum of 200 WBCs should be counted under oil immersion. Interpretation of blood smear films requires some experience because artifacts are common. Before a thick smear is judged to be negative, 100–200 fields should be examined under oil immersion. In high-transmission areas, the presence of up to 10,000 parasites/μL of blood may be tolerated without symptoms or signs in partially immune individuals. Thus in these areas the detection of malaria parasites is sensitive but has low specificity in identifying malaria as the cause of illness. Low-density parasitemia is common in other conditions causing fever.

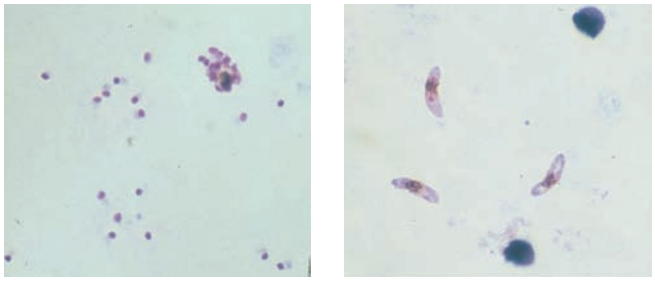
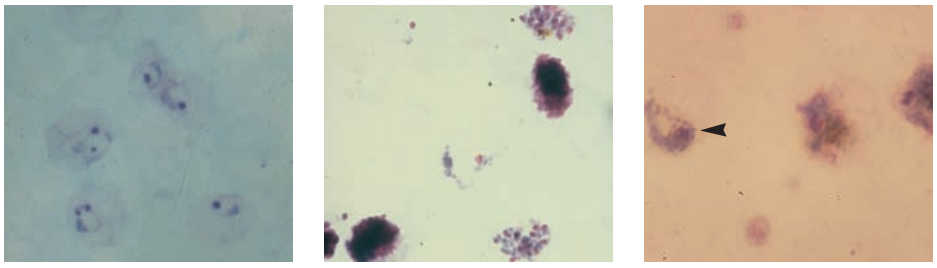


FIGURE 119-6
Thick blood films of ***Plasmodium falciparum*. *A.*** Trophozoites. ***B.*** Gametocytes. (*Reproduced from Bench Aids for the Diagnosis of Malaria Infections, 2nd ed, with the permission of the World Health Organization.*)

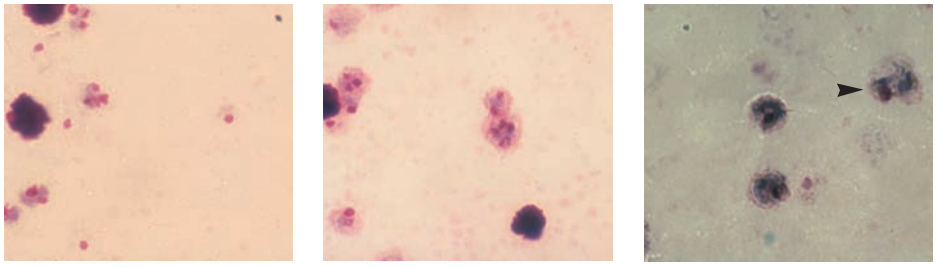
Rapid, simple, sensitive, and specific antibody-based diagnostic stick or card tests that detect *P. falciparum*–specific, histidine-rich protein 2 (PfHRP2) or lactate dehydrogenase antigens in finger-prick blood samples are now being used widely in control programs **(Table 119-5)**. Some of these rapid diagnostic tests (RDTs) carry a second antibody, which allows falciparum malaria to be distinguished from the less dangerous malarias. PfHRP2-based tests may remain positive for several weeks after acute infection. This feature is a disadvantage in high-transmission areas where infections are frequent but is of value in the diagnosis of severe malaria in patients who have taken antimalarial drugs and cleared peripheral parasitemia (but in whom the PfHRP2 test remains strongly positive). RDTs are replacing microscopy in many areas because of their simplicity and speed, but they are relatively expensive and do not quantify parasitemia.

The relationship between parasitemia and prognosis is complex; in general, patients with $>10^5$ parasites/μL



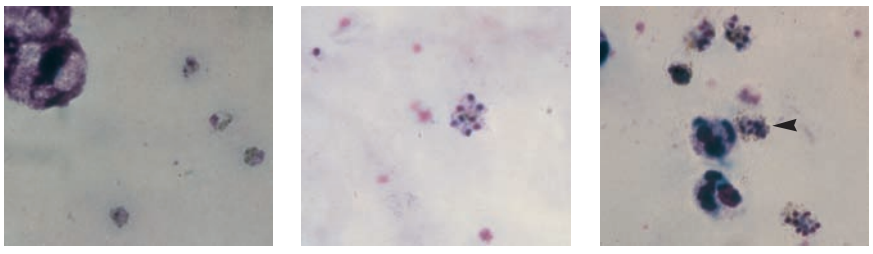
A B C

FIGURE 119-7
Thick blood films of *Plasmodium vivax*. *A.* Trophozoites. ***B.*** Schizonts. ***C.*** Gametocytes. (*Reproduced from Bench Aids for the Diagnosis of Malaria Infections, 2nd ed, with the permission of the World Health Organization.*)



A B C

FIGURE 119-8
Thick blood films of *Plasmodium ovale*. *A.* Trophozoites. ***B.*** Schizonts. ***C.*** Gametocytes. (*Reproduced from Bench Aids for the Diagnosis of Malaria Infections, 2nd ed, with the permission of the World Health Organization.*)



A B C

FIGURE 119-9
Thick blood films of *Plasmodium malariae*. *A.* Trophozoites. ***B.*** Schizonts. ***C.*** Gametocytes. (*Reproduced from Bench Aids for the Diagnosis of Malaria Infections, 2nd ed, with the permission of the World Health Organization.*)

are at increased risk of dying, but nonimmune patients may die with much lower counts, and partially immune persons may tolerate parasitemia levels many times higher with only minor symptoms. In severe malaria, a poor prognosis is indicated by a predominance of more mature *P. falciparum* parasites (i.e., >20% of parasites with visible pigment) in the peripheral-blood film or by the presence of phagocytosed malarial pigment in >5% of neutrophils. In *P. falciparum* infections, gametocytemia peaks 1 week after the peak of asexual parasites. Because the mature gametocytes of *P. falciparum* are not affected by most antimalarial drugs, their persistence does not constitute evidence of drug resistance. Phagocytosed malarial pigment is sometimes seen inside peripheral-blood monocytes or polymorphonuclear leukocytes and may provide a clue to recent infection if malaria parasites are not detectable. After the clearance of the parasites, this intraphagocytic malarial

TABLE 119-5

METHODS FOR THE DIAGNOSIS OF MALARIA[a]

METHOD	PROCEDURE	ADVANTAGES	DISADVANTAGES
Thick blood film[b]	Blood should be uneven in thickness but sufficiently thin to read the hands of a watch through part of the spot. Stain dried, unfixed blood spot with Giemsa, Field's, or another Romanowsky stain. Count number of asexual parasites per 200 WBCs (or per 500 at low densities). Count gametocytes separately.[c]	Sensitive (0.001% parasitemia); species specific; inexpensive	Requires experience (artifacts may be misinterpreted as low-level parasitemia); underestimates true count
Thin blood film[d]	Stain fixed smear with Giemsa, Field's, or another Romanowsky stain. Count number of RBCs containing asexual parasites per 1000 RBCs. In severe malaria, assess stage of parasite development and count neutrophils containing malaria pigment.[e] Count gametocytes separately.[c]	Rapid; species specific; inexpensive; in severe malaria, provides prognostic information[e]	Insensitive (<0.05% parasitemia); uneven distribution of *P. vivax*, as enlarged infected red cells concentrate at leading edge
PfHRP2 dipstick or card test	A drop of blood is placed on the stick or card, which is then immersed in washing solutions. Monoclonal antibody captures the parasite antigen and reads out as a colored band.	Robust and relatively inexpensive; rapid; sensitivity similar to or slightly lower than that of thick films (~0.001% parasitemia)	Detects only *Plasmodium falciparum*; remains positive for weeks after infection[f]; does not quantitate *P. falciparum* parasitemia
Plasmodium LDH dipstick or card test	A drop of blood is placed on the stick or card, which is then immersed in washing solutions. Monoclonal antibodies capture the parasite antigens and read out as colored bands. One band is genus specific (all malarias), and the other is specific for *P. falciparum.*	Rapid; sensitivity similar to or slightly lower than that of thick films for *P. falciparum* (~0.001% parasitemia)	Slightly more difficult preparation than PfHRP2 tests; may miss low-level parasitemia with *P. vivax, P. ovale*, and *P. malariae* and does not speciate these organisms; does not quantitate *P. falciparum* parasitemia
Microtube concentration methods with acridine orange staining	Blood is collected in a specialized tube containing acridine orange, anticoagulant, and a float. After centrifugation, which concentrates the parasitized cells around the float, fluorescence microscopy is performed.	Sensitivity similar or superior to that of thick films (~0.001% parasitemia); ideal for processing large numbers of samples rapidly	Does not speciate or quantitate; requires fluorescence microscopy

[a]Malaria cannot be diagnosed clinically with accuracy, but treatment should be started on clinical grounds if laboratory confirmation is likely to be delayed. In areas of the world where malaria is endemic and transmission is high, low-level asymptomatic parasitemia is common in otherwise healthy people. Thus malaria may not be the cause of a fever, although in this context the presence of >10,000 parasites/μL (~0.2% parasitemia) *does* indicate that malaria is the cause. Antibody and polymerase chain reaction tests have no role in the diagnosis of malaria except that PCR is increasingly used for genotyping and speciation in mixed infections.

[b]Asexual parasites/200 WBCs × 40 = parasite count/μL (assumes a WBC count of 8000/μL). See Figs. 119-6 through 119-9.

[c]Gametocytemia may persist for days or weeks after clearance of asexual parasites. Gametocytemia without asexual parasitemia does not indicate active infection.

[d]Parasitized RBCs (%) × hematocrit × 1256 = parasite count/μL. See Figs. 119-4 and 119-5.

[e]The presence of >100,000 parasites/μL (~2% parasitemia) is associated with an increased risk of severe malaria, but some patients have severe malaria with lower counts. At any level of parasitemia, the finding that >50% of parasites are tiny rings (cytoplasm width less than half of nucleus width) carries a relatively good prognosis. The presence of visible pigment in >20% of parasites or of phagocytosed pigment in >5% of polymorphonuclear leukocytes (indicating massive recent schizogony) carries a worse prognosis.

[f]Persistence of PfHRP2 is a disadvantage in high-transmission settings, where many asymptomatic people have positive tests, but can be used to diagnostic advantage in low-transmission settings when a sick patient has received previous unknown treatment (which, in endemic areas, often consists of antimalarial drugs). A positive PfHRP2 test indicates that the illness is falciparum malaria, even if the blood smear is negative.

Abbreviations: LDH, lactate dehydrogenase; PfHRP2, *P. falciparum* histidine-rich protein 2; RBCs, red blood cells; WBCs, white blood cells.

pigment is often evident for several days in the peripheral blood or for longer in bone marrow aspirates or smears of fluid expressed after intradermal puncture. Staining of parasites with the fluorescent dye acridine orange allows more rapid diagnosis of malaria (but not speciation of the infection) in patients with low-level parasitemia.

LABORATORY FINDINGS

Normochromic, normocytic anemia is usual. The leukocyte count is generally normal, although it may be raised in very severe infections. There is slight monocytosis, lymphopenia, and eosinopenia, with reactive lymphocytosis and eosinophilia in the weeks after the acute infection. The erythrocyte sedimentation rate, plasma viscosity, and levels of C-reactive protein and other acute-phase proteins are high. The platelet count is usually reduced to ~10^5/μL. Severe infections may be accompanied by prolonged prothrombin and partial thromboplastin times and by more severe thrombocytopenia. Levels of antithrombin III are reduced even in mild infection. In uncomplicated malaria, plasma concentrations of electrolytes, blood urea nitrogen (BUN), and creatinine are usually normal. Findings in severe malaria may include metabolic acidosis, with low plasma concentrations of glucose, sodium, bicarbonate, calcium, phosphate, and albumin together with elevations in lactate, BUN, creatinine, urate, muscle and liver enzymes, and conjugated and unconjugated bilirubin. Hypergammaglobulinemia is usual in immune and semi-immune subjects. Urinalysis generally gives normal results. In adults and children with cerebral malaria, the mean opening pressure at lumbar puncture is ~160 mm of cerebrospinal fluid (CSF); usually the CSF is normal or has a slightly elevated total protein level (<1.0 g/L [<100 mg/dL]) and cell count (<20/μL).

TREATMENT Malaria

(Table 119-6) When a patient in or from a malarious area presents with fever, thick and thin blood smears should be prepared and *examined immediately* to confirm the diagnosis and identify the species of infecting parasite (Figs. 119-4 through 119-9). Repeat blood smears should be performed at least every 12–24 h for 2 days if the first smears are negative and malaria is strongly suspected. Alternatively, a rapid antigen detection card or stick test should be performed. Patients with severe malaria or those unable to take oral drugs should receive parenteral antimalarial therapy. If there is any doubt about the resistance status of the infecting organism, it should be considered resistant. Antimalarial drug susceptibility testing can be performed but is rarely available, has poor predictive value in an individual case, and yields results too slowly to influence the choice of treatment. Several drugs are available for oral treatment. The choice of drug depends on the likely sensitivity of the infecting parasites. Despite increasing evidence of chloroquine resistance in *P. vivax* (from parts of Indonesia, Oceania, eastern and southern Asia, and Central and South America), chloroquine remains the treatment of choice for the non-falciparum malarias (*P. vivax*, *P. ovale*, *P. malariae*, *P. knowlesi*) except in Indonesia and Papua New Guinea, where high levels of resistance in *P. vivax* are prevalent.

The treatment of falciparum malaria has changed radically in recent years. In all endemic areas, the World Health Organization (WHO) now recommends artemisinin-based combinations as first-line treatment for uncomplicated falciparum malaria. These rapidly and reliably effective drugs are sometimes unavailable in temperate countries, where treatment recommendations are limited by the registered available drugs. Fake or substandard antimalarials are commonly sold in many Asian and African countries. Thus, careful attention is required at the time of purchase and later, especially when the patient fails to respond as expected. Characteristics of antimalarial drugs are shown in Table 119-7.

SEVERE MALARIA In large studies conducted in Asia, parenteral artesunate, a water-soluble artemisinin derivative, has been shown to reduce mortality rates in severe falciparum malaria among adults by 35% from rates obtained with quinine. Recently, the largest trial ever in severe malaria showed that parenteral artesunate reduced the mortality rate among African children by 22.5% compared with that obtained with quinine. Artesunate has, therefore, become the drug of choice for all patients with severe malaria everywhere. Artesunate is given by IV injection but can also be given by IM injection. Artemether and the closely related drug artemotil (arteether) are oil-based formulations given by IM injection; they are erratically absorbed and do not confer the same survival benefit as artesunate. A rectal formulation of artesunate has been developed as a community-based pre-referral treatment for patients in the rural tropics who cannot take oral medications. Pre-referral administration of rectal artesunate has been shown to decrease mortality risk among severely ill children in communities without access to immediate parenteral treatment. Although the artemisinin compounds are safer than quinine and considerably safer than quinidine, only one formulation is available in the United States. IV artesunate has been approved by the U.S. Food and Drug Administration for emergency use against severe malaria through the Centers for Disease Control and Prevention (CDC) Drug Service (see end of chapter for contact information). The antiarrhythmic quinidine gluconate is as effective as quinine and, as it was more readily available, replaced quinine for the treatment of malaria in the United States. The administration of quinidine must be closely monitored if dysrhythmias and hypotension are to be avoided. A total plasma level >8 μg/mL, a QT_c interval >0.6 s,

TABLE 119-6

REGIMENS FOR THE TREATMENT OF MALARIA

TYPE OF DISEASE OR TREATMENT	REGIMEN(S)
Uncomplicated Malaria	
Known chloroquine-sensitive strains of *Plasmodium vivax, P. malariae, P. ovale, P. knowlesi, P. falciparum*[a]	Chloroquine (10 mg of base/kg stat followed by 5 mg/kg at 12, 24, and 36 h or by 10 mg/kg at 24 h and 5 mg/kg at 48 h) *or* Amodiaquine (10–12 mg of base/kg qd for 3 days)
Radical treatment for *P. vivax or P. ovale* infection	In addition to chloroquine or amodiaquine as detailed above, primaquine (0.5 mg of base/kg qd) should be given for 14 days to prevent relapse. In mild G6PD deficiency, 0.75 mg of base/kg should be given once weekly for 6–8 weeks. Primaquine should not be given in severe G6PD deficiency.
Sensitive *P. falciparum* malaria[b]	Artesunate[c] (4 mg/kg qd for 3 days) plus sulfadoxine (25 mg/kg)/pyrimethamine (1.25 mg/kg) as a single dose *or* Artesunate[c] (4 mg/kg qd for 3 days) plus amodiaquine (10 mg of base/kg qd for 3 days)[d]
Multidrug-resistant *P. falciparum* malaria	Either artemether-lumefantrine[c] (1.5/9 mg/kg bid for 3 days with food) *or* Artesunate[c] (4 mg/kg qd for 3 days) *plus* Mefloquine (25 mg of base/kg—either 8 mg/kg qd for 3 days or 15 mg/kg on day 2 and then 10 mg/kg on day 3)[d]
Second-line treatment/treatment of imported malaria	Either artesunate[c] (2 mg/kg qd for 7 days) or quinine (10 mg of salt/kg tid for 7 days) *plus 1 of the following 3:* 1. Tetracycline[e] (4 mg/kg qid for 7 days) 2. Doxycycline[e] (3 mg/kg qd for 7 days) 3. Clindamycin (10 mg/kg bid for 7 days) *or* Atovaquone-proguanil (20/8 mg/kg qd for 3 days with food)
Severe Falciparum Malaria[f]	
	Artesunate[c] (2.4 mg/kg stat IV followed by 2.4 mg/kg at 12 and 24 h and then daily if necessary)[g] *or, if unavailable, one of the following:* Artemether[c] (3.2 mg/kg stat IM followed by 1.6 mg/kg qd) *or* Quinine dihydrochloride (20 mg of salt/kg[h] infused over 4 h, followed by 10 mg of salt/kg infused over 2–8 h q8h[i]) *or* Quinidine (10 mg of base/kg[h] infused over 1–2 h, followed by 1.2 mg of base/kg per hour[i] with electrocardiographic monitoring)

[a]Very few areas now have chloroquine-sensitive *P. falciparum* malaria (Fig. 119-2).
[b]In areas where the partner drug to artesunate is known to be effective.
[c]Artemisinin derivatives are not readily available in some temperate countries.
[d]Fixed-dose coformulated combinations are available. The World Health Organization now recommends artemisinin combination regimens as first-line therapy for falciparum malaria in all tropical countries and advocates use of fixed-dose combinations.
[e]Tetracycline and doxycycline should not be given to pregnant women or to children <8 years of age.
[f]Oral treatment should be substituted as soon as the patient recovers sufficiently to take fluids by mouth.
[g]Artesunate is the drug of choice when available. The data from large studies in Southeast Asia showed a 35% lower mortality rate than with quinine, and very large studies in Africa showed a 22.5% reduction in mortality rate compared with quinine.
[h]A loading dose should not be given if therapeutic doses of quinine or quinidine have definitely been administered in the previous 24 h. Some authorities recommend a lower dose of quinidine.
[i]Infusions can be given in 0.9% saline and 5–10% dextrose in water. Infusion rates for quinine and quinidine should be carefully controlled.
Abbreviation: G6PD, glucose-6-phosphate dehydrogenase.

TABLE 119-7

PROPERTIES OF ANTIMALARIAL DRUGS

DRUG(S)	PHARMACOKINETIC PROPERTIES	ANTIMALARIAL ACTIVITY	MINOR TOXICITY	MAJOR TOXICITY
Quinine, quinidine	Good oral and IM absorption (quinine); *Cl* and V_d reduced, but plasma protein binding (principally to α1 acid glycoprotein) increased (90%) in malaria; quinine $t_{1/2}$: 16 h in malaria, 11 h in healthy persons; quinidine $t_{1/2}$: 13 h in malaria, 8 h in healthy persons	Acts mainly on trophozoite blood stage; kills gametocytes of *P. vivax*, *P. ovale*, and *P. malariae* (but not *P. falciparum*); no action on liver stages	*Common:* "Cinchonism": tinnitus, high-tone hearing loss, nausea, vomiting, dysphoria, postural hypotension; ECG QT_c interval prolongation (quinine usually by <10% but quinidine by up to 25%) *Rare:* Diarrhea, visual disturbance, rashes *Note:* Very bitter taste	*Common:* Hypoglycemia *Rare:* Hypotension, blindness, deafness, cardiac arrhythmias, thrombocytopenia, hemolysis, hemolytic-uremic syndrome, vasculitis, cholestatic hepatitis, neuromuscular paralysis *Note:* Quinidine more cardiotoxic
Chloroquine	Good oral absorption, very rapid IM and SC absorption; complex pharmacokinetics; enormous *Cl* and V_d (unaffected by malaria); blood concentration profile determined by distribution processes in malaria; $t_{1/2}$: 1–2 months	As for quinine but acts slightly earlier in asexual cycle	*Common:* Nausea, dysphoria, pruritus in dark-skinned patients, postural hypotension *Rare:* Accommodation difficulties, keratopathy, rash *Note:* Bitter taste, well tolerated	*Acute:* Hypotensive shock (parenteral), cardiac arrhythmias, neuropsychiatric reactions *Chronic:* Retinopathy (cumulative dose, >100 g), skeletal and cardiac myopathy
Piperaquine	Adequate oral absorption, enhanced by fats; similar pharmacokinetics to chloroquine; $t_{1/2}$: 21–28 days	As for chloroquine, but retains activity against multidrug-resistant *P. falciparum*	Epigastric pain, diarrhea, slight ECG QT_c prolongation	None identified
Amodiaquine	Good oral absorption; largely converted to active metabolite desethylamodiaquine	As for chloroquine	Nausea (tastes better than chloroquine)	Agranulocytosis; hepatitis, mainly with prophylactic use; should not be used with efavirenz
Primaquine	Complete oral absorption; active metabolite not known; $t_{1/2}$: 7 h	Radical cure; eradicates hepatic forms of *P. vivax* and *P. ovale;* kills all stages of gametocyte development of *P. falciparum*	Nausea, vomiting, diarrhea, abdominal pain, hemolysis, methemoglobinemia	Massive hemolysis in subjects with severe G6PD deficiency
Mefloquine	Adequate oral absorption; no parenteral preparation; $t_{1/2}$: 14–20 days (shorter in malaria)	As for quinine	Nausea, giddiness, dysphoria, fuzzy thinking, sleeplessness, nightmares, sense of dissociation	Neuropsychiatric reactions, convulsions, encephalopathy

(*continued*)

TABLE 119-7

PROPERTIES OF ANTIMALARIAL DRUGS (*CONTINUED*)

DRUG(S)	PHARMACOKINETIC PROPERTIES	ANTIMALARIAL ACTIVITY	MINOR TOXICITY	MAJOR TOXICITY
Halofantrine[b]	Highly variable absorption related to fat intake; $t_{1/2}$: 1–3 days (active desbutyl metabolite $t_{1/2}$: 3–7 days)	As for quinine	Diarrhea	Cardiac conduction disturbances; atrioventricular block; ECG QT_c interval prolongation; potentially lethal ventricular tachyarrhythmias
Lumefantrine	Highly variable absorption related to fat intake; $t_{1/2}$: 3–4 days	As for quinine	None identified	None identified
Artemisinin and derivatives (artemether, artesunate)	Good oral absorption, slow and variable absorption of IM artemether; artesunate and artemether biotransformed to active metabolite dihydroartemisinin; all drugs eliminated very rapidly; $t_{1/2}$: <1 h	Broader stage specificity and more rapid than other drugs; no action on liver stages; kills all but fully mature gametocytes of *P. falciparum*	Reduction in reticulocyte count (but not anemia); neutropenia at high doses	Anaphylaxis, urticaria, fever
Pyrimethamine	Good oral absorption, variable IM absorption; $t_{1/2}$: 4 days	For blood stages, acts mainly on mature forms; causal prophylactic	Well tolerated	Megaloblastic anemia, pancytopenia, pulmonary infiltration
Proguanil (chloroguanide)	Good oral absorption; biotransformed to active metabolite cycloguanil; $t_{1/2}$: 16 h; biotransformation reduced by oral contraceptive use and in pregnancy	Causal prophylactic; not used alone for treatment	Well tolerated; mouth ulcers and rare alopecia	Megaloblastic anemia in renal failure
Atovaquone	Highly variable absorption related to fat intake; $t_{1/2}$: 30–70 h	Acts mainly on trophozoite blood stage	None identified	None identified
Tetracycline, doxycycline[a]	Excellent absorption; $t_{1/2}$: 8 h for tetracycline, 18 h for doxycycline	Weak antimalarial activity; should not be used alone for treatment	Gastrointestinal intolerance, deposition in growing bones and teeth, photosensitivity, moniliasis, benign intracranial hypertension	Renal failure in patients with impaired renal function (tetracycline)

[a]Tetracycline and doxycycline should not be given to pregnant women or to children <8 years of age.
[b]Halofantrine should not be used by patients with long ECG QT_c intervals or known conduction disturbances or by those taking drugs that may affect ventricular repolarization, e.g., quinidine, quinine, mefloquine, chloroquine, neuroleptics, antiarrhythmics, tricyclic antidepressants, terfenidine, or astemizole.
Abbreviations: *Cl*, systemic clearance; ECG, electrocardiogram; G6PD, glucose-6-phosphate dehydrogenase; V_d, total apparent volume of distribution.

or QRS widening beyond 25% of baseline is an indication for slowing infusion rates. If arrhythmia or saline-unresponsive hypotension develops, treatment with this drug should be discontinued. Quinine is safer than quinidine; cardiovascular monitoring is not required except when the recipient has cardiac disease.

Severe falciparum malaria constitutes a medical emergency requiring intensive nursing care and careful management. The patient should be weighed and, if comatose, placed on his or her side or prone. Frequent evaluation of the patient's condition is essential. Ancillary drugs such as high-dose glucocorticoids, urea, heparin, dextran, desferrioxamine, antibody to tumor necrosis factor α, and high-dose phenobarbital (20 mg/kg) have proved either ineffective or harmful in clinical trials and should not be used. In acute renal failure or severe metabolic acidosis, hemofiltration or hemodialysis should be started as early as possible.

Parenteral antimalarial treatment should be started as soon as possible. Artesunate, given by either IV or IM injection, is the agent of choice; it is simple to administer, safe, and rapidly effective. If artesunate is unavailable and artemether, quinine, or quinidine is used, an initial loading dose must be given so that therapeutic concentrations are reached as soon as possible. Both quinine and quinidine will cause dangerous hypotension if injected rapidly; when given IV, they must be administered carefully by rate-controlled infusion only. If this approach is not possible, quinine may be given by deep IM injections into the anterior thigh. The optimal therapeutic range for quinine and quinidine in severe malaria is not known with certainty, but total plasma concentrations of 8–15 mg/L for quinine and 3.5–8.0 mg/L for quinidine are effective and do not cause serious toxicity. The systemic clearance and apparent volume of distribution of these alkaloids are markedly reduced and plasma protein binding is increased in severe malaria, so that the blood concentrations attained with a given dose are higher. If the patient remains seriously ill or in acute renal failure for >2 days, maintenance doses of quinine or quinidine should be reduced by 30–50% to prevent toxic accumulation of the drug. The initial doses should never be reduced. If one of the artemisinin derivatives is given, dose reductions are unnecessary, even in renal failure. Exchange transfusion may be considered for severely ill patients, although the precise indications for this procedure have not been agreed upon. It has been recommended that—if safe and feasible—exchange should be considered for patients with severe malaria, but there is no clear evidence that this measure is beneficial, particularly if artesunate is used. The role of prophylactic anticonvulsants in children is also uncertain. If respiratory support is not available, then a full loading dose of phenobarbital (20 mg/kg) to prevent convulsions should not be given as it may cause respiratory arrest.

When the patient is unconscious, the blood glucose level should be measured every 4–6 h. All patients should receive a continuous infusion of dextrose, and blood concentrations ideally should be maintained above 4 mmol/L. Hypoglycemia (<2.2 mmol/L or 40 mg/dL) should be treated immediately with bolus glucose. The parasite count and hematocrit level should be measured every 6–12 h. Anemia develops rapidly; if the hematocrit falls to <20%, then whole blood (preferably fresh) or packed cells should be transfused slowly, with careful attention to circulatory status. Renal function should be checked daily. Children presenting with severe anemia and acidotic breathing are often hypovolemic; in this situation, resuscitation with crystalloids or blood is indicated. Accurate assessment is vital. Management of fluid balance is difficult in severe malaria, particularly in adults, because of the thin dividing line between overhydration (leading to pulmonary edema) and underhydration (contributing to renal impairment). As soon as the patient can take fluids, oral therapy should be substituted for parenteral treatment.

UNCOMPLICATED MALARIA Infections due to *P. vivax*, *P. knowlesi*, *P. malariae*, and *P. ovale* should be treated with oral chloroquine (total dose, 25 mg of base/kg). In much of the tropics, drug-resistant *P. falciparum* has been increasing in distribution, frequency, and intensity. It is now accepted that, to prevent resistance, falciparum malaria should be treated with drug combinations and not with single drugs in endemic areas; the same rationale has been applied successfully to the treatment of tuberculosis, HIV/AIDS, and cancers. This combination strategy is based on simultaneous use of two or more drugs with different modes of action. Artemisinin combination treatment (ACT) regimens are now recommended as first-line treatment for falciparum malaria throughout the malaria-affected world. The artemisinin component is usually an artemisinin derivative (artesunate, artemether, or dihydroartemisinin) given for 3 days, and the partner drug is usually a slower-acting antimalarial to which *P. falciparum* is sensitive. Five ACT regimens are currently recommended by the WHO. In areas with multidrug-resistant falciparum malaria (parts of Asia and South America, including those with mefloquine-resistant parasites; Fig. 119-10), artemether-lumefantrine, artesunate-mefloquine, or dihydroartemisinin-piperaquine should be used; these regimens provide cure rates of >90%. In areas with sensitive parasites, the aforementioned combinations, artesunate-sulfadoxine-pyrimethamine, or artesunate-amodiaquine may also be used. Atovaquone-proguanil is also highly effective everywhere, although it is seldom used in endemic areas because of its high cost. Of great concern is the emergence of artemisinin-resistant *P. falciparum* in western Cambodia and adjacent Thailand. Infections with these parasites are cleared slowly from the blood, with clearance times typically exceeding 3 days.

The 3-day ACT regimens are all well tolerated, although mefloquine is associated with increased rates of vomiting and dizziness. As second-line treatments for

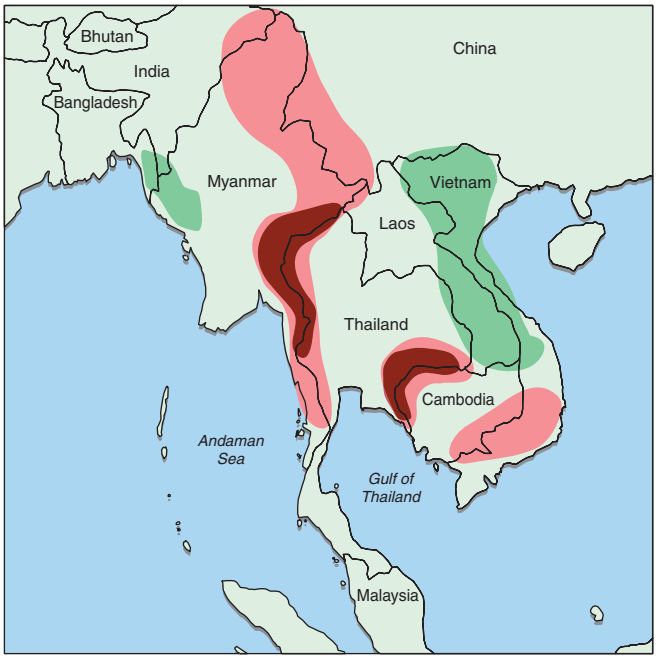


FIGURE 119-10
Mefloquine resistance in *Plasmodium falciparum* in Southeast Asia: high-level mefloquine resistance (*brown*), low-level mefloquine resistance (*red*), and mefloquine sensitivity (failure rate, <20%; *dark green*). There is insufficient information for other areas.

recrudescence following first-line therapy, a different ACT regimen may be given; another alternative is a 7-day course of either artesunate or quinine plus tetracycline, doxycycline, or clindamycin. Tetracycline and doxycycline cannot be given to pregnant women or to children <8 years of age. Oral quinine is extremely bitter and regularly produces cinchonism comprising tinnitus, high-tone deafness, nausea, vomiting, and dysphoria. Adherence is poor with the required 7-day regimens of quinine.

Patients should be monitored for vomiting for 1 h after the administration of any oral antimalarial drug. If there is vomiting, the dose should be repeated. Symptom-based treatment, with tepid sponging and acetaminophen administration, lowers fever and thereby reduces the patient's propensity to vomit these drugs. Minor central nervous system reactions (nausea, dizziness, sleep disturbances) are common. The incidence of serious adverse neuropsychiatric reactions to mefloquine treatment is ~1 in 1000 in Asia, but may be as high as 1 in 200 among Africans and Caucasians. All the antimalarial quinolines (chloroquine, mefloquine, and quinine) exacerbate the orthostatic hypotension associated with malaria, and all are tolerated better by children than by adults. Pregnant women, young children, patients unable to tolerate oral therapy, and nonimmune individuals (e.g., travelers) with suspected malaria should be evaluated carefully and hospitalization considered. If there is any doubt as to the identity of the infecting malarial species, treatment for falciparum malaria should be given. A negative blood smear makes malaria unlikely but does not rule it out completely; thick blood films should be checked again 1 and 2 days later to exclude the diagnosis. Nonimmune patients receiving treatment for malaria should have daily parasite counts performed until the thick films are negative. If the level of parasitemia does not fall below 25% of the admission value in 48 h or if parasitemia has not cleared by 7 days (and adherence is assured), drug resistance is likely and the regimen should be changed.

To eradicate persistent liver stages and prevent relapse (radical treatment), primaquine (0.5 mg of base/kg, adult dose) should be given daily for 14 days to patients with *P. vivax* or *P. ovale* infections after laboratory tests for G6PD deficiency have proved negative. If the patient has a mild variant of G6PD deficiency, primaquine can be given in a dose of 0.75 mg of base/kg (45 mg maximum) once weekly for 6 weeks. Pregnant women with vivax or ovale malaria should not be given primaquine but should receive suppressive prophylaxis with chloroquine (5 mg of base/kg per week) until delivery, after which radical treatment can be given.

COMPLICATIONS

Acute Renal Failure If the level of BUN or creatinine rises despite adequate rehydration, fluid administration should be restricted to prevent volume overload. As in other forms of hypercatabolic acute renal failure, renal replacement therapy is best performed early. Hemofiltration and hemodialysis are more effective than peritoneal dialysis and are associated with lower mortality. Some patients with renal impairment pass small volumes of urine sufficient to allow control of fluid balance; these cases can be managed conservatively if other indications for dialysis do not arise. Renal function usually improves within days, but full recovery may take weeks.

Acute Pulmonary Edema (Acute Respiratory Distress Syndrome) Patients should be positioned with the head of the bed at a 45° elevation and given oxygen and IV diuretics. Pulmonary artery occlusion pressures may be normal, indicating increased pulmonary capillary permeability. Positive-pressure ventilation should be started early if the immediate measures fail.

Hypoglycemia An initial slow injection of 50% dextrose (0.5 g/kg) should be followed by an infusion of 10% dextrose (0.10 g/kg per hour). The blood glucose level should be checked regularly thereafter as recurrent hypoglycemia is common, particularly among patients receiving quinine or quinidine. In severely ill patients, hypoglycemia commonly occurs together with metabolic (lactic) acidosis and carries a poor prognosis.

Other Complications Patients who develop spontaneous bleeding should be given fresh blood and IV vitamin K. Convulsions should be treated with IV or

rectal benzodiazepines and, if necessary, respiratory support. Aspiration pneumonia should be suspected in any unconscious patient with convulsions, particularly with persistent hyperventilation; IV antimicrobial agents and oxygen should be administered, and pulmonary toilet should be undertaken. Hypoglycemia or gram-negative septicemia should be suspected when the condition of any patient suddenly deteriorates for no obvious reason during antimalarial treatment. In malaria-endemic areas where a high proportion of children are parasitemic, it is usually impossible to distinguish severe malaria from bacterial sepsis with confidence. It is increasingly accepted that these children should be treated with both antimalarials and broad-spectrum antibiotics from the outset. Because nontyphoidal *Salmonella* infections are particularly common, empirical antibiotics should be selected to cover these organisms. Antibiotics should be considered for severely ill patients of any age who are not responding to antimalarial treatment.

PREVENTION

In recent years, considerable progress has been made in malaria prevention, control, and research. New drugs have been discovered and developed, and one vaccine candidate has reached the stage of advanced field testing. Highly effective drugs, insecticide-treated nets, and insecticides for spraying dwellings are being purchased for endemic countries by the Global Fund to Fight AIDS, Tuberculosis, and Malaria; the President's Malaria Initiative; UNICEF; and other organizations. Malaria research and control are being strongly supported by the National Institute of Allergy and Infectious Diseases, the Wellcome Trust, the Bill & Melinda Gates Foundation, the WHO, the Multilateral Initiative on Malaria, the Roll Back Malaria Partnership, and the Global Health Council, among others. Still, the eradication of malaria is not feasible in the immediate future because of the widespread distribution of *Anopheles* breeding sites; the great number of infected persons; the continued use of ineffective antimalarial drugs; and inadequacies in human and material resources, infrastructure, and control programs. The call for and commitment to ultimate eradication of malaria by the Gates Foundation in 2007—seconded by Margaret Chan, Director General of the WHO—added great impetus to all malaria initiatives, especially those aimed at discovery and implementation of new interventions and other critical goals. Malaria may be contained by judicious use of insecticides to kill the mosquito vector, rapid diagnosis, appropriate patient management, and—where effective and feasible—administration of intermittent preventive treatment or chemoprophylaxis to high-risk groups such as pregnant women, young children, and travelers from nonendemic regions. Malaria researchers are intensifying their efforts to gain a better understanding of parasite-human-mosquito interactions and to develop more effective control and prevention interventions. Despite the enormous investment in efforts to develop a malaria vaccine and the 30–60% efficacy of a recombinant protein sporozoite-targeted adjuvanted vaccine in limited field trials, no safe, effective, long-lasting vaccine is likely to be available for general use in the near future (Chap. 4). While there is great promise for one or more malaria vaccines on the more distant horizon, prevention and control measures continue to rely on antivector and drug-use strategies.

PERSONAL PROTECTION AGAINST MALARIA

Simple measures to reduce the frequency of infected-mosquito bites in malarious areas are very important. These measures include the avoidance of exposure to mosquitoes at their peak feeding times (usually dusk to dawn) as well as the use of insect repellents containing 10–35% DEET (or, if DEET is unacceptable, 7% picaridin), suitable clothing, and insecticide-impregnated bed nets or other materials. Widespread use of bed nets treated with residual pyrethroids reduces the incidence of malaria in areas where vectors bite indoors at night and has been shown to reduce mortality rates in western and eastern Africa.

CHEMOPROPHYLAXIS

(**Table 119-8**; *wwwnc.cdc.gov/travel/yellowbook/2010/chapter-2/malaria.aspx*) Recommendations for prophylaxis depend on knowledge of local patterns of *Plasmodium* species drug sensitivity and the likelihood of acquiring malarial infection. When there is uncertainty, drugs effective against resistant *P. falciparum* should be used (atovaquone-proguanil [Malarone], doxycycline, or mefloquine). Chemoprophylaxis is never entirely reliable, and malaria should always be considered in the differential diagnosis of fever in patients who have traveled to endemic areas, even if they are taking prophylactic antimalarial drugs.

Pregnant women traveling to malarious areas should be warned about the potential risks. All pregnant women at risk in endemic areas should be encouraged to attend regular antenatal clinics. Mefloquine is the only drug advised for pregnant women traveling to areas with drug-resistant malaria; this drug is generally considered safe in the second and third trimesters of pregnancy, and the data on first-trimester exposure, although limited, are reassuring. Chloroquine and proguanil are regarded as safe. The safety of other prophylactic antimalarial agents in pregnancy has not been established. Antimalarial prophylaxis has been shown to reduce mortality rates among children between the ages of 3 months and 4 years in

TABLE 119-8

DRUGS USED IN THE PROPHYLAXIS OF MALARIA

DRUG	USAGE	ADULT DOSE	PEDIATRIC DOSE	COMMENTS
Atovaquone/proguanil (Malarone)	Prophylaxis in areas with chloroquine- or mefloquine-resistant *Plasmodium falciparum*	1 adult tablet PO[a]	5–8 kg: 1/2 pediatric tablet[b] daily ≥8–10 kg: 3/4 pediatric tablet daily ≥10–20 kg: 1 pediatric tablet daily ≥20–30 kg: 2 pediatric tablets daily ≥30–40 kg: 3 pediatric tablets daily ≥40 kg: 1 adult tablet daily	Begin 1–2 days before travel to malarious areas. Take daily at the same time each day while in the malarious areas and for 7 days after leaving such areas. Atovaquone-proguanil is contraindicated in persons with severe renal impairment (creatinine clearance rate <30 mL/min). In the absence of data, it is not recommended for children weighing <5 kg, pregnant women, or women breast-feeding infants weighing <5 kg. Atovaquone/proguanil should be taken with food or a milky drink.
Chloroquine phosphate (Aralen and generic)	Prophylaxis only in areas with chloroquine-sensitive *P. falciparum*[c] or *P. vivax* only	300 mg of base (500 mg of salt) PO once weekly	5 mg/kg of base (8.3 mg of salt/kg) PO once weekly, up to maximum adult dose of 300 mg of base	Begin 1–2 weeks before travel to malarious areas. Take weekly on the same day of the week while in the malarious areas and for 4 weeks after leaving such areas. Chloroquine phosphate may exacerbate psoriasis.
Doxycycline (many brand names and generic)	Prophylaxis in areas with chloroquine- or mefloquine-resistant *P. falciparum*[c]	100 mg PO qd	≥8 years of age: 2 mg/kg, up to adult dose	Begin 1–2 days before travel to malarious areas. Take daily at the same time each day while in the malarious areas and for 4 weeks after leaving such areas. Doxycycline is contraindicated in children <8 years of age and in pregnant women.
Hydroxychloroquine sulfate (Plaquenil)	An alternative to chloroquine for primary prophylaxis only in areas with chloroquine-sensitive *P. falciparum*[c] or *P. vivax* only	310 mg of base (400 mg of salt) PO once weekly	5 mg of base/kg (6.5 mg of salt/kg) PO once weekly, up to maximum adult dose of 310 mg of base	Begin 1–2 weeks before travel to malarious areas. Take weekly on the same day of the week while in the malarious areas and for 4 weeks after leaving such areas. Hydroxychloroquine may exacerbate psoriasis.
Mefloquine (Lariam and generic)	Prophylaxis in areas with chloroquine-resistant *P. falciparum*	228 mg of base (250 mg of salt) PO once weekly	≤9 kg: 4.6 mg of base/kg (5 mg of salt/kg) PO once weekly 10–19 kg: 1/4 tablet once weekly 20–30 kg: 1/2 tablet once weekly 31–45 kg: 3/4 tablet once weekly ≥46 kg: 1 tablet once weekly	Begin 1–2 weeks before travel to malarious areas. Take weekly on the same day of the week while in the malarious areas and for 4 weeks after leaving such areas. Mefloquine is contraindicated in persons allergic to this drug or related compounds (e.g., quinine and quinidine) and in persons with active or recent depression, generalized anxiety disorder, psychosis, schizophrenia, other major psychiatric disorders, or seizures. Use with caution in persons with psychiatric disturbances or a history of depression. Mefloquine is not recommended for persons with cardiac conduction abnormalities.

(*continued*)

TABLE 119-8

DRUGS USED IN THE PROPHYLAXIS OF MALARIA (*CONTINUED*)

DRUG	USAGE	ADULT DOSE	PEDIATRIC DOSE	COMMENTS
Primaquine	For prevention of malaria in areas with mainly *P. vivax*	30 mg of base (52.6 mg of salt) PO qd	0.5 mg of base/kg (0.8 mg of salt/kg) PO qd, up to adult dose; should be taken with food	Begin 1–2 days before travel to malarious areas. Take daily at the same time each day while in the malarious areas and for 7 days after leaving such areas. Primaquine is contraindicated in persons with G6PD deficiency. It is also contraindicated during pregnancy and in lactation unless the infant being breast-fed has a documented normal G6PD level.
Primaquine	Used for presumptive antirelapse therapy (terminal prophylaxis) to decrease risk of relapses of *P. vivax and P. ovale*	30 mg of base (52.6 mg of salt) PO qd for 14 days after departure from the malarious area	0.5 mg of base/kg (0.8 mg of salt/kg), up to adult dose, PO qd for 14 days after departure from the malarious area	This therapy is indicated for persons who have had prolonged exposure to *P. vivax* and/or *P. ovale*. It is contraindicated in persons with G6PD deficiency as well as during pregnancy and in lactation unless the infant being breast-fed has a documented normal G6PD level.

[a]An adult tablet contains 250 mg of atovaquone and 100 mg of proguanil hydrochloride.
[b]A pediatric tablet contains 62.5 mg of atovaquone and 25 mg of proguanil hydrochloride.
[c]Very few areas now have chloroquine-sensitive malaria (Fig. 119-2).
Source: CDC: *http://wwwn.cdc.gov/travel/contentMalariaDrugsHC.aspx*.

malaria-endemic areas; however, it is not a logistically or economically feasible option in many countries. The alternative—to give intermittent treatment doses (intermittent preventive treatment [IPT])—shows promise for more widespread use in infants, young children, and pregnant women. Children born to nonimmune mothers in endemic areas (usually expatriates moving to malaria-endemic areas) should receive prophylaxis from birth.

Travelers should start taking antimalarial drugs 2 days to 2 weeks before departure so that any untoward reactions can be detected and so that therapeutic antimalarial blood concentrations will be present when needed (Table 119-8). Antimalarial prophylaxis should continue for 4 weeks after the traveler has left the endemic area, except if atovaquone-proguanil or primaquine has been taken; these drugs have significant activities against the liver stage of the infection (causal prophylaxis) and can be discontinued 1 week after departure from the endemic area. If suspected malaria develops while a traveler is abroad, obtaining a reliable diagnosis and antimalarial treatment locally is a top priority. Presumptive self-treatment for malaria with atovaquone-proguanil (for 3 consecutive days) or another drug can be considered under special circumstances; medical advice on self-treatment should be sought before departure for malarious areas and as soon as possible after illness begins. Every effort should be made to confirm the diagnosis by parasitologic studies.

Atovaquone-proguanil (Malarone; 3.75/1.5 mg/kg or 250/100 mg, daily adult dose) is a fixed-combination, once-daily prophylactic agent that is very well tolerated by adults and children, with fewer adverse gastrointestinal effects than chloroquine-proguanil and fewer adverse central nervous system effects than mefloquine. It is proguanil itself, rather than the antifolate metabolite cycloguanil, that acts synergistically with atovaquone. This combination is effective against all types of malaria, including multidrug-resistant falciparum malaria. Atovaquone-proguanil is best taken with food or a milky drink to optimize absorption. There are insufficient data on the safety of this regimen in pregnancy.

Mefloquine (250 mg of salt weekly, adult dose) has been widely used for malarial prophylaxis because it is usually effective against multidrug-resistant falciparum malaria and is reasonably well tolerated. The drug has been associated with rare episodes of psychosis and seizures at prophylactic doses; these reactions are more frequent at the higher doses used for treatment. More common side effects with prophylactic doses of mefloquine include mild nausea, dizziness, fuzzy thinking, disturbed sleep patterns, vivid dreams, and malaise. The drug is contraindicated for use by travelers with known hypersensitivity to mefloquine or related compounds (e.g., quinine, quinidine) and by persons with active or recent depression, anxiety disorder, psychosis, schizophrenia, another major psychiatric disorder, or seizures; mefloquine is not recommended for

persons with cardiac conduction abnormalities. The role of mefloquine prophylaxis during pregnancy remains uncertain; in studies in Africa, mefloquine prophylaxis was found to be effective and safe during pregnancy. However, in one study from Thailand, treatment of malaria with mefloquine was associated with an increased risk of stillbirth.

Daily administration of doxycycline (100 mg daily, adult dose) is an effective alternative to atovaquone-proguanil or mefloquine. Doxycycline is generally well tolerated but may cause vulvovaginal thrush, diarrhea, and photosensitivity and cannot be used by children <8 years old or by pregnant women.

Chloroquine can no longer be relied upon to prevent *P. falciparum* infections in most areas but is used to prevent and treat malaria due to the other human *Plasmodium* species and for *P. falciparum* malaria in Central American countries west and north of the Panama Canal, Caribbean countries, and some countries in the Middle East. Chloroquine-resistant *P. vivax* has been reported from parts of eastern Asia, Oceania, and Central and South America. This drug is generally well tolerated, although some patients cannot take it because of malaise, headache, visual symptoms (due to reversible keratopathy), gastrointestinal intolerance, or pruritus. Chloroquine is considered safe in pregnancy. With chronic administration for >5 years, a characteristic dose-related retinopathy may develop, but this condition is rare at the doses used for antimalarial prophylaxis. Idiosyncratic or allergic reactions are also rare. Skeletal and/or cardiac myopathy, a potential problem with protracted prophylactic use, is more likely to occur at the high doses used in the treatment of rheumatoid arthritis. Neuropsychiatric reactions and skin rashes are unusual. When used continuously, amodiaquine, a related aminoquinoline, is associated with a high risk of agranulocytosis (~1 person in 2000) and hepatotoxicity (~1 person in 16,000); thus this agent should not be used for prophylaxis.

Primaquine (daily adult dose, 0.5 mg of base/kg or 30 mg taken with food), an 8-aminoquinoline compound, has proved safe and effective in the prevention of drug-resistant falciparum and vivax malaria in adults. This drug can be considered for persons who are traveling to areas with or without drug-resistant *P. falciparum* and who are intolerant to other recommended drugs. Abdominal pain and oxidant hemolysis—the principal adverse effects—are not common as long as the drug is taken with food and is not given to G6PD-deficient persons, in whom it can cause hemolysis that is sometimes fatal. Travelers must be tested for G6PD deficiency and be shown to have a level in the normal range before receiving primaquine. Primaquine should not be given to pregnant women or neonates. The 8-aminoquinolines (primaquine, tafenoquine) given in a single dose with ACT are being considered for widespread use in treatment regimens in malaria elimination programs because of their gametocytocidal effect on *P. falciparum*.

In the past, the dihydrofolate reductase inhibitors pyrimethamine and proguanil (chloroguanide) were administered widely, but the rapid selection of resistance in both *P. falciparum* and *P. vivax* has limited their use. Whereas antimalarial quinolines such as chloroquine (a 4-aminoquinoline) act on the erythrocyte stage of parasitic development, the dihydrofolate reductase inhibitors also inhibit preerythrocytic growth in the liver (causal prophylaxis) and development in the mosquito (sporontocidal activity). Proguanil is safe and well tolerated, although mouth ulceration occurs in ~8% of persons using this drug; it is considered safe for antimalarial prophylaxis in pregnancy. The prophylactic use of the combination of pyrimethamine and sulfadoxine is not recommended because of an unacceptable incidence of severe toxicity, principally exfoliative dermatitis and other skin rashes, agranulocytosis, hepatitis, and pulmonary eosinophilia (incidence, 1:7000; fatal reactions, 1:18,000). The combination of pyrimethamine with dapsone (0.2/1.5 mg/kg weekly; 12.5/100 mg, adult dose) has been used in some countries. Dapsone may cause methemoglobinemia and allergic reactions and (at higher doses) may pose a significant risk of agranulocytosis. Proguanil and the pyrimethamine-dapsone combination are not available in the United States.

Because of the increasing spread and intensity of antimalarial drug resistance (Figs. 119-2 and 119-10), the CDC recommends that travelers and their providers consider their destination, type of travel, and current medications and health risks when choosing antimalarial chemoprophylaxis. Consultation for the evaluation of prophylaxis failures or treatment of malaria can be obtained from state and local health departments and the CDC Malaria Hotline (770-488-7788) or the CDC Emergency Operations Center (770-488-7100).

CHAPTER 120

BABESIOSIS

Edouard Vannier ■ Jeffrey A. Gelfand

Babesiosis is a tick-borne infectious disease caused by parasites of the genus *Babesia*. These protozoans are obligate parasites of red blood cells (RBCs). Wild and domestic animals are the natural reservoirs of *Babesia*. Transmission to humans is incidental and was recognized only half a century ago. The vast majority of cases occur in the United States, where babesiosis has the status of an emerging infectious disease. Sporadic cases are reported in Europe and the rest of the world (see "Global Considerations").

EPIDEMIOLOGY

Geographic distribution

Babesia microti, a parasite of small rodents, is the etiologic agent of babesiosis in the northeastern United States. Highly endemic areas include Nantucket Island, Martha's Vineyard, Block Island, Shelter Island, eastern Long Island, and Fire Island. On the mainland, babesiosis is endemic in southeastern Massachusetts, coastal Rhode Island and Connecticut, central New Jersey, Wisconsin, and Minnesota. On the West Coast, the etiologic agent is *Babesia duncani*, a species closely related to those found in wildlife. The index case of infection with this species was reported from Washington State. Several cases were identified in northern California, and one case may have been contracted in central Oregon. Three cases of babesiosis caused by *Babesia divergens*–like organisms—from Washington State, Missouri, and Kentucky, respectively—have been reported.

Prevalence

The number of cases of *B. microti* illness has increased steadily over the last decade. In 2009, more than 700 cases were reported to the public health departments in endemic states. The prevalence of babesiosis caused by *B. microti* is underestimated because young healthy individuals typically experience a mild and self-limiting illness and may not seek medical attention. Accordingly, seroprevalence is much higher than the prevalence of clinical babesiosis.

Modes of transmission

The nymphal stage of the deer tick *Ixodes scapularis* is the primary vector for transmission of *B. microti*. Transmission occurs from May through September. The incubation period is 1–6 weeks long, with three-fourths of cases presenting in June and July. The vectors for transmission of *B. duncani* and *B. divergens*–like organisms remain unknown.

Babesiosis is occasionally acquired by transfusion of blood products, primarily packed RBCs; more than 70 such cases have been caused by *B. microti*, and two cases caused by *B. duncani* have been transmitted by this route. The incubation period lasts 1–9 weeks. Most cases occur in endemic areas during fall and winter. Some cases are diagnosed in nonendemic areas to which blood products have been imported from endemic areas. Of the 11 transfusion-related babesiosis deaths reported to the U.S. Food and Drug Administration since 1998, 10 have occurred since 2005.

Three cases of congenital babesiosis have been attributed to *B. microti*. Other cases of neonatal babesiosis have been acquired by transfusion or tick bite.

CLINICAL MANIFESTATIONS

Mild B. microti illness

Patients experience a gradual onset of malaise, fatigue, and weakness. Fever exceeds 38°C, can reach 40.6°C, and is accompanied by one or several of the following: chills, sweats, headache, myalgia, anorexia, dry cough, arthralgia, and nausea. Less common symptoms include neck stiffness, sore throat, shortness of breath, abdominal pain, and weight loss. On physical examination, fever is the salient feature. Development of *erythema chronicum migrans* is suggestive of intercurrent Lyme disease. Ecchymoses and petechiae have been reported. Mild splenomegaly and hepatomegaly are occasionally noted. Lymphadenopathy is absent. Jaundice, slight pharyngeal erythema, retinal infarcts, and retinopathy with splinter hemorrhages are rare.

Severe B. microti illness

Severe babesiosis is associated with parasitemia levels of >4% and requires hospitalization. Risk factors include an age of>50 years, male gender, asplenia, HIV/AIDS, malignancy, and immunosuppression. Compared with patients hospitalized for other febrile illnesses, patients with severe babesiosis are more likely to report malaise, myalgia or arthralgia, and shortness of breath. Complications develop in ~40% of hospitalized patients. Risk factors for complications are severe anemia (hemoglobin level ≤10 g/dL) and high-level parasitemia (>10%). Acute respiratory distress syndrome is the most common complication. Other complications include disseminated intravascular coagulation, congestive heart failure, and renal failure. Splenic infarcts and rupture have been reported. Strong predictors of poor outcome—defined as hospitalization for >2 weeks, stay in an intensive care unit for >2 days, or death—are male gender, alkaline phosphatase levels of >125 U/L, and white blood cell (WBC) counts of >5 × 10^9/L. The fatality rate is 5% among all hospitalized patients but is much higher (20%) among immunocompromised patients.

Other babesial infections

Cases of *B. duncani* infection range in severity from asymptomatic to fatal. Clinical manifestations are those reported for *B. microti*. All three reported patients infected with *B. divergens*–like organisms required hospitalization; one died.

DIAGNOSIS

A diagnosis of babesiosis should be considered for any patient who (1) presents with flu-like symptoms and has recently resided in or traveled to an endemic area or received a blood transfusion or (2) presents with symptoms of or has been diagnosed with Lyme disease or human granulocytotropic anaplasmosis.

Babesiosis is diagnosed by microscopic examination of Giemsa-stained thin blood smears, on which *Babesia* species appear as round or pear-shaped organisms. The ring form is most common and lacks the central brownish deposit (hemozoin) typical of *Plasmodiumfalciparum* trophozoites (Chap. 121). Other distinguishing features are the absence of schizonts and gametocytes and the occasional presence of tetrads ("Maltese crosses"), which are pathognomonic of infection with *B. microti* or *B. duncani* but are also noted in human RBCs infected with *B. divergens*–like organisms. When parasitized RBCs are rare (particularly at the onset of symptoms), identification of the parasite may require multiple blood smears over several days. If babesiosis is suspected but the parasite cannot be identified by microscopy, amplification of babesial 18S rRNA by polymerase chain reaction (PCR) is recommended. Serology is useful to confirm the diagnosis. An indirect immunofluorescent antibody test for *B. microti* is available through the Centers for Disease Control and Prevention. IgM titers of ≥1:64 and IgG titers of ≥1:1024 signify active or recent infection. Titers typically decline over 6–12 months. Titers of <1:64 suggest complete clearance. Titers that remain positive (≥1:64) suggest persistent low-level parasitemia. Antibodies to *B. microti* do not react with *B. duncani* or *B. divergens*–like organisms.

Parasitemia levels typically range from 1% to 20% in immunocompetent hosts but can reach 85% in asplenic patients. Low hematocrit, low hemoglobin, low haptoglobin, and elevated lactate dehydrogenase levels are consistent with hemolytic anemia. Reticulocyte counts are elevated; thrombocytopenia is common. WBC counts are normal or slightly depressed. Liver function tests (alkaline phosphatase, aspartate and alanine aminotransferases, bilirubin) yield elevated values. Urinalysis may detect hemoglobinuria, excess urobilinogen, and proteinuria. Elevated concentrations of blood urea nitrogen and serum creatinine indicate renal compromise.

TREATMENT Babesiosis

(See Table 120-1) Whether *B. microti* infection should be treated depends on the clinical context. Asymptomatic infections need not be treated unless *Babesia* organisms are detected on blood smear or by PCR for >3 months. Symptomatic infections need not be treated if *Babesia* is not detected, despite positive serology. When *Babesia* is detected in symptomatic patients, treatment should be initiated.

MILD *B. MICROTI* ILLNESS The recommended regimen for treatment of mild illness due to *B. microti* is oral atovaquone plus azithromycin for 7–10 days. Clindamycin plus quinine is the second choice. The two regimens are equally effective, but atovaquone plus azithromycin is better tolerated. Symptoms should begin to abate within 48 h of the initiation of therapy and should resolve within 3 months. For immunocompromised patients, high-dose azithromycin (600–1000 mg/d) is recommended. Relevant antimicrobial therapy should be initiated when patients are also diagnosed with Lyme disease (Chap. 78) or human granulocytotropic anaplasmosis (Chap. 79)—conditions that should be sought whenever *B. microti* is diagnosed.

SEVERE *B. MICROTI* ILLNESS The recommended regimen for treatment of severe illness caused by *B. microti* is IV clindamycin plus oral quinine for 7–10 days. Oral quinine may be replaced with IV quinidine. Partial or complete RBC exchange transfusion is advised in cases of high-level parasitemia (>10%); severe anemia (hemoglobin, ≤10 g/dL); or pulmonary, hepatic, or renal compromise. Parasitemia and hematocrit should be monitored every day or every other day until symptoms recede and the parasitemia level is <5%.

A single course of standard antimicrobial therapy is often insufficient to eradicate symptoms and parasitemia

TABLE 120-1

TREATMENT OF HUMAN BABESIOSIS

ORGANISM	SEVERITY	ADULTS	CHILDREN
B. microti	Mild[a]	Atovaquone (750 mg q12h PO) *plus* Azithromycin (500–1000 mg/d PO on day 1, 250 mg/d PO thereafter)	Atovaquone (20 mg/kg q12h PO; maximum, 750 mg/dose) *plus* Azithromycin [10 mg/kg qd PO on day 1 (maximum, 500 mg/dose), 5 mg/kg qd PO thereafter (maximum, 250 mg/dose)]
	Severe[a]	Clindamycin (300–600 mg q6h IV or 600 mg q8h PO) *plus* Quinine (650 mg q6–8h PO) *plus* Consider RBC exchange transfusion	Clindamycin (7–10 mg/kg q6–8h IV or 7–10 mg/kg q6–8h PO; maximum, 600 mg/dose) *plus* Quinine (8 mg/kg q8h PO; maximum, 650 mg/dose) *plus* Consider RBC exchange transfusion
B. divergens[b]		Immediate complete RBC exchange transfusion *plus* Clindamycin (600 mg q6–8h IV) *plus* Quinine (650 mg q8h PO)	Immediate complete RBC exchange transfusion *plus* Clindamycin (7–10 mg/kg q6–8h IV; maximum, 600 mg/dose) *plus* Quinine (8 mg/kg q8h PO; maximum, 650 mg/dose)

[a]Treatment for 7–10 days. In asplenic individuals and in immunocompromised patients, therapy should last for at least 6 weeks, including 2 weeks after parasites are no longer detected on blood smear.
[b]Treatment for 7–10 days, but duration may vary.
Abbreviation: RBC, red blood cell.

in patients immunocompromised by splenectomy, HIV/AIDS, malignancy, or immunosuppressive therapy, including rituximab (anti-CD20) therapy for B cell lymphomas. In these patients, cure is more likely when therapy is administered for at least 6 weeks, including 2 weeks after parasites are no longer observed on blood smear. In immunocompromised patients with relapsing babesiosis, a second course of atovaquone plus azithromycin may fail to result in cure, despite >28 days of uninterrupted therapy. In the setting of severe disease, consideration should always be given to the possibility of intercurrent Lyme disease or human granulocytotropic anaplasmosis and empirical therapy for these infections considered until they are excluded.

When clindamycin plus quinine fails to clear *B. microti* or when quinine must be discontinued, alternative regimens have been successful according to anecdotal reports. These empirical regimens have consisted of two- or three-drug combinations such as azithromycin plus quinine and clindamycin plus azithromycin added to doxycycline. In one immunocompromised patient, *B. microti* was cleared after administration of a five-drug regimen that consisted of clindamycin, quinine, azithromycin, atovaquone, and the combination of atovaquone-proguanil.

OTHER BABESIAL INFECTIONS The regimen for *B. duncani* infections typically consists of IV clindamycin (600 mg tid/qid or 1200 mg bid) plus oral quinine (600–650 mg tid) for 7–10 days. One relapse was cured with IV clindamycin (1200 mg tid) for 10 days. A pediatric case was successfully treated with IV clindamycin (40 mg/kg per day) plus oral quinine (25 mg/kg per day) for 15 days. The regimen for *B. divergens*–like infections typically consists of IV clindamycin (600 mg tid/qid, 900 mg tid, or 1200 mg bid) plus oral quinine or quinidine (650 mg tid).

PREVENTION

No vaccine is available for human use. There is no role for antibiotic prophylaxis. Individuals who reside in or travel to endemic areas, especially those at risk for severe babesiosis, should wear clothing that covers the lower part of the body, apply tick repellents (such as DEET) to clothing, and limit outdoor activities from May through September. A thorough skin examination should be conducted after outdoor activities and ticks removed using tweezers. Individuals with a history of symptomatic babesiosis or with positive antibody titers are indefinitely deferred from donating blood.

GLOBAL CONSIDERATIONS

Europe

About 30 cases of babesiosis have been attributed to *B. divergens*, a pathogen of cattle. Most cases have occurred in France, Ireland, and Great Britain. Sporadic cases have been reported from Croatia (index case), Spain, Portugal, and Sweden. Three cases—in Italy, Austria, and Germany, respectively—were caused by *Babesia* EU1, a parasite of roe deer. Both parasites are transmitted by the sheep tick *Ixodes ricinus*. The single reported case of *B. microti* infection was probably acquired by transfusion of a contaminated platelet concentrate.

Asplenia is a major risk factor for symptomatic *B. divergens* infection. The incubation period is 1–3 weeks long. The onset of hemoglobinuria and jaundice is sudden. Other symptoms include persistent fever (>41°C), shaking chills, drenching sweats, headache, myalgia, and lumbar and abdominal pain. Mild hepatomegaly may be noted. If the infection is not rapidly treated, the patient's condition deteriorates, with pulmonary edema and renal failure. In the past, most patients with severe cases died. Since exchange transfusion has been combined with chemotherapy, fatal cases have been rare. The overall fatality rate remains ~40%. All patients infected with *Babesia* EU1 had been splenectomized, but their illness ranged from mild to severe; none died.

Because *B. divergens* infections are fulminant, the parasite is readily identified on blood smears. The parasitemia level may reach 80%. Serology is of no use because symptoms appear before antibody levels rise. In *Babesia* EU1 infection, the parasitemia level ranges from 1% to 30%. No serologic test specific for *Babesia* EU1 is available, but sera from patients infected with *Babesia* EU1 react with *B. divergens* antigen.

Babesiosis caused by *B. divergens* is a medical emergency. The recommended treatment is immediate complete blood exchange transfusion and therapy with IV clindamycin plus oral quinine or IV quinidine. In some cases, cure has been obtained with exchange transfusion and clindamycin monotherapy. Although uninfected RBCs are introduced by exchange transfusion, anemia may persist for >1 month. If so, additional transfusion is needed. One mild case was cured with IV pentamidine plus oral trimethoprim-sulfamethoxazole. *Babesia* EU1 infections have been treated with IV or oral clindamycin (600 mg tid) alone or in combination with oral quinine (650 mg tid). One patient who became intolerant to quinine was treated with oral atovaquone (750 mg bid) plus oral azithromycin (500 mg/d).

Rest of the world

A case of *B. divergens*–like infection has been identified on the Canary Islands, and isolated cases have been reported from South Africa, Mozambique, Egypt, and India. Two cases of *B. microti*–like infection have been reported in Taiwan and another in Japan. A patient in South Korea was infected with a *Babesia* species (KO1) related to species found in sheep. Asymptomatic infections have been identified in Mexico (*B. bigemina*, *B. canis*) and Colombia (*B. bigemina*, *B. bovis*). A case of *B. microti* infection diagnosed in Poland most likely was imported from Brazil.

CHAPTER 121

ATLAS OF BLOOD SMEARS OF MALARIA AND BABESIOSIS

Nicholas J. White ■ Joel G. Breman

Five species of blood protozoan parasites cause human malaria: the potentially lethal and often drug-resistant *Plasmodium falciparum*; the relapsing parasites *P. vivax* and *P. ovale; P. malariae*, which can persist at low densities for years; and *P. knowlesi*, a monkey parasite that causes occasional infections in humans in tropical forests in Southeast Asia. *P. knowlesi* resembles *P. falciparum* and *P. malariae* microscopically but is identified definitively by molecular methods (see **Table 121-1**, footnote *a*).

TABLE 121-1

MORPHOLOGIC CHARACTERISTICS OF HUMAN MALARIA PARASITES[a]

	P. falciparum	*P. vivax*	*P. ovale*	*P. malariae*
Asexual parasites	Usually only fine blue ring forms (some resembling stereo headsets) are seen. Parasitemia level may exceed 2%.	Irregular, large, fairly thick rings become highly pleomorphic as the parasite grows. Parasitemia level is low.	Regular, dense ring enlarges to compact, blue, mature trophozoite (rectangular or band-form). Parasitemia level is low.	Dense, thick rings mature to dense, round trophozoites. Parasitemia level is low.
Schizonts	Rare in peripheral blood; 8–32 merozoites, dark brown-black pigment	Common; 12–18 merozoites, orange-brown pigment	8–14 merozoites, brown or black pigment	8–10 merozoites, dark brown or black pigment
Gametocytes	Banana-shaped; male: light blue; female: darker blue; a few scattered blue-black pigment granules in cytoplasm	Round or oval; male: round, pale blue; female: oval, dark blue; triangular nucleus, a few orange pigment granules	Large, round, dense, and blue (like *P. malariae*), but prominent James's dots; brown pigment	Large, oval; male: pale blue; female: dense blue; large black pigment granules
RBC changes	RBCs are normal in size. As the parasite matures, the RBC cytoplasm becomes pale, the cells become crenated, and a few small red dots may appear over the cytoplasm (Maurer's clefts).	RBCs are enlarged. Pale red Schüffner's dots increase in number as the parasite matures.	RBCs become oval with tufted ends. Red James's dots are prominent.	RBCs are normal in size and shape. No red dots are seen.

[a]The early trophozoites of *P. knowlesi* resemble those of *P. falciparum*. The late and mature trophozoites, schizonts, and gametocytes of *P. knowlesi* appear very similar to those of *P. malariae*; the differences are that *P. knowlesi* trophozoites may have double chromatin dots and two or three parasites per RBC and that *P. knowlesi* mature schizonts have 16 merozoites rather than the 8–10 found with *P. malariae.*
Abbreviation: RBC, red blood cell.

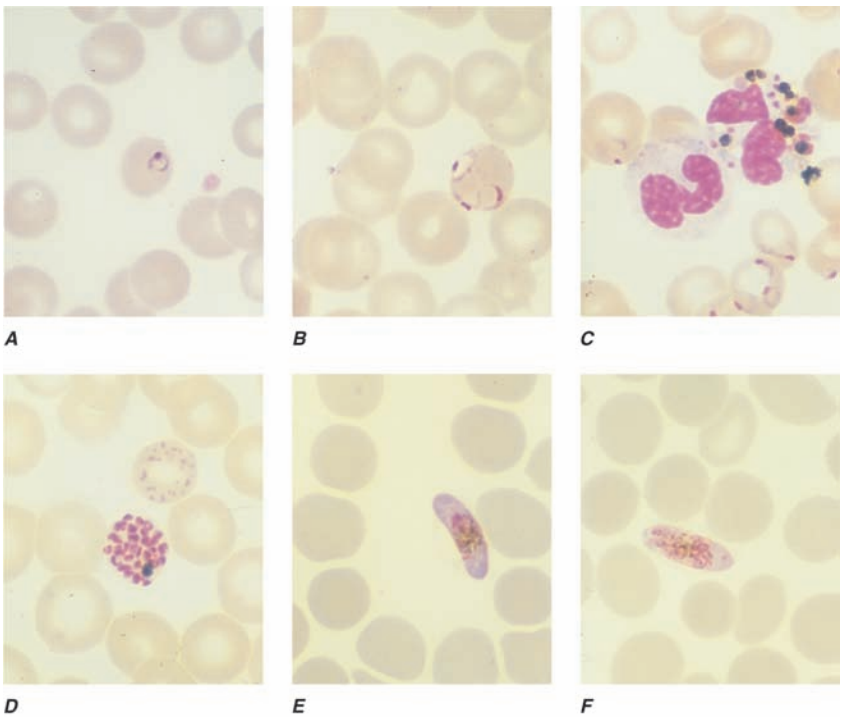


FIGURE 121-1

Thin blood films of *Plasmodium falciparum*. *A.* Young trophozoites. ***B.*** Old trophozoites. ***C.*** Pigment in polymorphonuclear cells and trophozoites. ***D.*** Mature schizonts. ***E.*** Female gametocytes. ***F.*** Male gametocytes. (*Reproduced from Bench Aids for the Diagnosis of Malaria Infections, 2nd ed, with the permission of the World Health Organization.*)

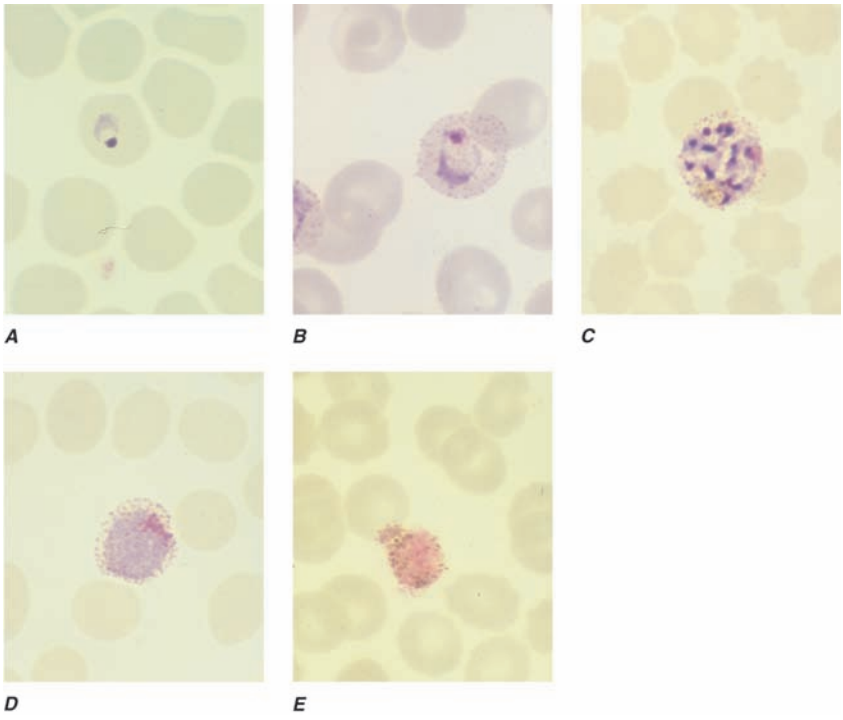


FIGURE 121-2
Thin blood films of *Plasmodium vivax*. *A.* Young trophozoites. ***B.*** Old trophozoites. ***C.*** Mature schizonts. ***D.*** Female gametocytes. ***E.*** Male gametocytes. (*Reproduced from Bench Aids for the Diagnosis of Malaria Infections, 2nd ed, with the permission of the World Health Organization.*)

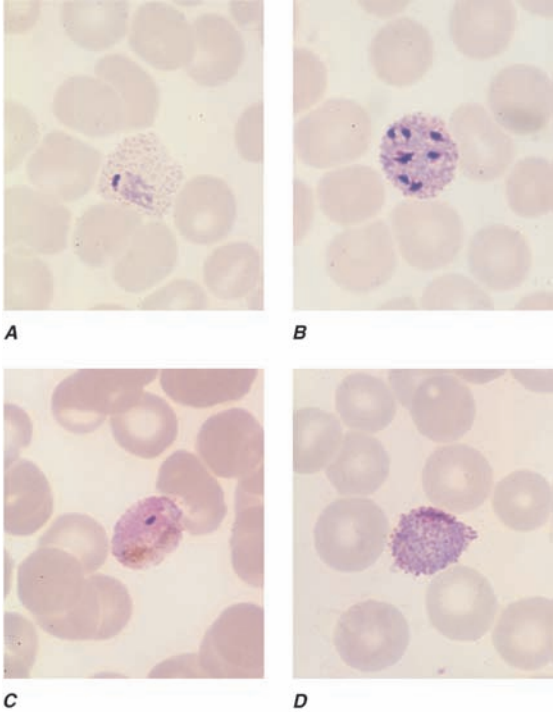


FIGURE 121-3
Thin blood films of *Plasmodium ovale*. *A.* Old trophozoites. ***B.*** Mature schizonts. ***C.*** Male gametocytes. ***D.*** Female gametocytes. (*Reproduced from Bench Aids for the Diagnosis of Malaria Infections, 2nd ed, with the permission of the World Health Organization.*)

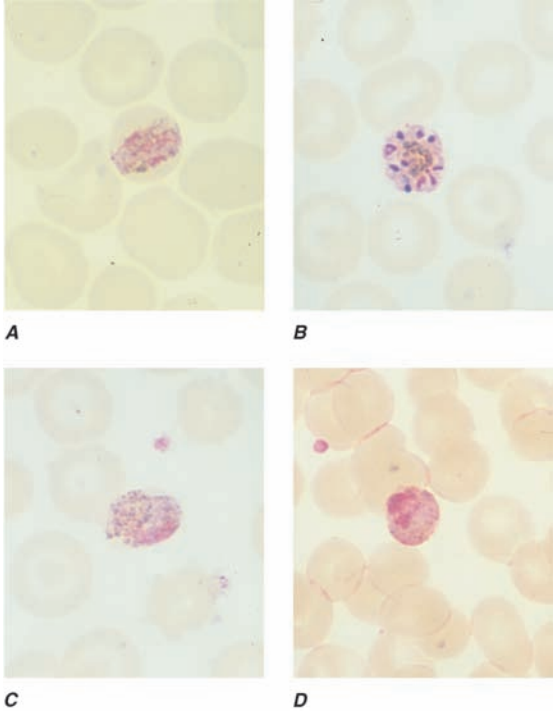


FIGURE 121-4
Thin blood films of *Plasmodium malariae*. *A.* Old trophozoites. ***B.*** Mature schizonts. ***C.*** Male gametocytes. ***D.*** Female gametocytes. (*Reproduced from Bench Aids for the Diagnosis of Malaria Infections, 2nd ed, with the permission of the World Health Organization.*)

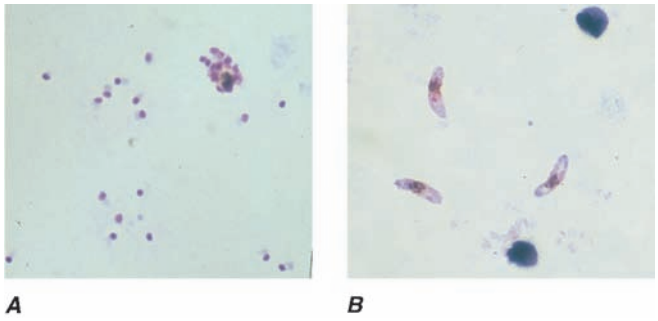


FIGURE 121-5
Thick blood films of *Plasmodium falciparum*. *A.* Trophozoites. ***B.*** Gametocytes. (*Reproduced from Bench Aids for the Diagnosis of Malaria Infections, 2nd ed, with the permission of the World Health Organization.*)

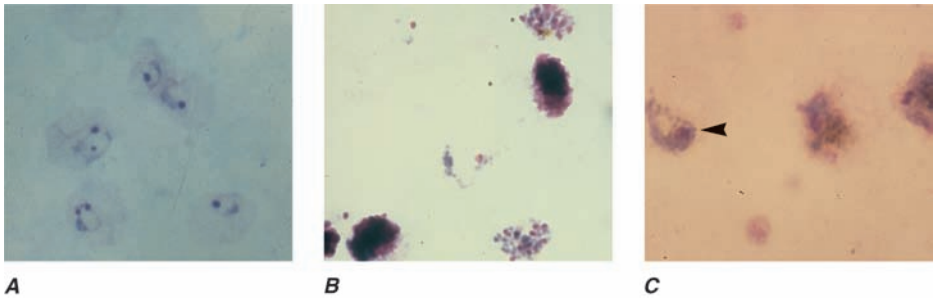


FIGURE 121-6
Thick blood films of *Plasmodium vivax*. *A.* Trophozoites. ***B.*** Schizonts. ***C.*** Gametocytes. (*Reproduced from Bench Aids for the Diagnosis of Malaria Infections, 2nd ed, with the permission of the World Health Organization.*)

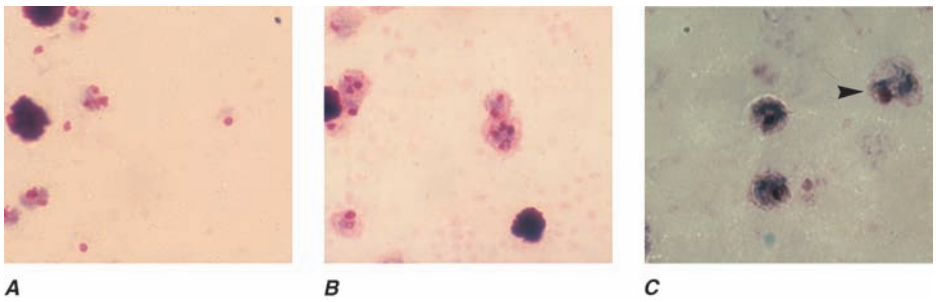


FIGURE 121-7
Thick blood films of *Plasmodium ovale*. *A.* Trophozoites. ***B.*** Schizonts. ***C.*** Gametocytes. (*Reproduced from Bench Aids for the Diagnosis of Malaria Infections, 2nd ed, with the permission of the World Health Organization.*)

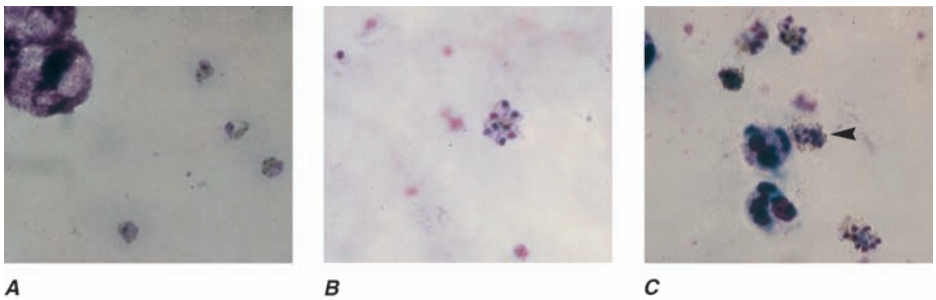


FIGURE 121-8
Thick blood films of *Plasmodium malariae*. *A.* Trophozoites. ***B.*** Schizonts. ***C.*** Gametocytes. (*Reproduced from Bench Aids for the Diagnosis of Malaria Infections, 2nd ed, with the permission of the World Health Organization.*)

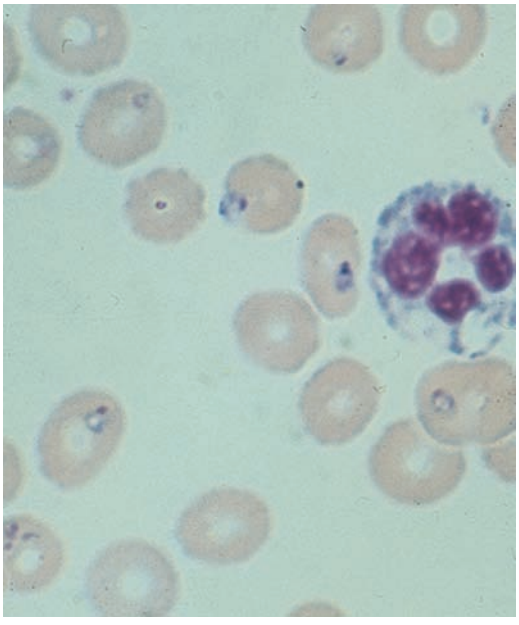


FIGURE 121-9
Thin blood film showing trophozoites of *Babesia*. (*Reproduced from Bench Aids for the Diagnosis of Malaria Infections, 2nd ed, with the permission of the World Health Organization.*)

The malaria parasites are readily seen under the microscope (×1000 magnification) in thick and thin blood smears stained with supravital dyes (e.g., Giemsa's, Field's, Wright's, Leishman's). The morphologic characteristics of the parasites are summarized in Table 121-1. In the thick film, lysis of red blood cells by water leaves the stained white cells and parasites, allowing detection of densities as low as 50 parasites/μL. This degree of sensitivity is up to 100 times greater than that of the thin film, in which the red cells are fixed and the malaria parasites are seen inside the cells. The thin film is better for speciation and provides useful prognostic information in severe falciparum malaria. Several findings are associated with increased mortality risk: high parasite counts, more mature parasites (>20% containing visible malaria pigment), and phagocytosed malaria pigment in >5% of neutrophils.

Babesia microti appears as a small ring form resembling *P. falciparum*. Unlike *Plasmodium, Babesia* does not cause the production of pigment in parasites, nor are schizonts or gametocytes formed.

CHAPTER 122

LEISHMANIASIS

Shyam Sundar

DEFINITION

Encompassing a complex group of disorders, leishmaniasis is caused by unicellular eukaryotic obligatory intracellular protozoa of the genus *Leishmania* and primarily affects the host's reticuloendothelial system. *Leishmania* species produce widely varying clinical syndromes ranging from self-healing cutaneous ulcers to fatal visceral disease. These syndromes fall into three broad categories: visceral leishmaniasis (VL), cutaneous leishmaniasis (CL), and mucosal leishmaniasis (ML).

ETIOLOGY AND LIFE CYCLE

Leishmaniasis is caused by ~20 species of the genus *Leishmania* in the order Kinetoplastida and the family Trypanosomatidae **(Table 122-1)**. Several clinically important species are of the subspecies *Viannia*. The organisms are transmitted by phlebotomine sandflies of the genus *Phlebotomus* in the "Old World" (Asia, Africa, and Europe) and the genus *Lutzomyia* in the "New World" (the Americas). Transmission may be anthroponotic (i.e., the vector transmits the infection from infected humans to healthy humans) or zoonotic (i.e., the vector transmits the infection from an animal reservoir to humans). Human-to-human transmission via shared infected needles has been documented in IV drug users in the Mediterranean region. In utero transmission to the fetus occurs rarely.

Leishmania organisms occur in two forms: extracellular, flagellate promastigotes (length, 10–20 μm) in the sandfly vector and intracellular, nonflagellate amastigotes

TABLE 122-1

GEOGRAPHIC DISTRIBUTION AND CHARACTERISTIC EPIDEMIOLOGY OF LEISHMANIASES

ORGANISM, ENDEMIC REGION	CLINICAL SYNDROME	SPECIES	VECTOR	RESERVOIR	TRANSMISSION	SETTING
***L. donovani* Complex**						
South Asia	VL, PKDL	*L. donovani*	*Phlebotomus argentipes*	Humans	Anthroponotic	Rural, domestic
Sudan, Somalia, Ethiopia, Kenya, Uganda	VL, PKDL	*L. donovani*	*P. orientalis, P. martini*	Humans, rodents in Sudan, canines	Anthroponotic, occasionally zoonotic	Majority peridomestic, occasionally sylvatic
Mediterranean basin, Middle East, Central Asia, China	VL, CL	*L. infantum*	*P. perniciosus, P. ariasi*	Dogs, foxes, jackals	Zoonotic	Domestic, peridomestic
Middle East, Saudi Arabia, Yemen	VL	*L. donovani*	*P. perniciosus, P. ariasi*	Dogs, foxes, jackals	Zoonotic	Domestic, peridomestic
Central and South America	VL, CL	*L. infantum*	*Lutzomyia longipalpis*	Foxes, dogs, opossums	Zoonotic	Domestic, peridomestic, periurban
Azerbaijan, Armenia, Georgia, Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan, Uzbekistan	VL	*L. infantum*	*P. turanicus*	Humans, dogs, foxes	Anthroponotic, zoonotic	Domestic
L. tropica						
Western India to Turkey, parts of North and East Africa	CL, leishmaniasis recidivans	*L. tropica*	*P. sergenti*	Humans	Anthroponotic	Urban domestic, peridomestic
L. major						
Western and central Asia, northern and sub-Saharan Africa	CL	*L. major*	*P. papatasi, P. duboscqi*	Nile rats, rodents	Zoonotic	Sylvatic, peridomestic
Kazakhstan, Turkmenistan, and Uzbekistan	CL	*L. major*	*P. papatasi, P. duboscqi*	Gerbils	Zoonotic	Rural
L. aethiopica						
Ethiopia, Uganda, Kenya	CL, DCL	*L. aethiopica*	*P. longipes, P. pedifer*	Hyraxes	Zoonotic	Sylvatic, peridomestic
Subspecies *Viannia*						
Peru, Ecuador	CL, ML	*L. (V.) peruviana*	*Lutzomyia verrucarum, L. peruensis*	Wild rodents	Zoonotic	Andean valleys
Guyana, Surinam, French Guyana, Ecuador, Brazil, Colombia, Bolivia	CL, ML	*L. (V.) guyanensis*	*L. umbratilis*	Sloths, arboreal anteaters, opossums	Zoonotic	Tropical forests
Central America, Ecuador, Colombia	CL, ML	*L. (V.) panamensis*	*L. trapidoi*	Sloths	Zoonotic	Tropical forest and deforested areas
South and Central America	CL, ML	*L. (V.) braziliensis*	*Lutzomyia* spp., *L. umbratilis, Psychodopygus wellcomei*	Forest rodents, peridomestic animals	Zoonotic	Tropical forest and deforested areas

(*continued*)

TABLE 122-1

GEOGRAPHIC DISTRIBUTION AND CHARACTERISTIC EPIDEMIOLOGY OF LEISHMANIASES (*CONTINUED*)

ORGANISM, ENDEMIC REGION	CLINICAL SYNDROME	SPECIES	VECTOR	RESERVOIR	TRANS-MISSION	SETTING
***L. mexicana* Complex**						
Central America and northern parts of South America	CL, ML, DCL	*L. amazonensis*	*L. flaviscutellata*	Forest rodents	Zoonotic	Tropical forest and deforested areas
	CL, ML, DCL	*L. mexicana*	*L. olmeca*	Variety of forest rodents and marsupials	Zoonotic	
	CL, DCL	*L. pifanoi*	*L. olmeca*	Variety of forest rodents and marsupials	Zoonotic	Tropical forest and deforested areas

Abbreviations: CL, cutaneous leishmaniasis; DCL, diffuse cutaneous leishmaniasis; ML, mucosal leishmaniasis; PKDL, post–kala-azar dermal leishmaniasis; VL, visceral leishmaniasis.

(length, 2–4 μm; Fig. 122-1) in vertebrate hosts, including humans. Promastigotes are introduced through the proboscis of the female sandfly into the skin of the vertebrate host. Neutrophils predominate among the host cells that first encounter and take up promastigotes at the site of parasite delivery. The infected neutrophils may undergo apoptosis and release viable parasites that are taken up by macrophages, or the apoptotic cells may themselves be taken up by macrophages and dendritic cells. The parasites multiply as amastigotes inside macrophages, causing cell rupture with subsequent invasion of other macrophages. While feeding on infected hosts, sandflies pick up amastigotes, which transform into the flagellate form in the flies' posterior midgut and multiply by binary fission; the promastigotes then migrate to the anterior midgut and can infect a new host when flies take another blood meal.

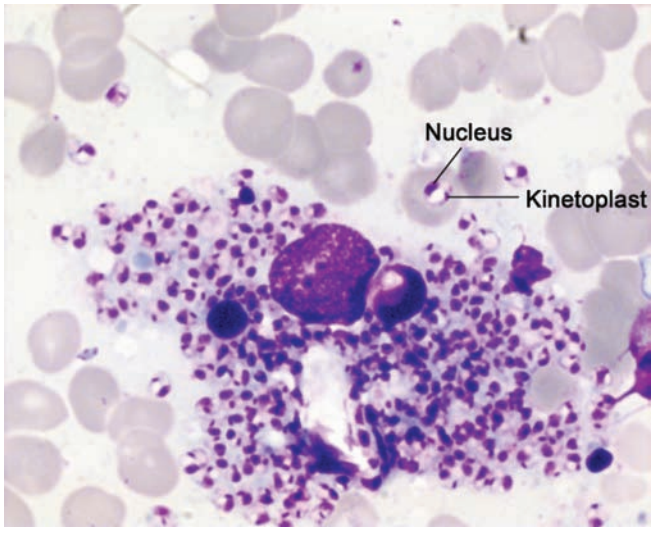


FIGURE 122-1
A macrophage with numerous intracellular amastigotes (2–4 μm) in a Giemsa-stained splenic smear from a patient with visceral leishmaniasis. Each amastigote contains a nucleus and a characteristic kinetoplast consisting of multiple copies of mitochondrial DNA. A few extracellular parasites are also visible.

EPIDEMIOLOGY

Leishmaniasis occurs in 98 countries—most of them developing—in tropical and temperate regions (Fig. 122-2). Two million cases occur annually, of which 1–1.5 million are CL (and its variations) and 500,000 are VL. More than 350 million people are at risk, with an overall prevalence of 12 million. Although the distribution of *Leishmania* is limited by the distribution of sandfly vectors, human leishmaniasis is on the increase worldwide.

VISCERAL LEISHMANIASIS

VL (also known as *kala-azar*, a Hindi term meaning "black fever") is caused by the *L. donovani* complex, which includes *L. donovani* and *L. infantum* (the latter designated *L. chagasi* in the New World); these species are responsible for anthroponotic and zoonotic transmission, respectively. India and neighboring Nepal, Bangladesh, Sudan, and Brazil are the four largest foci of VL and account for 90% of the world's VL burden, with India the worst affected. Zoonotic VL is reported from all countries in the Middle East, Pakistan, and other countries from western Asia to China. Endemic foci also exist in the independent states of the former Soviet Union, mainly Georgia and Azerbaijan. In the Horn of Africa, Sudan, Ethiopia, Kenya, Uganda, and Somalia report VL. In Sudan, large outbreaks are thought to be anthroponotic, although zoonotic transmission also occurs. VL is rare in West and sub-Saharan Africa.

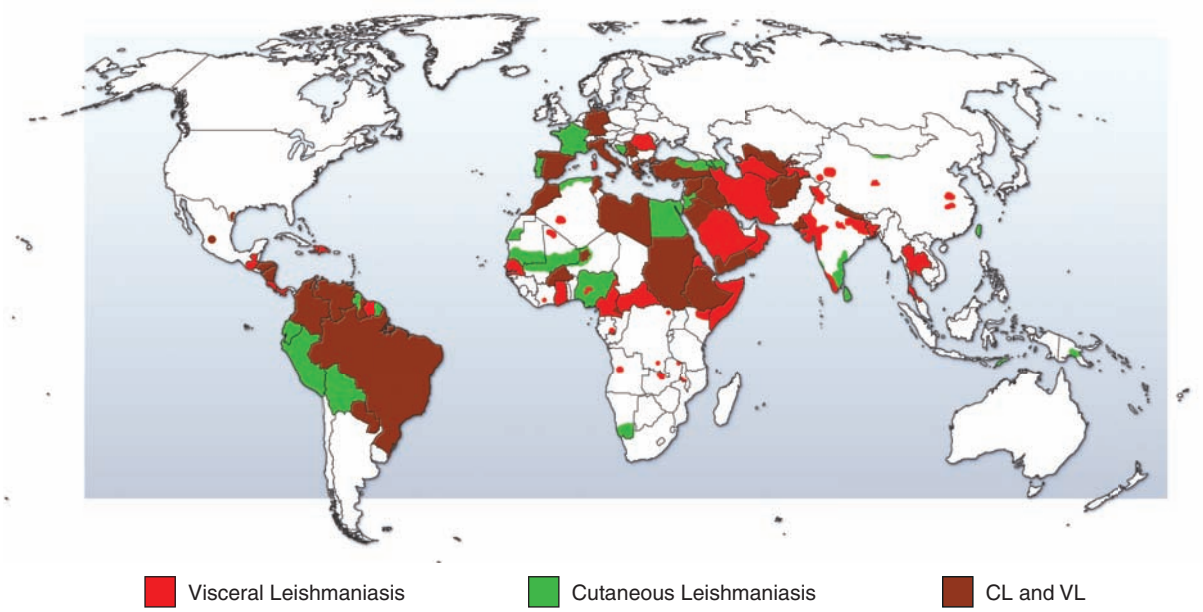


FIGURE 122-2
Worldwide distribution of human leishmaniasis.

Mediterranean VL, long an established endemic disease due to *L. infantum*, has a large canine reservoir and was seen primarily in infants before the advent of HIV. In Mediterranean Europe, 70% of adult VL cases are associated with HIV co-infection. The combination is deadly because of the impact of the two infections together on the immune system. IV drug users are at particular risk. Other forms of immunosuppression (e.g., that associated with organ transplantation) also predispose to VL. In the Americas, disease caused by *L. infantum* is endemic from Mexico to Argentina, but 90% of cases in the New World are reported from northeastern Brazil.

Immunopathogenesis

The majority of individuals infected by *L. donovani* or *L. infantum* mount a successful immune response and control the infection, never developing symptomatic disease. Forty-eight hours after intradermal injection of killed promastigotes, these individuals exhibit delayed-type hypersensitivity (DTH) to leishmanial antigens in the leishmanin skin test (also called the Montenegro skin test). Results in mouse models indicate that the development of acquired resistance to leishmanial infection is controlled by the production of interleukin (IL) 12 by antigen-presenting cells and the subsequent secretion of interferon (IFN) γ, tumor necrosis factor (TNF) α, and other proinflammatory cytokines by the T helper 1 (T_H1) subset of T lymphocytes. The immune response in patients developing active VL is complex; in addition to increased production of multiple proinflammatory cytokines and chemokines, patients with active disease have markedly elevated levels of IL-10 in serum as well as enhanced IL-10 mRNA expression in lesional tissues. The main disease-promoting activity of IL-10 in VL may be to condition host macrophages for enhanced survival and growth of the parasite. IL-10 can render macrophages unresponsive to activation signals and inhibit killing of amastigotes by downregulating the production of TNF-α and nitric oxide. Multiple antigen-presentation functions of dendritic cells and macrophages are also suppressed by IL-10. Patients with such suppression do not have positive leishmanin skin tests, nor do their peripheral-blood mononuclear cells respond to leishmanial antigens in vitro. Organs of the reticuloendothelial system are predominantly affected, with remarkable enlargement of the spleen, the liver, and lymph nodes in some regions. The tonsils and intestinal submucosa are also heavily infiltrated with parasites. Bone marrow dysfunction results in pancytopenia.

Clinical features

On the Indian subcontinent and in the Horn of Africa, persons of all ages are affected by VL. In endemic areas of the Americas and the Mediterranean basin, immunocompetent infants and small children and immunodeficient adults are affected especially often. The most common presentation of VL is an abrupt onset of moderate- to high-grade fever associated with rigor and chills. Fever may continue for several weeks with decreasing intensity, and the patient may become afebrile for a short period before experiencing another bout of fever. The spleen may be palpable by the second week of illness and, depending on the duration of illness, may become hugely enlarged **(Fig. 122-3)**. Hepatomegaly (usually moderate in degree) soon follows. Lymphadenopathy is common in most endemic regions of the world except the Indian subcontinent, where it is rare. Patients lose weight and feel weak, and the skin gradually develops dark discoloration due to

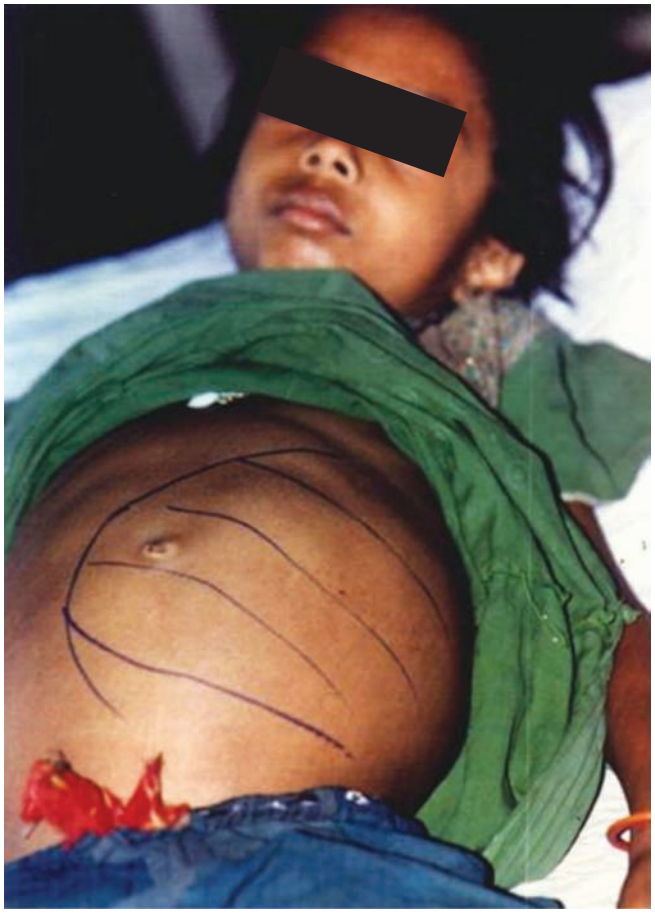


FIGURE 122-3
A patient with visceral leishmaniasis has a hugely enlarged spleen visible through the surface of the abdomen. Splenomegaly is the most important feature of visceral leishmaniasis.

hyperpigmentation that is most easily seen in brown-skinned individuals. In advanced illness, hypoalbuminemia may manifest as pedal edema and ascites. Anemia appears early and may become severe enough to cause congestive heart failure. Epistaxis, retinal hemorrhages, and gastrointestinal bleeding are associated with thrombocytopenia. Secondary infections such as measles, pneumonia, tuberculosis, bacillary or amebic dysentery, and gastroenteritis are common. Herpes zoster, chickenpox, boils in the skin, and scabies may also occur. Untreated, the disease is fatal in most patients, including 100% of those with HIV co-infection.

Leukopenia and anemia occur early and are followed by thrombocytopenia. There is a marked polyclonal increase in serum immunoglobulins. Serum levels of hepatic aminotransferases are raised in a significant proportion of patients, and serum bilirubin levels are elevated occasionally. Renal dysfunction is uncommon.

Laboratory diagnosis

Demonstration of amastigotes in smears of tissue aspirates is the gold standard for the diagnosis of VL (Fig. 122-1). The sensitivity of splenic smears is >95%, whereas smears of bone marrow (60–85%) and lymph node aspirates (50%) are less sensitive. Culture of tissue aspirates increases sensitivity. Splenic aspiration is invasive and may be dangerous in untrained hands. Several serologic techniques are currently used to detect antibodies to *Leishmania*. An enzyme-linked immunosorbent assay (ELISA) and the indirect immunofluorescent antibody test (IFAT) are used in sophisticated laboratories. In the field, however, a rapid immunochromatographic test based on the detection of antibodies to a recombinant antigen (rK39) consisting of 39 amino acids conserved in the kinesin region of *L. infantum* is used worldwide. The test requires only a drop of fingerprick blood or serum, and the result can be read within 15 minutes. Except in East Africa (where both its sensitivity and its specificity are lower), the sensitivity of the rK39 rapid diagnostic test in immunocompetent individuals is ~98% and its specificity is 90%. Qualitative detection of leishmanial nucleic acid by polymerase chain reaction (PCR) and quantitative detection by real-time PCR are confined to specialized laboratories and have yet to be used for routine diagnosis of VL in endemic areas. PCR can distinguish among the major species of *Leishmania* infecting humans.

Differential diagnosis

VL is easily mistaken for malaria. Other febrile illnesses that may mimic VL include typhoid fever, tuberculosis, brucellosis, schistosomiasis, and histoplasmosis. Splenomegaly due to portal hypertension, chronic myeloid leukemia, tropical splenomegaly syndrome, and (in Africa) schistosomiasis may also be confused with VL. Fever with neutropenia or pancytopenia in patients from an endemic region strongly suggests a diagnosis of VL; hypergammaglobulinemia in patients with long-standing illness strengthens the diagnosis. In non-endemic countries, a careful travel history is essential when any patient presents with fever.

TREATMENT **Visceral Leishmaniasis**

GENERAL CONSIDERATIONS Severe anemia should be corrected by blood transfusion, and other comorbid conditions should be managed promptly. Treatment of VL is complex, as the optimal drug, dosage, and duration vary with the endemic region. In spite of completing recommended treatment, some patients experience relapse (most often within 6 months), and prolonged follow-up is recommended. A pentavalent antimonial is the drug of choice in most endemic regions of the world, but there is widespread resistance to antimony in the Indian state of Bihar, where either amphotericin B (AmB) deoxycholate or miltefosine is preferred. Dose requirements for AmB are lower in India than in the

Americas, Africa, or the Mediterranean region. In Mediterranean countries, where cost is seldom an issue, liposomal AmB is the drug of choice. In immunocompetent patients, relapses are uncommon with AmB in its deoxycholate and lipid formulations. Antileishmanial therapy has recently evolved as new drugs and delivery systems have become available and resistance to antimonial compounds has emerged.

Except for AmB (deoxycholate and lipid formulations), antileishmanial drugs are available in the United States only from the Centers for Disease Control and Prevention.

PENTAVALENT ANTIMONIAL COMPOUNDS Two pentavalent antimonial (Sb^V) preparations are available: sodium stibogluconate (100 mg of Sb^V/mL) and meglumine antimonate (85 mg of Sb^V/mL). The daily dose is 20 mg/kg by rapid IV infusion or IM injection, and therapy continues for 28–30 days. Cure rates exceed 90% in Africa, the Americas, and most of the Old World but are <50% in Bihar, India, as a result of resistance. Adverse reactions to Sb^V treatment are common and include arthralgia, myalgia, and elevated serum levels of aminotransferases. Electrocardiographic changes are common. Concave ST segment elevation is not significant, but prolongation of QT_c to >0.5 s may herald ventricular arrhythmia and sudden death. Chemical pancreatitis is common but usually does not require discontinuation of treatment; severe clinical pancreatitis occurs in immunosuppressed patients.

AMPHOTERICIN B AmB is currently used as a first-line drug in Bihar. In others parts of the world, it is used when initial antimonial treatment fails. Conventional AmB deoxycholate is administered in doses of 0.75–1.0 mg/kg on alternate days for a total of 15 infusions. Fever with chills is an almost universal adverse reaction to AmB infusions. Nausea and vomiting are also common, as is thrombophlebitis in the infused veins. Acute toxicities can be minimized by administration of antihistamines like chlorpheniramine and antipyretic agents like acetaminophen before each infusion. AmB can cause renal dysfunction and hypokalemia and in rare instances elicits hypersensitivity reactions, bone marrow suppression, and myocarditis, all of which can be fatal.

The several lipid formulations of AmB developed to replace the deoxycholate formulation are preferentially taken up by reticuloendothelial tissues. Because very little free drug is available to cause toxicity, a large amount of drug can be delivered over a short period. Liposomal AmB has been used extensively to treat VL in all parts of the world. With a terminal half-life of ~150 h, liposomal AmB can be detected in the liver and spleen of animals for several weeks after a single dose. This is the only drug approved by the U.S. Food and Drug Administration (FDA) for the treatment of VL; the regimen is 3 mg/kg daily on days 1–5, 14, and 21 (total dose, 21 mg/kg). However, the total dose requirement for different regions of the world varies widely. In Asia, it is 10–15 mg/kg; in Africa, ~18 mg/kg; and in Mediterranean/American regions, not less than 20 mg/kg. The daily dose is flexible (1–10 mg/kg). In a study in India, a single dose of 10 mg/kg cured infection in 96% of patients. Adverse effects of liposomal AmB are usually mild and include infusion reactions, backache, and occasional reversible nephrotoxicity.

PAROMOMYCIN Paromomycin (aminosidine) is an aminocyclitol-aminoglycoside antibiotic with antileishmanial activity. Its mechanism of action against *Leishmania* has yet to be established. Paromomycin is approved in India for the treatment of VL at an IM dose of 11 mg of base/kg daily for 21 days; this regimen produces a cure rate of 95%. However, the optimal dose has not been established in other endemic regions. Paromomycin is a relatively safe drug, but some patients develop hepatotoxicity, reversible ototoxicity, and (in rare instances) nephrotoxicity and tetany.

MILTEFOSINE Miltefosine, an alkylphosphocholine, is the first oral compound approved for the treatment of leishmaniasis. This drug has a long half-life (150–200 h); its mechanism of action is not clearly understood. The recommended therapeutic regimens for patients on the Indian subcontinent are a daily dose of 50 mg for 28 days for patients weighing <25 kg, a twice-daily dose of 50 mg for 28 days for patients weighing ≥25 kg, and 2.5 mg/kg for 28 days for children 2–11 years of age. These regimens result in a cure rate of 94% in India. Doses in other regions remain to be established. Because of its long half-life, miltefosine is prone to induce resistance in *Leishmania*. Its adverse effects include mild to moderate vomiting and diarrhea in 40% and 20% of patients, respectively; these reactions usually clear spontaneously after a few days. Rare cases of severe allergic dermatitis, hepatotoxicity, and nephrotoxicity have been reported. Because miltefosine is expensive and is associated with significant adverse events, it is best administered as directly observed therapy to ensure completion of treatment and to minimize the risk of resistance induction. Because miltefosine is teratogenic in rats, its use is contraindicated during pregnancy and (unless contraceptive measures are strictly adhered to for at least 3 months after treatment) in women of childbearing age.

MULTIDRUG THERAPY Multidrug therapy for leishmaniasis is likely to be preferred in the future. Its potential advantages in VL include (1) better compliance and lower costs associated with shorter treatment courses and decreased hospitalization, (2) less toxicity due to lower drug doses and/or shorter duration of treatment, and (3) a reduced likelihood that resistance to either agent will develop. Trials of multidrug therapy are under way in Asia and Africa.

PROGNOSIS OF TREATED VL PATIENTS
Recovery from VL is quick. Within a week of the start of treatment, defervescence, regression of splenomegaly, weight gain, and recovery of hematologic parameters are evident. With effective treatment, no parasites are recovered from tissue aspirates at the posttreatment evaluation. Continued clinical improvement over 6–12 months is suggestive of cure. A small percentage of patients (with the exact figure depending on the regimen used) relapse but respond well to treatment with AmB deoxycholate or lipid formulations.

VL IN THE IMMUNOCOMPROMISED HOST
HIV/VL co-infection has been reported from 35 countries. VL behaves as an opportunistic infection in HIV-1-infected patients where both infections are endemic. HIV infection can increase the risk of developing VL severalfold in endemic areas. Co-infected patients usually show the classic signs of VL, but they may present with atypical features due to loss of immunity and involvement of unusual anatomic locations, with, for example, infiltration of the skin, oral mucosa, gastrointestinal tract, lungs, and other organs. Serodiagnostic tests are commonly negative. Parasites can be recovered from unusual sites such as bronchoalveolar lavage fluid and buffy coat. Liposomal AmB is the drug of choice for HIV/VL co-infection—both for primary treatment and for treatment of relapses. A total dose of 40 mg/kg, administered as 4 mg/kg on days 1–5, 10, 17, 24, 31, and 38, is considered optimal and is approved by the FDA, but most patients relapse within 1 year. Pentavalent antimonials and AmB deoxycholate can also be used where liposomal AmB is not accessible. Reconstitution of patients' immunity by antiretroviral therapy has led to a dramatic decline in the incidence of co-infection in the Mediterranean basin. In contrast, HIV/VL co-infection is on the rise in African and Asian countries. Ethiopia is worst affected: up to 30% of VL patients are also infected with HIV. Since restoration of the CD4+ T cell count to >200/μL does decrease the frequency of relapse, antiretroviral therapy (in addition to antileishmanial therapy) is a cornerstone for the management of HIV/VL co-infection. Secondary prophylaxis with liposomal AmB has been shown to delay relapses, but no regimen has been established as optimal.

POST–KALA-AZAR DERMAL LEISHMANIASIS

On the Indian subcontinent and in Sudan and other East African countries, 2–50% of patients develop skin lesions concurrent with or after the cure of VL. Most common are hypopigmented macules, papules, and/or nodules or diffuse infiltration of the skin and sometimes of the oral mucosa. The African and Indian diseases differ in several respects; important features of post–kala-azar dermal leishmaniasis (PKDL) in these two regions are listed in Table 122-2, and disease in an Indian patient is depicted in Fig. 122-4.

In PKDL, parasites are scanty in hypopigmented macules but may be seen and cultured more easily from nodular lesions. Cellular infiltrates are heavier in nodules than in macules. Lymphocytes are the dominant cells; next most common are histiocytes and plasma cells. In about half of cases, epithelioid cells—scattered individually or forming compact granulomas—are seen. The diagnosis is based on history and clinical findings, but rK39 and other serologic tests are positive in most cases. Indian PKDL is treated with pentavalent antimonials for 60–120 days. This prolonged course frequently leads to noncompliance. The alternative—several courses of AmB spread over several months—is expensive and unacceptable for most patients. In East Africa, a majority of patients experience spontaneous healing. In those with persistent lesions, the response to 60 days of treatment with a pentavalent antimonial is good.

CUTANEOUS LEISHMANIASIS

CL can be broadly divided into Old World and New World forms. Old World CL caused by *L. tropica* is

TABLE 122-2
CLINICAL, EPIDEMIOLOGIC, AND THERAPEUTIC FEATURES OF POST–KALA-AZAR DERMAL LEISHMANIASIS: EAST AFRICA AND THE INDIAN SUBCONTINENT

FEATURE	EAST AFRICA	INDIAN SUBCONTINENT
Most affected country	Sudan	Bangladesh
Incidence among patients with VL	~50%	~2%
Interval between VL and PKDL	During VL to 6 months	6 months to 3 years
Age distribution	Mainly children	Any age
History of prior VL	Yes	Not necessarily
Rashes of PKDL in presence of active VL	Yes	No
Treatment with sodium stibogluconate	2–3 months	2–4 months
Natural course	Spontaneous cure in majority of patients	Spontaneous cure not reported

Abbreviations: PKDL, post–kala-azar dermal leishmaniasis; VL, visceral leishmaniasis.

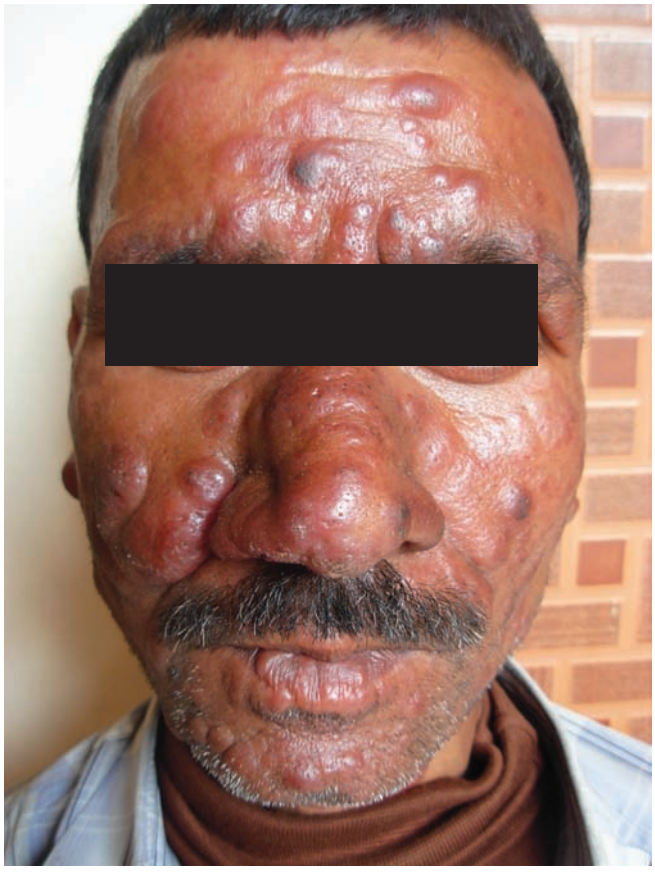


FIGURE 122-4
Post–kala-azar dermal leishmaniasis in an Indian patient. Note nodules of varying size involving the entire face. The face is erythematous, and the surface of some of the large nodules is discolored.

anthroponotic and is confined to urban or suburban areas throughout its range. Zoonotic CL is most commonly due to *L. major*, which naturally parasitizes several species of desert rodents that act as reservoirs over wide areas of the Middle East, Africa, and central and southern Asia. Local outbreaks of human disease are common. Major outbreaks currently affect Afghanistan and Pakistan in association with refugees and population movement. CL is increasingly seen in tourists and military personnel on mission in CL-endemic regions of countries like Afghanistan and Iraq and as a co-infection in HIV-infected patients. *L. aethiopica* is restricted to the highlands of Ethiopia, Kenya, and Uganda, where it is a natural parasite of hyraxes. New World CL is mainly zoonotic and is most often caused by *L. mexicana*, *L. (V.) panamensis*, and *L. amazonensis*. A wide range of forest animals act as reservoirs, and human infections with these species are predominantly rural. As a result of extensive urbanization and deforestation, *L. (V.) braziliensis* has adapted to peridomestic and urban animals, and CL due to this organism is increasingly becoming an urban disease. In the United States, a few cases of CL have been acquired indigenously in Texas.

Immunopathogenesis

As in VL, the proinflammatory (T_H1) response in CL may result in either asymptomatic or subclinical infection. However, in some individuals, the immune response causes ulcerative skin lesions, the majority of which will heal spontaneously, leaving a scar. Healing is usually followed by immunity to reinfection with that species of parasite.

Clinical features

A few days or weeks after the bite of a sandfly, a papule develops and grows into a nodule that ulcerates over some weeks or months. The base of the ulcer, which is usually painless, consists of necrotic tissue and crusted serum, but secondary bacterial infection sometimes occurs. The margins of the ulcer are raised and indurated. Lesions may be single or multiple and vary in size from 0.5 to >3 cm **(Fig. 122-5)**. Lymphatic spread and lymph gland involvement may be palpable and may precede the appearance of the skin lesion. There may be satellite lesions, especially in *L. major* and *L. tropica* infections. The lesions usually heal spontaneously after 2–15 months. Lesions due to *L. major* and *L. mexicana* tend to heal rapidly, while those due to *L. tropica* and parasites of subspecies *Viannia* heal more slowly. In CL caused by *L. tropica*, new lesions—usually scaly, erythematous papules and nodules—develop in the center or periphery of a healed sore, a condition known as *leishmaniasis recidivans*. Lesions of *L. mexicana* and *L. (V.) peruviana* closely resemble those seen in the Old World; however, lesions on the pinna of the ear are common, chronic, and destructive in the former infections. *L. mexicana* is responsible for chiclero's ulcer, the so-called self-healing sore of Mexico. CL lesions on exposed body parts (e.g., the face

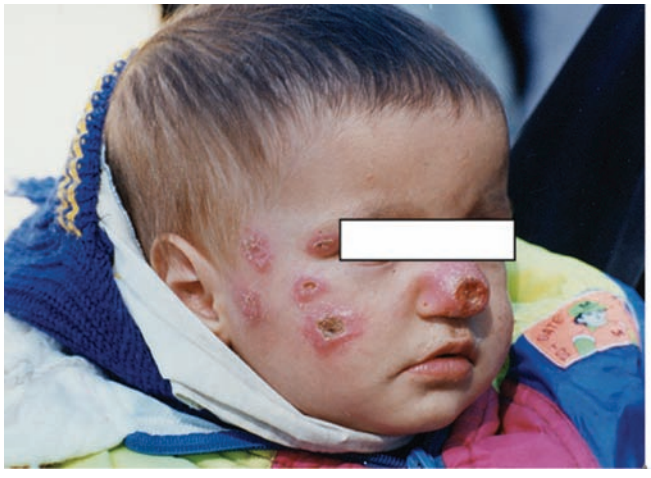


FIGURE 122-5
Cutaneous leishmaniasis in a Bolivian child. There are multiple ulcers resulting from several sandfly bites. The edges of the ulcers are raised. (*Courtesy of P. Desjeux.*)

and hands), permanent scar formation, and social stigmatization may cause anxiety and depression and may affect the quality of life of CL patients.

Differential diagnosis

A typical history (an insect bite followed by the events leading to ulceration) in a resident of or a traveler to an endemic focus strongly suggests CL. Cutaneous tuberculosis, fungal infections, leprosy, sarcoidosis, and malignant ulcers are sometimes mistaken for CL.

Laboratory diagnosis

Demonstration of amastigotes in material obtained from a lesion remains the diagnostic gold standard. Microscopic examination of slit skin smears, aspirates, or biopsies of the lesion is used for detection of parasites. Culture of smear or biopsy material may yield *Leishmania*. PCR is more sensitive than microscopy and culture and allows identification of *Leishmania* to the species level. This information is important in decisions about therapy since responses to treatment can vary with the species. Isoenzyme profiling is used to determine species for research purposes.

TREATMENT Cutaneous Leishmaniasis

Although lesions heal spontaneously in the majority of cases, their spread or persistence indicates that treatment may be needed. One or a few small lesions due to "self-healing species" can be treated with topical agents. Systemic treatment is required for lesions over the face, hands, or joints; multiple lesions; large ulcers; lymphatic spread; New World CL with the potential for development of ML; and CL in HIV-coinfected patients.

A pentavalent antimonial is the first-line drug for all forms of CL and is used in a dose of 20 mg/kg for 20 days, as for VL. The exceptions to this rule are CL caused by *L. (V.) guyanensis*, for which pentamidine isethionate is the drug of choice (two injections of 4 mg of salt/kg separated by a 48-h interval), and CL due to *L. aethiopica*, which responds to paromomycin (16 mg/kg daily) but not to antimonials. Relapses usually respond to a second course of treatment. In Peru, topical imiquimod (5–7.5%) plus parenteral antimonials have been shown to cure CL more rapidly than antimonials alone. Azoles and triazoles have been used with mixed responses in both Old and New World CL but have not been adequately assessed for this indication in clinical trials. In *L. major* infection, oral fluconazole (200 mg/d for 6 weeks) resulted in a higher rate of cure than placebo (79% vs. 34%) and also cured infection faster. Adverse effects include gastrointestinal symptoms and hepatotoxicity. Ketoconazole (600 mg/d for 28 days) is 76–90% effective in CL due to *L. (V.) panamensis* and *L. mexicana* in Panama and Guatemala. Miltefosine has been used in CL in doses of 2.5 mg/kg for 28 days. This agent is effective against *L. major* infections. In Colombia, where CL is due to *L. (V.) panamensis*, miltefosine was also effective, with a cure rate of 91%. For *L. (V.) braziliensis* infections, however, the results with miltefosine are less consistent. Other drugs, such as dapsone, allopurinol, rifampin, azithromycin, and pentoxifylline, have been used either alone or in combinations, but most of the relevant studies have had design limitations that preclude meaningful conclusions.

Small lesions (≥3 cm in diameter) may conveniently be treated weekly until cure with an intralesional injection of a pentavalent antimonial at a dose adequate to blanch the lesion (0.2–2.0 mL). An ointment containing 15% paromomycin sulfate plus 12% methylbenzonium chloride cures 70% of lesions due to *L. major* in 20 days and may be suitable for lesions caused by other species. Heat therapy with an FDA-approved radiofrequency generator and cryotherapy with liquid nitrogen have also been used successfully.

Diffuse cutaneous leishmaniasis (DCL)

DCL is a rare form of leishmaniasis caused by *L. amazonensis* and *L. mexicana* in South and Central America and by *L. aethiopica* in Ethiopia and Kenya. DCL is characterized by the lack of a cell-mediated immune response to the parasite, the uncontrolled multiplication of which thus continues unabated. The DTH response is negative, and lymphocytes do not respond to leishmanial antigens in vitro. DCL patients have a polarized immune response with high levels of immunosuppressive cytokines, including IL-10, transforming growth factor (TGF) β, and IL-4, and low concentrations of IFN-γ. Profound immunosuppression leads to widespread cutaneous disease. Lesions may initially be confined to the face or a limb but spread over months or years to other areas of the skin. They may be symmetrically or asymmetrically distributed and include papules, nodules, plaques, and areas of diffuse infiltration. These lesions do not ulcerate. The overlying skin is usually erythematous in pale-skinned patients. The lesions are teeming with parasites, which are therefore easy to recover. DCL does not heal spontaneously and is difficult to treat. If relapse and drug resistance are to be prevented, treatment should be continued for some time after lesions have healed and parasites can no longer be isolated. In the New World, repeated 20-day courses of pentavalent antimonials are given, with an intervening drug-free period of 10 days. Miltefosine has been used for several months with a good initial response. Combinations should be tried. In Ethiopia, a combination of paromomycin (14 mg/kg per day) and sodium stibogluconate (10 mg/kg per day) is effective.

MUCOSAL LEISHMANIASIS

The subgenus *Viannia* is widespread from the Amazon basin to Paraguay and Costa Rica and is responsible for deep sores and for ML (Table 122-1). In *L. (V.) braziliensis* infections, cutaneous lesions may be simultaneously accompanied by mucosal spread of the disease or followed by spread years later. ML is caused typically by *L. (V.) braziliensis* and rarely by *L. amazonensis*, *L. (V.) guyanensis*, and *L. (V.) panamensis*. Young men with chronic lesions of CL are at particular risk. Overall, ~3% of infected persons develop ML. Not every patient with ML has a history of prior CL. ML is almost entirely confined to the Americas. In rare cases, ML may also be caused by Old World species like *L. major*, *L. infantum*, or *L. donovani*.

Immunopathogenesis and clinical features

The immune response is polarized toward a T_H1 response, with marked increases of IFN-γ and TNF-α and varying levels of T_H2 cytokines (IL-10 and TGF-β). Patients have a stronger DTH response with ML than with CL, and their peripheral-blood mononuclear cells respond strongly to leishmanial antigens. The parasite spreads via the lymphatics or the bloodstream to mucosal tissues of the upper respiratory tract. Intense inflammation leads to destruction, and severe disability ensues. Lesions in or around the nose or mouth (espundia; **Fig. 122-6**) are the typical presentation of ML. Patients usually provide a history of self-healed CL preceding ML by 1–5 years. Typically, ML presents as nasal stuffiness and bleeding followed by destruction of nasal cartilage, perforation of the nasal septum, and collapse of the nasal bridge. Subsequent involvement of the pharynx and larynx leads to difficulty in swallowing and phonation. The lips, cheeks, and soft palate may also be affected. Secondary bacterial infection is common, and aspiration pneumonia may be fatal. Despite the high degree of T_H1 immunity and the strong DTH response, ML does not heal spontaneously.

Laboratory diagnosis

Tissue biopsy is essential for identification of parasites, but the rate of detection is poor unless PCR techniques are used. The strongly positive DTH response fails to distinguish between past and present infection.

TREATMENT Mucosal Leishmaniasis

The regimen of choice is a pentavalent antimonial agent administered at a dose of 20 mg of Sb^V/kg for 30 days. Patients with ML require long-term follow-up with repeated oropharyngeal and nasal examination. With failure of therapy or relapse, patients may receive another course of an antimonial but then become unresponsive, presumably because of resistance in the parasite. In this situation, AmB should be used. An AmB deoxycholate dose totaling 25–45 mg/kg is appropriate. There are no controlled trials of liposomal AmB, but administration of 2–3 mg/kg for 20 days is considered adequate. Miltefosine (2.5 mg/kg for 28 days) cured 71% of ML patients in Bolivia. The more extensive the disease, the worse the prognosis; thus prompt, effective treatment and regular follow-up are essential.

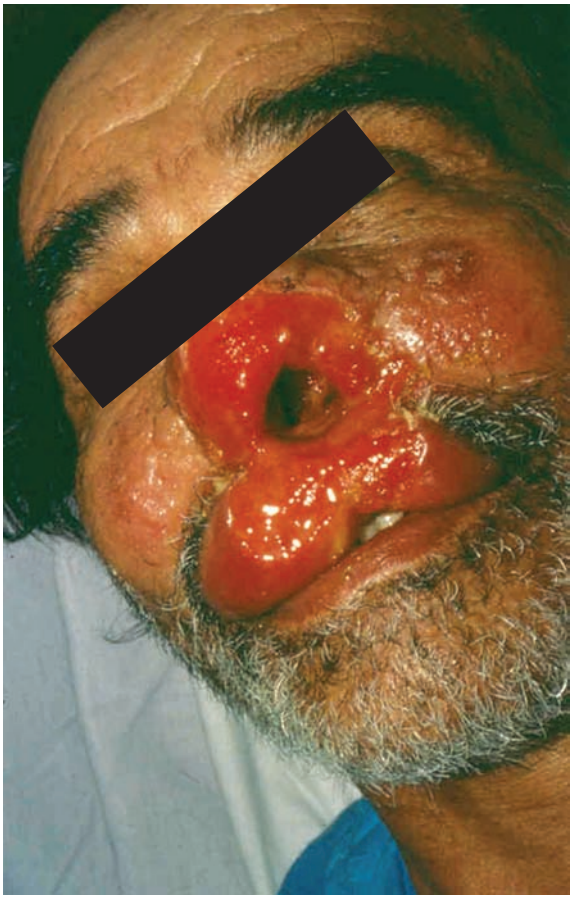


FIGURE 122-6
Mucosal leishmaniasis in a Brazilian patient. There is extensive inflammation around the nose and mouth, destruction of the nasal mucosa, ulceration of the upper lip and nose, and destruction of the nasal septum. (*Courtesy of R. Dietz.*)

PREVENTION OF LEISHMANIASIS

No vaccine is available for any form of leishmaniasis. Inoculation with live *L. major* ("leishmanization") is practiced in Iran. Anthroponotic leishmaniasis is controlled by case finding, treatment, and vector control with insecticide-impregnated bed nets and curtains and residual insecticide spraying. Control of zoonotic leishmaniasis is more difficult. Use of insecticide-impregnated collars for dogs, treatment of infected domestic dogs, and culling of street dogs are measures that have been used with uncertain efficacy to prevent transmission of *L. infantum*. Personal prophylaxis with bed nets and repellants may reduce the risk of CL infections in the New World.

CHAPTER 123

CHAGAS' DISEASE AND TRYPANOSOMIASIS

Louis V. Kirchhoff ■ Anis Rassi, Jr.

Although the genus *Trypanosoma* contains many species of protozoans, only *T. cruzi*, *T. brucei gambiense*, and *T. brucei rhodesiense* cause disease in humans. *T. cruzi* is the etiologic agent of Chagas' disease in the Americas; *T. b. gambiense* and *T. b. rhodesiense* cause African trypanosomiasis.

CHAGAS' DISEASE

DEFINITION

Chagas' disease, or American trypanosomiasis, is a zoonosis caused by the protozoan parasite *T. cruzi*. Acute Chagas' disease is usually a mild febrile illness that results from initial infection with the organism. After spontaneous resolution of the acute illness, most infected persons remain for life in the indeterminate phase of chronic Chagas' disease, which is characterized by subpatent parasitemia, easily detectable antibodies to *T. cruzi*, and an absence of associated signs and symptoms. In 10–30% of chronically infected patients, cardiac and/or gastrointestinal lesions develop that can result in serious morbidity and even death.

LIFE CYCLE AND TRANSMISSION

T. cruzi is transmitted among its mammalian hosts by hematophagous triatomine insects, often called reduviid bugs. The insects become infected by sucking blood from animals or humans who have circulating parasites. Ingested organisms multiply in the gut of the triatomines, and infective forms are discharged with the feces at the time of subsequent blood meals. Transmission to a second vertebrate host occurs when breaks in the skin, mucous membranes, or conjunctivae become contaminated with bug feces that contain infective parasites. *T. cruzi* can also be transmitted by the transfusion of blood donated by infected persons, by organ transplantation, from mother to unborn child, by ingestion of contaminated food or drink, and in laboratory accidents.

PATHOLOGY

Initial infection at the site of parasite entry is characterized by local histologic changes that include the presence of parasites within leukocytes and cells of subcutaneous tissues and the development of interstitial edema, lymphocytic infiltration, and reactive hyperplasia of adjacent lymph nodes. After dissemination of the organisms through the lymphatics and the bloodstream, primarily muscles (including the myocardium) (Fig. 123-1) and ganglion cells may become heavily parasitized. The characteristic pseudocysts present in sections of infected tissues are intracellular aggregates of multiplying parasites.

In individuals with chronic *T. cruzi* infections who develop related clinical manifestations, the heart is the organ most commonly affected. Changes include thinning of the ventricular walls, biventricular enlargement, apical aneurysms, and mural thrombi. Widespread lymphocytic infiltration, diffuse interstitial fibrosis, and atrophy of myocardial cells are often apparent, but parasites

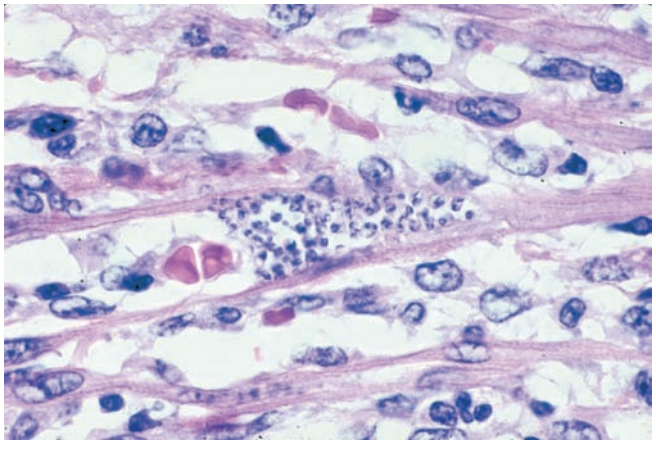


FIGURE 123-1
***Trypanosoma cruzi* in the heart muscle of a child who died of acute Chagas' myocarditis.** An infected myocyte containing several dozen *T. cruzi* amastigotes is in the center of the field (hematoxylin and eosin, 900×).

are difficult to find in myocardial tissue by conventional histologic methods. Conduction-system abnormalities often affect the right branch and the left anterior branch of the bundle of His. In chronic Chagas' disease of the gastrointestinal tract (megadisease), the esophagus and colon may exhibit varying degrees of dilatation. On microscopic examination, focal inflammatory lesions with lymphocytic infiltration are seen, and the number of neurons in the myenteric plexus may be markedly reduced. Accumulating evidence implicates the persistence of parasites and the accompanying chronic inflammation—rather than autoimmune mechanisms—as the basis for the pathology in patients with chronic *T. cruzi* infection.

EPIDEMIOLOGY

T. cruzi is found only in the Americas. Wild and domestic mammals harboring *T. cruzi* and infected triatomines are found in spotty distributions from the southern United States to southern Argentina. Humans become involved in the cycle of transmission when infected vectors take up residence in the primitive wood, adobe, and stone houses common in much of Latin America. Thus human *T. cruzi* infection is a health problem primarily among the poor in rural areas of Mexico and Central and South America. Most new *T. cruzi* infections in rural settings occur in children, but the incidence is unknown because most cases go undiagnosed. Historically, transfusion-associated transmission of *T. cruzi* was a serious public health problem in many endemic countries. However, with some notable exceptions, transmission by this route has been essentially eliminated as effective programs for the screening of donated blood have been implemented. Several dozen patients with HIV and chronic *T. cruzi* infections who underwent acute recrudescence of the latter have been described. These patients generally presented with *T. cruzi* brain abscesses, a manifestation of the illness that does not occur in immunocompetent persons. Currently, it is estimated that 8 million people are chronically infected with *T. cruzi* and that 14,000 deaths due to the illness occur each year. The resulting morbidity and mortality make Chagas' disease the most important parasitic disease burden in Latin America.

In recent years, the rate of *T. cruzi* transmission has decreased markedly in several endemic countries as a result of successful programs involving vector control, blood-bank screening, and education of at-risk populations. A major program, which began in 1991 in the "southern cone" nations of South America (Uruguay, Paraguay, Bolivia, Brazil, Chile, and Argentina), has provided the framework for much of this progress. Uruguay and Chile were certified free of transmission by the main domiciliary vector species (*Triatoma infestans*) in the late 1990s, and Brazil was declared transmission-free in 2006. Transmission has been reduced markedly in Argentina as well. Similar control programs have been initiated in the countries of northern South America and in the Central American nations.

Acute Chagas' disease is rare in the United States. Five cases of autochthonous transmission and five instances of transmission by blood transfusion have been reported. Moreover, *T. cruzi* was transmitted to five recipients of organs from three *T. cruzi*–infected donors. Two of these recipients became infected through cardiac transplants. Acute Chagas' disease has not been reported in tourists returning to the United States from Latin America, although three such instances have been reported in Europe. In contrast, the prevalence of chronic *T. cruzi* infections in the United States has increased considerably in recent years. An estimated 23 million immigrants from Chagas'-endemic countries currently live in the United States, ~17 million of whom are Mexicans. The total number of *T. cruzi*–infected persons living in the United States is estimated to be 300,000. Screening of the U.S. blood supply for *T. cruzi* infection began in January 2007. The overall prevalence of *T. cruzi* infection among donors is about 1 in 29,000, and to date more than 1200 infected donors have been identified and deferred permanently (see "Diagnosis").

CLINICAL COURSE

The first signs of acute Chagas' disease develop at least 1 week after invasion by the parasites. When the organisms enter through a break in the skin, an indurated area of erythema and swelling (the chagoma), accompanied by local lymphadenopathy, may appear. *Romaña's sign*—the classic finding in acute Chagas' disease, which consists of unilateral painless edema of the palpebrae and periocular tissues—can result when the conjunctiva is the portal of entry. These initial local signs may be followed by malaise, fever, anorexia, and edema of the face and lower extremities. Generalized lymphadenopathy and hepatosplenomegaly may develop. Severe myocarditis develops rarely; most deaths in acute Chagas' disease are due to heart failure. Neurologic signs are not common, but meningoencephalitis occurs occasionally, especially in children <2 years old. Usually within 4–8 weeks, acute signs and symptoms resolve spontaneously in virtually all patients, who then enter the asymptomatic or indeterminate phase of chronic *T. cruzi* infection.

Symptomatic chronic Chagas' disease becomes apparent years or even decades after the initial infection. The heart is commonly involved, and symptoms are caused by rhythm disturbances, segmental or dilated cardiomyopathy, and thromboembolism. Right bundle-branch block is a common electrocardiographic abnormality, but other types of intraventricular and atrioventricular blocks, premature ventricular contractions, and tachy- and bradyarrhythmias occur frequently. Cardiomyopathy often results in biventricular heart failure with a predominance of right-sided failure at advanced stages. Embolization of mural thrombi to the brain or other areas may take place. Sudden death is the main cause of death in Chagas' heart disease. Patients with megaesophagus suffer from dysphagia, odynophagia, chest pain, and regurgitation. Aspiration can occur (especially during sleep) in patients with severe esophageal dysfunction, and repeated episodes of aspiration pneumonitis are common. Weight loss, cachexia, and pulmonary infection can result in death.

Patients with megacolon are plagued by abdominal pain and chronic constipation, which predisposes to fecaloma formation. Advanced megacolon can cause obstruction, volvulus, septicemia, and death.

DIAGNOSIS

The diagnosis of acute Chagas' disease requires the detection of parasites. Microscopic examination of fresh anticoagulated blood or the buffy coat is the simplest way to see the motile organisms. Parasites also can be seen in Giemsa-stained thin and thick blood smears. Microhematocrit tubes containing acridine orange as a stain can be used for the same purpose. When used by experienced personnel, all of these methods yield positive results in a high proportion of cases of acute Chagas' disease. Serologic testing plays no role in diagnosing acute Chagas' disease.

Chronic Chagas' disease is diagnosed by the detection of specific IgG antibodies that bind to *T. cruzi* antigens. Demonstration of the parasite is not of primary importance. In Latin America, ~30 assays are commercially available, including several based on recombinant antigens. Although these tests usually show good sensitivity and reasonable specificity, false-positive reactions may occur—typically with samples from patients who have other infectious and parasitic diseases or autoimmune disorders. In addition, confirmatory testing has presented a persistent challenge. For these reasons, the World Health Organization recommends that specimens be tested in at least two assays and that well-characterized positive and negative comparison samples be included in each run. The radioimmune precipitation assay (Chagas RIPA) is a highly sensitive and specific confirmatory method for detecting antibodies to *T. cruzi* (approved under the Clinical Laboratory Improvement Amendment and available in the authors' laboratory). In December 2006, the U.S. Food and Drug Administration (FDA) approved a test to screen blood and organ donors for *T. cruzi* infection (Ortho *T. cruzi* ELISA Test System, Ortho-Clinical Diagnostics, Raritan, NJ). Since January 2007, the vast majority of U.S. blood donors have been screened with the Ortho test, and positive units have undergone confirmatory testing in the Chagas RIPA. A second test for donor screening was approved by the FDA in April 2010 (Abbott PRISM® Chagas Assay, Abbott Laboratories, Abbott Park, IL). The use of PCR assays to detect *T. cruzi* DNA in chronically infected persons has been studied extensively. The sensitivity of this approach has not been shown to be reliably greater than that of serology, and no PCR assays are commercially available.

TREATMENT Chagas' Disease

Therapy for Chagas' disease is still unsatisfactory. For many years now, only two drugs—nifurtimox and benznidazole—have been available for this purpose. Unfortunately, both drugs lack efficacy and may cause bothersome side effects.

In acute Chagas' disease, nifurtimox markedly reduces the duration of symptoms and parasitemia and decreases the mortality rate. Nevertheless, limited studies have shown that only ~70% of acute infections are cured parasitologically by a full course of treatment. Common adverse effects of nifurtimox include anorexia, nausea, vomiting, weight loss, and abdominal pain. Neurologic reactions to the drug may include restlessness, disorientation, insomnia, twitching, paresthesia, polyneuritis, and seizures. These symptoms usually disappear when the dosage is reduced or treatment is discontinued. The recommended daily dosage is 8–10 mg/kg for adults, 12.5–15 mg/kg for adolescents, and 15–20 mg/kg for children 1–10 years of age. The drug should be given orally in four divided doses each day, and therapy should be continued for 90–120 days. Nifurtimox is available from the Drug Service of the Centers for Disease Control and Prevention (CDC) in Atlanta (telephone number, 404-639-3670).

The efficacy of benznidazole is similar or even superior to that of nifurtimox. A cure rate of 90% among congenitally infected infants treated before their first birthday has been reported. Adverse effects include rash, peripheral neuropathy, and rarely granulocytopenia. The recommended oral dosage is 5 mg/kg per day for 60 days for adults and 5–10 mg/kg per day for 60 days for children, with administration of two or three divided doses. Benznidazole is generally considered the drug of choice in Latin America.

The question of whether adults in the indeterminate or chronic symptomatic phase of Chagas' disease should be treated with nifurtimox or benznidazole has been debated for years. The fact that parasitologic cure rates in chronically infected persons are notably inferior to those in patients with acute or recent chronic infection is central to this controversy. No convincing evidence from randomized controlled trials indicates that nifurtimox or benznidazole treatment of adults in the indeterminate or chronic symptomatic phase reduces either the appearance and progression of symptoms or mortality rates. On the basis of results of some observational studies, a panel of experts convened by the CDC in 2006 recommended that adults <50 years old with presumably long-standing indeterminate *T. cruzi* infections—or even with mild to moderate disease—be offered treatment. A large randomized clinical trial (the BENEFIT multicenter trial) designed to assess the parasitologic and clinical efficacy of benznidazole in adults (18–75 years old) with chronic Chagas' heart disease (without advanced lesions) is being performed in Brazil, Argentina, Colombia, and Bolivia, but results will not be available until 2012 at the earliest. In contrast, randomized studies have shown that treatment of children is useful, and the current consensus of Latin American authorities is that all *T. cruzi*–infected persons up to 18 years old and all adults known to have become infected recently should be given benznidazole or nifurtimox.

The usefulness of antifungal azoles for the treatment of Chagas' disease has been studied in laboratory animals and to a lesser extent in humans. To date, none of these drugs has exhibited a level of anti–*T. cruzi* activity that would justify its use in humans. Several newer drugs in this class have shown promise in animal studies and are likely to undergo human trials in the near future.

Patients who develop cardiac and/or gastrointestinal disease in association with *T. cruzi* infection should be referred to appropriate subspecialists for further evaluation and treatment. Cardiac transplantation is an option for patients with end-stage chagasic cardiomyopathy; more than 150 such transplantations have been done in Brazil and the United States. The survival rate among Chagas' disease cardiac transplant recipients seems to be higher than that among persons receiving cardiac transplants for other reasons. This better outcome may be due to the fact that lesions are limited to the heart in most patients with symptomatic chronic Chagas' disease.

PREVENTION

Since drug therapy has limitations and vaccines are not available, the control of *T. cruzi* transmission in endemic countries depends on the reduction of domiciliary vector populations by spraying of insecticides, improvements in housing, and education of at-risk persons. As noted earlier, these measures, coupled with serologic screening of blood donors, have markedly reduced transmission of the parasite in many endemic countries. Tourists would be wise to avoid sleeping in dilapidated houses in rural areas of endemic countries. Mosquito nets and insect repellent can provide additional protection.

In view of the possibly serious consequences of chronic *T. cruzi* infection, it would be prudent for all immigrants from endemic regions who are living in the United States to be tested for evidence of infection. Identification of persons harboring the parasite would permit periodic electrocardiographic monitoring, which can be important because pacemakers benefit some patients who develop ominous rhythm disturbances. The possibility of congenital transmission is yet another justification for screening. *T. cruzi* is classified as a Risk Group 2 agent in the United States and a Risk Group 3 agent in some European countries. Laboratory staff should work with the parasite or infected vectors at containment levels consistent with the risk group designation in their areas.

SLEEPING SICKNESS

DEFINITION

Sleeping sickness, or human African trypanosomiasis (HAT), is caused by flagellated protozoan parasites that belong to the *T. brucei* complex and are transmitted to humans by tsetse flies. In untreated patients, the trypanosomes first cause a febrile illness that is followed months or years later by progressive neurologic impairment and death.

THE PARASITES AND THEIR TRANSMISSION

The East African (*rhodesiense*) and the West African (*gambiense*) forms of sleeping sickness are caused, respectively, by two trypanosome subspecies: *T. b. rhodesiense* and *T. b. gambiense*. These subspecies are morphologically indistinguishable but cause illnesses that are epidemiologically and clinically distinct **(Table 123-1)**. The parasites are transmitted by blood-sucking tsetse flies of the genus *Glossina*. The insects acquire the infection when they ingest blood from infected mammalian hosts. After many cycles of multiplication in the midgut of the vector, the parasites migrate to the salivary glands. Their transmission takes place when they are inoculated into a mammalian host during a subsequent blood meal. The injected trypanosomes multiply in the blood **(Fig. 123-2)** and other extracellular spaces and evade immune destruction for long periods by undergoing antigenic variation, a process driven by gene switching in which the antigenic structure of the organisms' surface coat of glycoproteins changes periodically.

TABLE 123-1

COMPARISON OF WEST AFRICAN AND EAST AFRICAN TRYPANOSOMIASES

POINT OF COMPARISON	WEST AFRICAN (*GAMBIENSE*)	EAST AFRICAN (*RHODESIENSE*)
Organism	*T. b. gambiense*	*T. b. rhodesiense*
Vectors	Tsetse flies (palpalis group)	Tsetse flies (morsitans group)
Primary reservoir	Humans	Antelope and cattle
Human illness	Chronic (late CNS disease)	Acute (early CNS disease)
Duration of illness	Months to years	<9 months
Lymphadenopathy	Prominent	Minimal
Parasitemia	Low	High
Diagnosis by rodent inoculation	No	Yes
Epidemiology	Rural populations	Workers in wild areas, rural populations, tourists in game parks

Abbreviation: CNS, central nervous system.
Source: Reprinted with permission from LV Kirchhoff in GL Mandell et al (eds): *Principles and Practice of Infectious Diseases,* 7th ed. Philadelphia, Elsevier Churchill Livingstone, 2010.

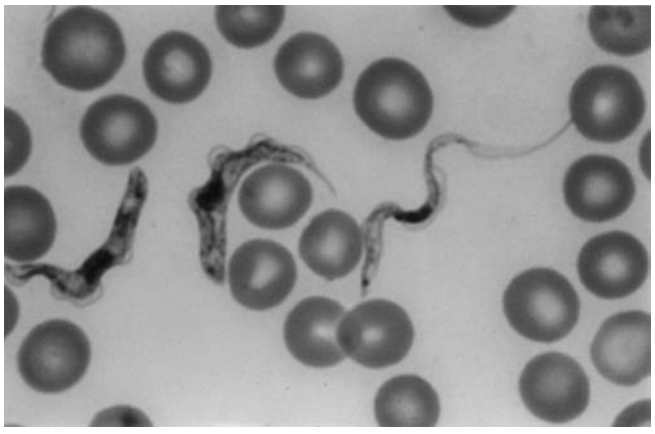


FIGURE 123-2
Trypanosoma brucei rhodesiense parasites in rat blood. The slender parasite is thought to be the form that multiplies in mammalian hosts, while the stumpy forms are nondividing and are capable of infecting insect vectors (Giemsa, 1200×). (*Courtesy of Dr. G. A. Cook, Madison, WI; with permission.*)

PATHOGENESIS AND PATHOLOGY

A self-limited inflammatory lesion (trypanosomal chancre) may appear a week or so after the bite of an infected tsetse fly. A systemic febrile illness then evolves as the parasites are disseminated through the lymphatics and bloodstream. Systemic HAT without central nervous system (CNS) involvement is generally referred to as *stage I disease*. In this stage, widespread lymphadenopathy and splenomegaly reflect marked lymphocytic and histiocytic proliferation and invasion of morular cells, which are plasmacytes that may be involved in the production of IgM. Endarteritis, with perivascular infiltration of both parasites and lymphocytes, may develop in lymph nodes and the spleen. Myocarditis develops frequently in patients with stage I disease and is especially common in *T. b. rhodesiense* infections.

Hematologic manifestations that accompany stage I HAT include moderate leukocytosis, thrombocytopenia, and anemia. High levels of immunoglobulins, consisting primarily of polyclonal IgM, are a constant feature, and heterophile antibodies, antibodies to DNA, and rheumatoid factor are often detected. High levels of antigen-antibody complexes may play a role in the tissue damage and increased vascular permeability that facilitate dissemination of the parasites.

Stage II disease involves invasion of the CNS. The presence of trypanosomes in perivascular areas is accompanied by intense infiltration of mononuclear cells. Abnormalities in cerebrospinal fluid (CSF) include increased pressure, elevated total protein concentration, and pleocytosis. In addition, trypanosomes are frequently found in CSF.

EPIDEMIOLOGY

The trypanosomes that cause sleeping sickness are found only in sub-Saharan Africa. After its near-eradication in the mid-1960s, sleeping sickness underwent a resurgence in the 1990s, primarily in Uganda, Sudan, the Central African Republic, the Democratic Republic of the Congo, and Angola. Although a subsequent increase in control activities reduced the incidence in many endemic areas, the World Health Organization estimated that there were 50,000–70,000 new cases in 2004, the vast majority of which were caused by *T. b. gambiense*. Approximately 50 million persons are at risk of acquiring HAT.

Humans are the only reservoir of *T. b. gambiense*, which occurs in widely distributed foci in tropical rain forests of Central and West Africa. *Gambiense* trypanosomiasis is primarily a problem in rural populations; tourists rarely become infected. Trypanotolerant antelope species in savanna and woodland areas of Central and East Africa are the principal reservoir of *T. b. rhodesiense*. Cattle can also be infected with this and other trypanosome species but generally succumb to the infection. Since risk results from contact with tsetse flies that feed on wild animals, humans acquire *T. b. rhodesiense* infection only incidentally, usually while visiting or working in areas where infected game and vectors are present. Roughly one or two imported cases of HAT acquired in East African parks are reported to the CDC each year.

CLINICAL COURSE

A painful trypanosomal chancre appears in some patients at the site of inoculation of the parasite. Hematogenous and lymphatic dissemination (stage I disease) is marked by the onset of fever. Typically, bouts of high temperatures lasting several days are separated by afebrile periods. Lymphadenopathy is prominent in *T. b. gambiense* trypanosomiasis. The nodes are discrete, movable, rubbery, and nontender. Cervical nodes are often visible, and enlargement of the nodes of the posterior cervical triangle, or *Winterbottom's sign*, is a classic finding. Pruritus and maculopapular rashes are common. Inconstant findings include malaise, headache, arthralgias, weight loss, edema, hepatosplenomegaly, and tachycardia. The differential diagnosis of stage I HAT includes many diseases that are common in the tropics and are associated with fevers. HIV infection, malaria, and typhoid fever are common in populations at risk for HAT and need to be considered.

CNS invasion (stage II disease) is characterized by the insidious development of protean neurologic manifestations that are accompanied by progressive abnormalities in the CSF. A picture of progressive indifference and daytime somnolence develops (hence the designation "sleeping sickness"), sometimes alternating with restlessness and insomnia at night. A listless gaze accompanies a loss of spontaneity, and speech may become halting and indistinct. Extrapyramidal signs may include choreiform movements, tremors, and fasciculations. Ataxia is frequent, and the patient may appear to have Parkinson's disease, with a shuffling gait, hypertonia, and tremors. In the final phase, progressive neurologic impairment ends in coma and death.

The most striking difference between the *gambiense* and *rhodesiense* forms of HAT is that the latter illness tends to follow a more acute course. Typically, in tourists with *T. b. rhodesiense* disease, systemic signs of infection, such as fever, malaise, and headache, appear before the end of the trip or shortly after the return home. Persistent tachycardia unrelated to fever is common early in the course of *T. b. rhodesiense* trypanosomiasis, and death may result from arrhythmias and congestive heart failure before CNS disease develops. In general, untreated *T. b. rhodesiense* trypanosomiasis leads to death in a matter of weeks to months, often without a clear distinction between the hemolymphatic and CNS stages. In contrast, *T. b. gambiense* disease can smolder for many months or even for years.

DIAGNOSIS

A definitive diagnosis of HAT requires detection of the parasite. If a chancre is present, fluid should be expressed and examined directly by light microscopy for the highly motile trypanosomes. The fluid also should be fixed and stained with Giemsa. Material obtained by needle aspiration of lymph nodes early in the illness should be examined similarly. Examination of wet preparations and Giemsa-stained thin and thick films of serial blood samples is also useful. If parasites are not seen initially in blood, efforts should be made to concentrate the organisms, which can be done in microhematocrit tubes containing acridine orange. Alternatively, the buffy coat from 10–15 mL of anticoagulated blood can be examined directly under a microscope. The likelihood of finding parasites in blood is higher in stage I than in stage II disease and in patients infected with *T. b. rhodesiense* rather than *T. b. gambiense*. Trypanosomes may also be seen in material aspirated from the bone marrow; the aspirate can be inoculated into liquid culture medium, as can blood, buffy coat, lymph node aspirates, and CSF. Finally, *T. b. rhodesiense* infection can be detected by inoculation of these specimens into mice or rats, which—when positive—results in patent parasitemias in a week or two. Although this method is highly sensitive for the detection of *T. b. rhodesiense*, it does not detect *T. b. gambiense* because of host specificity.

It is essential to examine CSF from all patients in whom HAT is suspected. Abnormalities in the CSF that may be associated with stage II disease include an increase in the CSF mononuclear cell count as well as increases in opening pressure and in levels of total protein and IgM. Trypanosomes may be seen in the sediment of centrifuged CSF. Any CSF abnormality in a patient in whom trypanosomes have been found at other sites must be viewed as pathognomonic for CNS involvement and thus must prompt specific treatment for CNS disease. In patients with CSF pleocytosis in whom parasites are not found, tuberculous meningitis and HIV-associated CNS infections such as cryptococcosis should be considered in the differential diagnosis.

A number of serologic assays, such as the card agglutination test for trypanosomes (CATT) for *T. b. gambiense*, are available to aid in the diagnosis of HAT, but their variable sensitivity and specificity mandate that decisions about treatment be based on demonstration of the parasite. These tests are of value for epidemiologic surveys. PCR assays for detecting African trypanosomes in humans have been developed, but none is commercially available.

TREATMENT Sleeping Sickness

The drugs used for treatment of HAT are suramin, pentamidine, eflornithine, and the organic arsenical melarsoprol. In the United States, these drugs can be obtained from the CDC. Therapy for HAT must be individualized on the basis of the infecting subspecies, the presence or absence of CNS disease, adverse reactions, and occasionally drug resistance. The choices of drugs for the treatment of HAT are summarized in Table 123-2.

Suramin is highly effective against stage I *rhodesiense* HAT. However, it can cause serious adverse effects and must be administered under the close supervision of a physician. A 100- to 200-mg IV test dose should be given to detect hypersensitivity. The dosage for adults is 20 mg/kg on days 1, 5, 12, 18, and 26. The drug is given by slow IV infusion of a freshly prepared 10% aqueous solution. Approximately 1 patient in 20,000 has an immediate, severe, and potentially fatal reaction to the drug, developing nausea, vomiting, shock, and seizures. Less severe reactions include fever, photophobia, pruritus, arthralgias, and skin eruptions. Renal damage is the most common important adverse effect of suramin. Transient proteinuria often appears during treatment. A urinalysis should be done before each dose, and treatment should be discontinued if proteinuria increases or if casts and red cells appear in the sediment. Suramin should not be given to patients with renal insufficiency.

Pentamidine is the first-line drug for treatment of stage I *gambiense* HAT. The dose for both adults and children is 4 mg/kg per day, given IM or IV for 7–10 days. Frequent, immediate adverse reactions include nausea, vomiting, tachycardia, and hypotension. These reactions are usually transient and do not warrant cessation of therapy. Other adverse reactions include nephrotoxicity,

TABLE 123-2

TREATMENT OF HUMAN AFRICAN TRYPANOSOMIASES[a]

CAUSATIVE ORGANISM	CLINICAL STAGE	
	I (NORMAL CSF)	II (ABNORMAL CSF)
T. brucei gambiense (West African)	Pentamidine Alternative: Suramin	Eflornithine Alternative: Melarsoprol
T. brucei rhodesiense (East African)	Suramin	Melarsoprol

[a]For doses and duration, see text.
Abbreviation: CSF, cerebrospinal fluid.

abnormal liver function tests, neutropenia, rashes, hypoglycemia, and sterile abscesses. Suramin is an alternative agent for stage I *T. b. gambiense* disease.

Eflornithine is highly effective for treatment of both stages of *gambiense* sleeping sickness. In the trials on which the FDA based its approval, this agent cured >90% of 600 patients with stage II disease. The recommended treatment schedule is 400 mg/kg per day, given IV in four divided doses, for 2 weeks. Adverse reactions include diarrhea, anemia, thrombocytopenia, seizures, and hearing loss. The high dosage and duration of therapy required are disadvantages that make widespread use of eflornithine difficult. A randomized trial comparing the standard eflornithine regimen (400 mg/kg per day infused over 6 h for 14 days) with nifurtimox-eflornithine combination therapy (oral nifurtimox, 15 mg/kg per day for 10 days; plus eflornithine, 400 mg/kg per day infused over 12 h for 7 days) in adults with stage II *gambiense* HAT showed improved efficacy and reduced adverse effects with combination therapy, making it suitable for first-line use.

The arsenical melarsoprol is the drug of choice for the treatment of *rhodesiense* HAT with CNS involvement and is an alternative agent for stage II *gambiense* disease. For *rhodesiense* disease, the drug should be given to adults in three courses of 3 days each. The dosage is 2.0–3.6 mg/kg per day, given IV in three divided doses for 3 days and followed 1 week later by 3.6 mg/kg per day, also in three divided doses and for 3 days. The latter course is repeated 7 days later. In debilitated patients, suramin is administered for 2–4 days before therapy with melarsoprol is initiated; an 18-mg initial dose of the latter drug, followed by progressive increases to the standard dose, has been recommended. For children, a total of 18–25 mg/kg should be given over 1 month. An IV starting dose of 0.36 mg/kg should be increased gradually to a maximum of 3.6 mg/kg at 1- to 5-day intervals, for a total of 9 or 10 doses. The regimen for *gambiense* disease is 2.2 mg/kg per day, given IV for 10 days.

Melarsoprol is highly toxic and should be administered with great care. To reduce the likelihood of drug-induced encephalopathy, all patients receiving melarsoprol should be given prednisolone at a dose of 1 mg/kg (up to 40 mg) per day, beginning 1–2 days before the first dose of melarsoprol and continuing through the last dose. Without prednisolone prophylaxis, the incidence of reactive encephalopathy has been reported to be as high as 18% in some series. Clinical manifestations of reactive encephalopathy include high fever, headache, tremor, impaired speech, seizures, and even coma and death. Treatment with melarsoprol should be discontinued at the first sign of encephalopathy but may be restarted cautiously at lower doses a few days after signs have resolved. Extravasation of the drug results in intense local reactions. Vomiting, abdominal pain, nephrotoxicity, and myocardial damage can occur.

PREVENTION

HAT poses complex public-health and epizootic problems in Africa. Considerable progress has been made in some areas through control programs that focus on eradication of vectors and drug treatment of infected humans. People can reduce their risk of acquiring trypanosomiasis by avoiding areas known to harbor infected insects, by wearing protective clothing, and by using insect repellent. Chemoprophylaxis is not recommended, and no vaccine is available to prevent transmission of the parasites.

CHAPTER 124

TOXOPLASMA INFECTIONS

Kami Kim ■ Lloyd H. Kasper

DEFINITION

Toxoplasmosis is caused by infection with the obligate intracellular parasite *Toxoplasma gondii*. Acute infection acquired after birth may be asymptomatic but is thought to result in the lifelong chronic persistence of cysts in the host's tissues. In both acute and chronic toxoplasmosis, the parasite is responsible for clinically evident disease, including lymphadenopathy, encephalitis, myocarditis, and pneumonitis.

Congenital toxoplasmosis is an infection of newborns that results from the transplacental passage of parasites from an infected mother to the fetus. These infants may be asymptomatic at birth, but most later manifest a wide range of signs and symptoms, including chorioretinitis, strabismus, epilepsy, and psychomotor retardation. In immunocompetent individuals, toxoplasmosis can also present as acute disease (typically chorioretinitis) associated with food- or waterborne sources.

ETIOLOGY

T. gondii is an intracellular coccidian that infects both birds and mammals. There are two distinct stages in the life cycle of *T. gondii* **(Fig. 124-1)**. In the *nonfeline* stage, tissue cysts that contain bradyzoites or sporulated oocysts are ingested by an intermediate host (e.g., a human, mouse, sheep, pig, or bird). The cyst is rapidly digested by the acidic-pH gastric secretions. Bradyzoites or sporozoites are released, enter the small-intestinal epithelium, and transform into rapidly dividing tachyzoites. The tachyzoites can infect and replicate in all mammalian cells except red blood cells. Once attached to the host cell, the parasite penetrates the cell and forms a parasitophorous vacuole within which it divides. Parasite replication continues until the number of parasites within the cell approaches a critical mass and the cell ruptures, releasing parasites that infect adjoining cells. As a result of this process, an infected organ soon shows evidence of cytopathology. Most tachyzoites are eliminated by the host's humoral and cell-mediated immune responses. Tissue cysts containing many bradyzoites develop 7–10 days after systemic tachyzoite infection. These tissue cysts occur in various host organs but persist principally within the central nervous system (CNS) and muscle. The development of this chronic stage completes the nonfeline portion of the life cycle. Active infection in the immunocompromised host is most likely to be due to the spontaneous release of encysted parasites that undergo rapid transformation into tachyzoites within the CNS.

The principal (*feline*) stage in the life cycle takes place in the cat (the definitive host) and its prey. The parasite's sexual phase is defined by the formation of oocysts within the feline host. This enteroepithelial cycle begins with the ingestion of the bradyzoite tissue cysts and culminates (after several intermediate stages) in the production of gametes. Gamete fusion produces a zygote, which envelops itself in a rigid wall and is secreted in the feces as an unsporulated oocyst. After 2–3 days of exposure to air at ambient temperature, the noninfectious oocyst sporulates to produce eight sporozoite progeny. The sporulated oocyst can be ingested by an intermediate host, such as a person emptying a cat's litter box or a pig rummaging in a barnyard. It is in the intermediate host that *T. gondii* completes its life cycle. Sporulated oocysts, which are environmentally hardy and very infectious, are thought to be sources of waterborne outbreaks such as those reported in Victoria (British Columbia, Canada) and in South America.

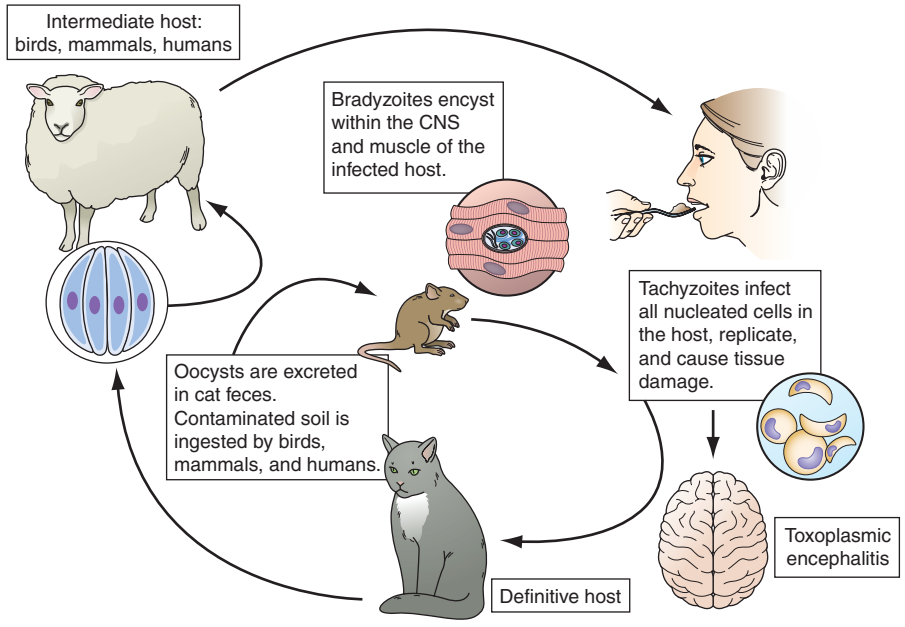


FIGURE 124-1
Life cycle of *Toxoplasma gondii*. The cat is the definitive host in which the sexual phase of the cycle is completed. Oocysts shed in cat feces can infect a wide range of animals, including birds, rodents, grazing domestic animals, and humans. The bradyzoites found in the muscle of food animals may infect humans who eat insufficiently cooked meat products, particularly lamb and pork. Although human disease can take many forms, congenital infection and encephalitis from reactivation of latent infection in the brains of immunosuppressed persons are the most important manifestations. CNS, central nervous system. (*Courtesy of Dominique Buzoni-Gatel, Institut Pasteur, Paris; with permission.*)

EPIDEMIOLOGY

T. gondii infects a wide range of mammals and birds. Its seroprevalence depends on the locale and the age of the population. Generally, hot arid climatic conditions are associated with a low prevalence of infection. In the United States and most European countries, the seroprevalence increases with age and exposure. For example, in the United States, 5–30% of individuals 10–19 years old and 10–67% of those >50 years old have serologic evidence of exposure. In Central America, France, Turkey, and Brazil, the seroprevalence is higher. Because of increased awareness of food-borne infections, the prevalence of seropositivity has decreased worldwide. There may be as many as 2100 cases of toxoplasmic encephalitis (TE) each year in the United States.

TRANSMISSION

Oral transmission

The principal source of human *Toxoplasma* infection remains uncertain, but infection is thought to occur by the oral route. Transmission can be attributable to ingestion of either sporulated oocysts from contaminated soil, food, or water or bradyzoites from undercooked meat. During acute feline infection, a cat may excrete as many as 100 million parasites per day. These very stable sporozoite-containing oocysts are highly infectious and may remain viable for many years in soil or water. Humans infected during a well-documented outbreak of oocyst-transmitted infection develop stage-specific antibodies to the oocyst/sporozoite.

Children and adults also can acquire infection from tissue cysts containing bradyzoites. The ingestion of a single cyst is all that is required for human infection. Undercooking or insufficient freezing of meat is an important source of infection in the developed world. In the United States, lamb products and pork products may show evidence of cysts that contain bradyzoites, but the overall prevalence of *T. gondii* has been gradually decreasing. The incidence in beef is much lower—perhaps as low as 1%. Direct ingestion of bradyzoite cysts in these various meat products leads to acute infection.

Transmission via blood or organs

In addition to being transmitted orally, *T. gondii* can be transmitted directly from a seropositive donor to a seronegative recipient in a transplanted heart, heart-lung, kidney, liver, or pancreas. Viable parasites can be cultured from refrigerated anticoagulated blood, which may be a source of infection in individuals receiving blood transfusions. *T. gondii* reactivation has been reported in bone marrow, hematopoietic stem cell, and liver transplant recipients as well as in individuals with AIDS. Although antibody titers generally are not useful in monitoring *T. gondii* infection, individuals with higher antibody titers reportedly may be at relatively high risk for reactivation after hematopoietic stem cell transplantation; thus routine polymerase chain reaction (PCR) screening of blood from these patients may be in order. Finally, laboratory personnel can be infected after contact with contaminated needles or glassware or with infected tissue.

Transplacental transmission

On average, about one-third of all women who acquire infection with *T. gondii* during pregnancy transmit the parasite to the fetus; the remainder give birth to normal, uninfected babies. Of the various factors that influence fetal outcome, gestational age at the time of infection is the most critical (see next). Few data support a role for recrudescent maternal infection as the source of congenital disease, although rare cases of transmission by immunocompromised women (e.g., those infected with HIV or those receiving high-dose glucocorticoids) have been reported. Thus, women who are seropositive before pregnancy usually are protected against acute infection and do not give birth to congenitally infected neonates.

The following general guidelines can be used to evaluate congenital infection. There is essentially no risk if the mother becomes infected ≥6 months before conception. If infection is acquired <6 months before conception, the likelihood of transplacental infection increases as the interval between infection and conception decreases. In pregnancy, if the mother becomes infected during the first trimester, the incidence of transplacental infection is lowest (~15%), but the disease in the neonate is most severe. If maternal infection occurs during the third trimester, the incidence of transplacental infection is greatest (65%), but the infant is usually asymptomatic at birth. Infected infants who are normal at birth may have a higher incidence of learning disabilities and chronic neurologic sequelae than uninfected children. Only a small proportion (20%) of women infected with *T. gondii* develop clinical signs of infection. Often the diagnosis is first appreciated when routine postconception serologic tests show evidence of specific antibody.

PATHOGENESIS

Upon the host's ingestion of either tissue cysts containing bradyzoites or oocysts containing sporozoites, the parasites are released from the cysts by a digestive process. Bradyzoites are resistant to the effect of pepsin and invade the host's gastrointestinal tract. Within enterocytes (or other gut-associated cells), the parasites undergo morphologic transformation, giving rise to invasive tachyzoites. These tachyzoites induce a parasite-specific secretory IgA response. From the gastrointestinal tract, parasites are disseminated to a variety of organs, particularly lymphatic tissue, skeletal muscle, myocardium, retina, placenta, and the CNS. At these sites, the parasite infects host cells, replicates, and invades the adjoining cells. In this fashion, the hallmarks of the infection develop: cell death and focal necrosis surrounded by an acute inflammatory response.

In the immunocompetent host, both the humoral and the cellular immune responses control infection; parasite virulence and tissue tropism may be strain specific. Tachyzoites are sequestered by a variety of immune mechanisms, including induction of parasiticidal antibody, activation of macrophages with radical intermediates, production of interferon γ (IFN-γ), and stimulation of CD8+ cytotoxic T lymphocytes. These antigen-specific lymphocytes are capable of killing both extracellular parasites and target cells infected with parasites. As tachyzoites are cleared from the acutely infected host, tissue cysts containing bradyzoites begin to appear, usually within the CNS and the retina. Studies indicate that *Toxoplasma* secretes signaling molecules into infected host cells and that these molecules modulate host gene expression, host metabolism, and host immune response.

In the immunocompromised or fetal host, the immune factors necessary to control the spread of tachyzoite infection are lacking. This altered immune state allows the persistence of tachyzoites and gives rise to progressive focal destruction that results in organ failure (i.e., necrotizing encephalitis, pneumonia, and myocarditis).

Persistence of infection with cysts containing bradyzoites is common in the immunocompetent host. This lifelong infection usually remains subclinical. Although bradyzoites are in a slow metabolic phase, cysts do degenerate and rupture within the CNS. This degenerative process, with the development of new bradyzoite-containing cysts, is the most probable source of recrudescent infection in immunocompromised individuals and the most likely stimulus for the persistence of antibody titers in the immunocompetent host. Although the concept is controversial, the persistence of toxoplasmosis has been hypothesized to be a contributing factor to a variety of neuropsychiatric conditions, including schizophrenia and bipolar disease. In rodents, infection clearly has significant effects on behavior, increasing predation.

PATHOLOGY

Cell death and focal necrosis due to replicating tachyzoites induce an intense mononuclear inflammatory response in any tissue or cell type infected. Tachyzoites rarely can be visualized by routine histopathologic staining of these inflammatory lesions. However, immunofluorescent staining with parasitic antigen–specific antibodies can reveal either the organism itself or evidence of antigen. In contrast to this inflammatory process caused by tachyzoites, bradyzoite-containing cysts cause inflammation only at the early stages of development, and even this inflammation may be a response to the presence of tachyzoite antigens. Once the cysts reach maturity, the inflammatory process can no longer be detected, and the cysts remain immunologically quiescent within the brain matrix until they rupture.

Lymph nodes

During acute infection, lymph node biopsy demonstrates characteristic findings, including follicular hyperplasia and irregular clusters of tissue macrophages with eosinophilic cytoplasm. Granulomas rarely are evident in these specimens. Although tachyzoites are not usually visible, they can be sought either by subinoculation of infected tissue into mice, with resultant disease, or by PCR. PCR amplification of DNA fragments of *Toxoplasma* genes is effective and sensitive in establishing lymph node infection by tachyzoites.

Eyes

In the eye, infiltrates of monocytes, lymphocytes, and plasma cells may produce uni- or multifocal lesions. Granulomatous lesions and chorioretinitis can be observed in the posterior chamber after acute necrotizing retinitis. Other ocular complications include iridocyclitis, cataracts, and glaucoma.

Central nervous system

During CNS involvement, both focal and diffuse meningoencephalitis can be documented, with evidence of necrosis and microglial nodules. Necrotizing encephalitis in patients without AIDS is characterized by small diffuse lesions with perivascular cuffing in contiguous areas. In the AIDS population, polymorphonuclear leukocytes may be present in addition to monocytes, lymphocytes, and plasma cells. Cysts containing bradyzoites frequently are found contiguous with the necrotic tissue border. As stated previously, it is estimated that there are as many as 2100 cases of TE in the United States each year.

Lungs and heart

Among patients with AIDS who die of toxoplasmosis, 40–70% have involvement of the lungs and heart. Interstitial pneumonitis can develop in neonates and immunocompromised patients. Thickened and edematous alveolar septa infiltrated with mononuclear and plasma cells are apparent. This inflammation may extend to the endothelial walls. Tachyzoites and bradyzoite-containing cysts have been observed within the alveolar membrane. Superimposed bronchopneumonia can be caused by other microbial agents. Cysts and aggregates of parasites in cardiac muscle tissue are evident in patients with AIDS who die of toxoplasmosis. Focal necrosis surrounded by inflammatory cells is associated with hyaline necrosis and disrupted myocardial cells. Pericarditis is associated with toxoplasmosis in some patients.

Gastrointestinal tract

Rare cases of human gastrointestinal tract infection with *T. gondii* have presented as ulcerations in the mucosa. Acute infection in certain strains of inbred mice (C57BL/6) results in lethal ileitis within 7–9 days. This inflammatory bowel disease has been recognized in several other mammalian species, including pigs and nonhuman primates. Although the association between human inflammatory bowel disease and either acute or recurrent

Toxoplasma infection has not been established, studies have demonstrated recognition of the infection by human intestinal epithelial cells, as evidenced by mitogen-activated protein kinase phosphorylation, nuclear factor κB translocation, and interleukin 8 (IL-8) secretion.

Other sites

Pathologic changes during disseminated infection are similar to those described for the lymph nodes, eyes, and CNS. In patients with AIDS, the skeletal muscle, pancreas, stomach, and kidneys can be involved, with necrosis, invasion by inflammatory cells, and (rarely) tachyzoites detectable by routine staining. Large necrotic lesions may cause direct tissue destruction. In addition, secondary effects from acute infection of these various organs, including pancreatitis, myositis, and glomerulonephritis, have been reported.

HOST IMMUNE RESPONSE

Acute *Toxoplasma* infection evokes a cascade of protective immune responses in the immunocompetent host. *Toxoplasma* enters the host at the gut mucosal level and evokes a mucosal immune response that includes the production of antigen-specific secretory IgA. Titers of serum IgA antibody directed at p30 (SAG-1) are a useful marker for congenital and acute toxoplasmosis. Milk-whey IgA from acutely infected mothers contains a high titer of antibody to *T. gondii* and can block infection of enterocytes in vitro. In mice, IgA intestinal secretions directed at the parasite are abundant and are associated with the induction of mucosal T cells.

Within the host, *T. gondii* rapidly induces detectable levels of both IgM and IgG serum antibodies. Monoclonal gammopathy of the IgG class can occur in congenitally infected infants. IgM levels may be increased in newborns with congenital infection. The polyclonal IgG antibodies evoked by infection are parasiticidal in vitro in the presence of serum complement and are the basis for the Sabin-Feldman dye test. However, cell-mediated immunity is the major protective response evoked by the parasite during host infection. Macrophages are activated after phagocytosis of antibody-opsonized parasites. This activation can lead to death of the parasite by either an oxygen-dependent or an oxygen-independent process. If the parasite is not phagocytosed and enters the macrophage by active penetration, it continues to replicate, and this replication may represent the mechanism for transport and dissemination to distant organs. *Toxoplasma* stimulates a robust IL-12 response by human dendritic cells. The requirement for costimulation via CD40/154 has been established. The CD4+ and CD8+ T cell responses are antigen-specific and further stimulate the production of a variety of important lymphokines that expand the T cell and natural killer cell repertoire. *T. gondii* is a potent inducer of a T_H1 phenotype, with IL-12 and IFN-γ playing an essential role in the control of the parasites' growth in the host. Regulation of the inflammatory response is at least partially under the control of a T_H2 response that includes the production of IL-4 and IL-10 in seropositive individuals. Both asymptomatic patients and those with active infection may have a depressed CD4+-to-CD8+ ratio. This shift may be correlated with a disease syndrome but is not necessarily correlated with disease outcome. Human T cell clones of both the CD4+ and the CD8+ phenotypes are cytolytic against parasite-infected macrophages. These T cell clones produce cytokines that are "microbistatic." IL-18, IL-7, and IL-15 upregulate the production of IFN-γ and may be important during acute and chronic infection. The effect of IFN-γ may be paradoxical, with stimulation of a host downregulatory response as well.

Although in patients with AIDS *T. gondii* infection is believed to be recrudescent, determination of antibody titers generally is not helpful in establishing reactivation. Because of the severe depletion in CD4+ T cells, quite frequently there is no observed increase in antibody titer during exacerbation of infection. T cells from AIDS patients with reactivation of toxoplasmosis fail to secrete both IFN-γ and IL-2. This alteration in the production of these critical immune cytokines contributes to the persistence of infection. *Toxoplasma* infection frequently develops late in the course of AIDS, when the loss of T cell–dependent protective mechanisms, particularly CD8+ T cells, becomes most pronounced.

CLINICAL MANIFESTATIONS

In persons whose immune systems are intact, acute toxoplasmosis is usually asymptomatic and self-limited. This condition can go unrecognized in 80–90% of adults and children with acquired infection. The asymptomatic nature of this infection makes diagnosis difficult in mothers infected during pregnancy. In contrast, the wide range of clinical manifestations in congenitally infected children includes severe neurologic complications such as hydrocephalus, microcephaly, mental retardation, and chorioretinitis. If prenatal infection is severe, multiorgan failure and subsequent intrauterine fetal death can occur. In children and adults, chronic infection can persist throughout life, with little consequence to the immunocompetent host.

Toxoplasmosis in immunocompetent patients

The most common manifestation of acute toxoplasmosis is cervical lymphadenopathy. The nodes may be single or multiple, are usually nontender, are discrete, and vary in firmness. Lymphadenopathy also may be found in suboccipital, supraclavicular, inguinal, and mediastinal areas. Generalized lymphadenopathy occurs in 20–30% of symptomatic patients. Between 20 and 40% of patients with lymphadenopathy also have headache, malaise, fatigue, and fever [usually with a temperature of <40°C (<104°F)]. A smaller proportion of symptomatic individuals have myalgia, sore throat, abdominal pain, maculopapular rash, meningoencephalitis, and confusion. Rare complications associated with infection in the normal

immune host include pneumonia, myocarditis, encephalopathy, pericarditis, and polymyositis. Signs and symptoms associated with acute infection usually resolve within several weeks, although the lymphadenopathy may persist for some months. In one epidemic, toxoplasmosis was diagnosed correctly in only 3 of the 25 patients who consulted physicians. If toxoplasmosis is considered in the differential diagnosis, routine laboratory and serologic screening should precede node biopsy. It is now appreciated that genotypes of *T. gondii* prevalent in South America may be more virulent than those typically seen in North America or Europe. These genotypes may be associated with acute or recurrent ocular disease in immunocompetent individuals. Thus a detailed history is critical for establishing a diagnosis.

The results of routine laboratory studies are usually unremarkable except for minimal lymphocytosis, an elevated erythrocyte sedimentation rate, and a nominal increase in serum aminotransferase levels. Evaluation of cerebrospinal fluid (CSF) in cases with evidence of encephalopathy or meningoencephalitis shows an elevation of intracranial pressure, mononuclear pleocytosis (10–50 cells/mL), a slight increase in protein concentration, and (occasionally) an increase in the gamma globulin level. PCR amplification of the *Toxoplasma* DNA target sequence in CSF may be beneficial. The CSF of chronically infected individuals is normal.

Infection of immunocompromised patients

Patients with AIDS and those receiving immunosuppressive therapy for lymphoproliferative disorders are at greatest risk for developing acute toxoplasmosis. This predilection may be due either to reactivation of latent infection or to acquisition of parasites from exogenous sources such as blood or transplanted organs. In individuals with AIDS, >95% of cases of TE are believed to be due to recrudescent infection. In most of these cases, encephalitis develops when the CD4+ T cell count falls below 100/μL. In immunocompromised hosts, the disease may be rapidly fatal if untreated. Thus, accurate diagnosis and initiation of appropriate therapy are necessary to prevent fulminant infection.

Toxoplasmosis is a principal opportunistic infection of the CNS in persons with AIDS. Although geographic origin may be related to frequency of infection, it has no correlation with the severity of disease in immunocompromised hosts. Individuals with AIDS who are seropositive for *T. gondii* are at high risk for encephalitis. Before the advent of current combination antiretroviral treatment (ART), about one-third of the 15–40% of adult AIDS patients in the United States who were latently infected with *T. gondii* developed TE. TE may still be a presenting infection in individuals who are unaware of their positive HIV status.

The signs and symptoms of acute toxoplasmosis in immunocompromised patients principally involve the CNS **(Fig. 124-2)**. More than 50% of patients with clinical manifestations have intracerebral involvement. Clinical findings at presentation range from nonfocal to focal dysfunction. CNS findings include encephalopathy, meningoencephalitis, and mass lesions. Patients may present with altered mental status (75%), fever (10–72%), seizures (33%), headaches (56%), and focal neurologic findings (60%), including motor deficits, cranial nerve palsies, movement disorders, dysmetria, visual-field loss, and aphasia. Patients who present with evidence of diffuse cortical dysfunction develop evidence of focal neurologic disease as infection progresses. This altered condition is due not only to the necrotizing encephalitis caused by direct invasion by the parasite but also to secondary effects, including vasculitis, edema, and hemorrhage. The onset of infection can range from an insidious process over several weeks to an acute confusional state with fulminant focal deficits, including hemiparesis, hemiplegia, visual-field defects, localized headache, and focal seizures.

Although lesions can occur anywhere in the CNS, the areas most often involved appear to be the brainstem, basal ganglia, pituitary gland, and corticomedullary junction. Brainstem involvement gives rise to a variety of neurologic dysfunctions, including cranial nerve palsy, dysmetria, and ataxia. With basal ganglionic infection, patients may develop hydrocephalus, choreiform movements, and choreoathetosis. Because *Toxoplasma* usually causes encephalitis, meningeal involvement is uncommon, and thus CSF findings may be unremarkable or

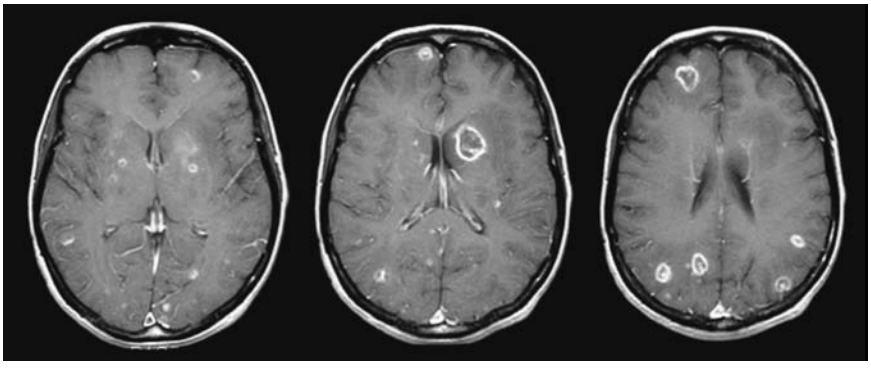


FIGURE 124-2

Toxoplasmic encephalitis in a 36-year-old patient with AIDS. The multiple lesions are demonstrated by magnetic resonance scanning (T1 weighted with gadolinium enhancement). (*Courtesy of Clifford Eskey, Dartmouth Hitchcock Medical Center, Hanover, NH; with permission.*)

may include a modest increase in cell count and in protein—but not glucose—concentration.

Cerebral toxoplasmosis must be differentiated from other opportunistic infections or tumors in the CNS of AIDS patients. The differential diagnosis includes herpes simplex encephalitis, cryptococcal meningitis, progressive multifocal leukoencephalopathy, and primary CNS lymphoma. Involvement of the pituitary gland can give rise to panhypopituitarism and hyponatremia from inappropriate secretion of vasopressin (antidiuretic hormone). HIV-associated neurocognitive disorder (HAND) may present as cognitive impairment, attention loss, and altered memory. Brain biopsy in patients who have been treated for TE but who continue to exhibit neurologic dysfunction often fails to identify organisms.

Autopsies of *Toxoplasma*-infected patients have demonstrated the involvement of multiple organs, including the lungs, gastrointestinal tract, pancreas, skin, eyes, heart, and liver. *Toxoplasma* pneumonia can be confused with *Pneumocystis* pneumonia (PcP). Respiratory involvement usually presents as dyspnea, fever, and a nonproductive cough and may rapidly progress to acute respiratory failure with hemoptysis, metabolic acidosis, hypotension, and (occasionally) disseminated intravascular coagulation. Histopathologic studies demonstrate necrosis and a mixed cellular infiltrate. The presence of organisms is a helpful diagnostic indicator, but organisms can also be found in healthy tissue. Infection of the heart is usually asymptomatic but can be associated with cardiac tamponade or biventricular failure. Infections of the gastrointestinal tract and the liver have been documented.

Congenital toxoplasmosis

Between 400 and 4000 infants born each year in the United States are affected by congenital toxoplasmosis. Acute infection in mothers acquiring *T. gondii* during pregnancy is usually asymptomatic; most such women are diagnosed via prenatal serologic screening. Infection of the placenta leads to hematogenous infection of the fetus. As gestation proceeds, the proportion of fetuses that become infected increases but the clinical severity of the infection declines. Although infected children may initially be asymptomatic, the persistence of *T. gondii* can result in reactivation and clinical disease—most frequently chorioretinitis—decades later. Factors associated with relatively severe disabilities include delays in diagnosis and in initiation of therapy, neonatal hypoxia and hypoglycemia, profound visual impairment (see "Ocular Infection"), uncorrected hydrocephalus, and increased intracranial pressure. If treated appropriately, upwards of 70% of children have normal developmental, neurologic, and ophthalmologic findings at follow-up evaluations. Treatment for 1 year with pyrimethamine, a sulfonamide, and folinic acid is tolerated with minimal toxicity (see "Treatment").

Ocular infection

Infection with *T. gondii* is estimated to cause 35% of all cases of chorioretinitis in the United States and Europe. Most ocular involvement is believed to be due to congenital infection, but acquired infection can be associated with outbreaks of ocular disease even in immunocompetent individuals (as seen in Victoria, British Columbia, and in South America). A variety of ocular manifestations are documented, including blurred vision, scotoma, photophobia, and eye pain. Macular involvement occurs, with loss of central vision, and nystagmus is secondary to poor fixation. Involvement of the extraocular muscles may lead to disorders of convergence and to strabismus. Ophthalmologic examination should be undertaken in newborns with suspected congenital infection. As the inflammation resolves, vision improves, but episodic flare-ups of chorioretinitis, which progressively destroy retinal tissue and lead to glaucoma, are common. The ophthalmologic examination reveals yellow-white, cotton-like patches with indistinct margins of hyperemia. As the lesions age, white plaques with distinct borders and black spots within the retinal pigment become more apparent. Lesions usually are located near the posterior pole of the retina; they may be single but are more commonly multiple. Congenital lesions may be unilateral or bilateral and show evidence of massive chorioretinal degeneration with extensive fibrosis. Surrounding these areas of involvement are a normal retina and vasculature. In patients with AIDS, retinal lesions are often large, with diffuse retinal necrosis, and include both free tachyzoites and cysts containing bradyzoites. Toxoplasmic chorioretinitis may be a prodrome to the development of encephalitis.

DIAGNOSIS

Tissue and body fluids

The differential diagnosis of acute toxoplasmosis can be made by appropriate culture, serologic testing, and PCR **(Table 124-1)**. Although difficult and available only at specialized laboratories, the isolation of *T. gondii* from blood or other body fluids can be accomplished after subinoculation of the sample into the peritoneal cavity of mice. If no parasites are found in the mouse's peritoneal fluid 6–10 days after inoculation, its anti-*Toxoplasma* serum titer can be evaluated 4–6 weeks after inoculation. Isolation of *T. gondii* from the patient's body fluids reflects acute infection, whereas isolation from biopsied tissue is an indication only of the presence of tissue cysts and should not be misinterpreted as evidence of acute toxoplasmosis. Persistent parasitemia in patients with latent, asymptomatic infection is rare. Histologic examination of lymph nodes may suggest the characteristic changes described earlier. Demonstration of tachyzoites in lymph nodes establishes the diagnosis of acute toxoplasmosis. Like subinoculation into mice, histologic demonstration of cysts containing bradyzoites confirms prior infection with *T. gondii* but is nondiagnostic for acute infection.

Serology

The procedures mentioned earlier have great diagnostic value but are limited by difficulties encountered either in the growth of parasites in vivo or in the identification

TABLE 124-1

DIFFERENTIAL LABORATORY DIAGNOSIS OF TOXOPLASMOSIS

CLINICAL SETTING	ALTERNATIVE DIAGNOSIS	DISTINGUISHING CHARACTERISTICS
Mononucleosis syndrome	Epstein-Barr virus	Serology
	Cytomegalovirus	Serology/PCR or culture
	HIV	Serology/viral load
	Bartonella (cat-scratch disease)	Biopsy (PCR or culture)/serology
	Lymphoma	Biopsy
Congenital infection	Cytomegalovirus	Viral culture/PCR
	Herpes simplex virus	Viral culture/PCR
	Rubella virus	Viral culture/ serology
	Syphilis	Serology
	Listeriosis	Bacterial culture
Chorioretinitis in immuno-competent individual	Tuberculosis	Bacterial culture
	Syphilis	Serology
	Histoplasmosis	Serology/culture
Chorioretinitis in AIDS patient	Cytomegalovirus	Viral culture/PCR
	Syphilis	Serology
	Herpes simplex virus	Viral culture/PCR
	Varicella-zoster virus	Viral culture/PCR
	Fungal infection	Culture
CNS lesions in AIDS patient	Lymphoma or metastatic tumor	Tissue biopsy
	Brain abscess	Bacterial culture
	Progressive multifocal leukoencephalopathy	PCR for JC Virus
	Fungal infection	Biopsy and culture
	Mycobacterial infection	Biopsy and culture

Source: Adapted from JD Schwartzman: Toxoplasmosis, *in Principles and Practice of Clinical Parasitology*. Hoboken, Wiley, 2001.

of tachyzoites by histochemical methods. Serologic testing has become the routine method of diagnosis.

Diagnosis of acute infection with *T. gondii* can be established by detection of the simultaneous presence of IgG and IgM antibodies to *Toxoplasma* in serum. The presence of circulating IgA favors the diagnosis of an acute infection. The Sabin-Feldman dye test, the indirect fluorescent antibody test, and the enzyme-linked immunosorbent assay (ELISA) all satisfactorily measure circulating IgG antibody to *Toxoplasma*. Positive IgG titers (>1:10) can be detected as early as 2–3 weeks after infection. These titers usually peak at 6–8 weeks and decline slowly to a new baseline level that persists for life. Antibody avidity increases with time and can be useful in difficult cases during pregnancy for establishing when infection may have occurred. The serum IgM titer should be measured in concert with the IgG titer to better establish the time of infection; either the double-sandwich IgM-ELISA or the IgM-immunosorbent assay (IgM-ISAGA) should be used. Both assays are specific and sensitive, with fewer false-positive results than other commercial tests. The double-sandwich IgA-ELISA is more sensitive than the IgM-ELISA for detecting congenital infection in the fetus and newborn. Although a negative IgM result with a positive IgG titer indicates distant infection, IgM can persist for >1 year and should not necessarily be considered a reflection of acute disease. If acute toxoplasmosis is suspected, a more extensive panel of serologic tests can be performed at the *Toxoplasma* reference laboratory at the Palo Alto Medical Foundation (http://www.pamf.org/serology/clinicianguide.html).

Molecular diagnostics

Molecular approaches can directly detect *T. gondii* in biologic samples independent of the serologic response. Results obtained with PCR have suggested high sensitivity, specificity, and clinical utility in the diagnosis of TE in resource-poor settings. Real-time PCR is a promising technique that can provide quantitative results. Isolates can be genotyped and polymorphic sequences can be obtained, with consequent identification of the precise strain. Molecular epidemiologic studies with polymorphic markers have been useful in correlating clinical signs and symptoms of disease with different *T. gondii* genotypes.

The immunocompetent adult or child

For the patient who presents with lymphadenopathy only, a positive IgM titer is an indication of acute infection—and an indication for therapy, if clinically warranted (see "Treatment"). The serum IgM titer should be determined again in 3 weeks. An elevation in the IgG titer without an increase in the IgM titer suggests that infection is present but is not acute. If there is a borderline increase in either IgG or IgM, the titers should be reassessed in 3–4 weeks.

The immunocompromised host

A presumptive clinical diagnosis of TE in patients with AIDS is based on clinical presentation, history of exposure (as evidenced by positive serology), and radiologic evaluation. To detect latent infection with *T. gondii*, HIV-infected persons should be tested for IgG antibody to *Toxoplasma* soon after HIV infection is diagnosed. When these criteria are used, the predictive value is as high as 80%. More than 97% of patients with AIDS and toxoplasmosis have IgG antibody to *T. gondii* in serum. IgM serum antibody usually is not detectable. Although IgG titers

do not correlate with active infection, serologic evidence of infection virtually always precedes the development of TE. It is therefore important to determine the *Toxoplasma* antibody status of all patients infected with HIV. Antibody titers may range from negative to 1:1024 in patients with AIDS and TE. Fewer than 3% of patients have no demonstrable antibody to *Toxoplasma* at diagnosis of TE.

Patients with TE have focal or multifocal abnormalities demonstrable by CT or MRI. Neuroradiologic evaluation should include double-dose contrast CT of the head. By this test, single and frequently multiple contrast-enhancing lesions (<2 cm) may be identified. MRI usually demonstrates multiple lesions located in both hemispheres, with the basal ganglia and corticomedullary junction most commonly involved; MRI provides a more sensitive evaluation of the efficacy of therapy than does CT (Fig. 124-2). These findings are not pathognomonic of *Toxoplasma* infection, since 40% of CNS lymphomas are multifocal and 50% are ring-enhancing. For both MRI and CT scans, the rate of false-negative results is ~10%. The finding of a single lesion on an MRI scan increases the likelihood of primary CNS lymphoma (in which solitary lesions are four times more likely than in TE) and strengthens the argument for the performance of a brain biopsy. A therapeutic trial of anti-*Toxoplasma* medications is frequently used to assess the diagnosis. Treatment of presumptive TE with pyrimethamine plus sulfadiazine or clindamycin results in quantifiable clinical improvement in >50% of patients by day 3. By day 7, >90% of treated patients show evidence of improvement. In contrast, if patients fail to respond or have lymphoma, clinical signs and symptoms worsen by day 7. Patients in this category require brain biopsy with or without a change in therapy. This procedure can now be performed by a stereotactic CT-guided method that reduces the potential for complications. Brain biopsy for *T. gondii* identifies organisms in 50–75% of cases. PCR amplification of CSF may also confirm toxoplasmosis or suggest alternative diagnoses, such as progressive multifocal leukoencephalopathy (JC virus positive) or primary CNS lymphoma (Epstein-Barr virus positive).

Both positron emission tomography (PET) and single-photon emission CT (SPECT) have been touted as means of detecting or ruling out *Toxoplasma* infection when a CNS lesion is suspected. However, CT and MRI are currently the standard diagnostic imaging tests for TE. As in other conditions, the radiologic response may lag behind the clinical response. Resolution of lesions may take from 3 weeks to 6 months. Some patients show clinical improvement despite worsening radiographic findings.

Congenital infection

The issue of concern when a pregnant woman has evidence of recent *T. gondii* infection is whether the fetus is infected. PCR analysis of the amniotic fluid for the B1 gene of *T. gondii* has replaced fetal blood sampling. Serologic diagnosis is based on the persistence of IgG antibody or a positive IgM titer after the first week of life (a time frame that excludes placental leak). The IgG determination should be repeated every 2 months. An increase in IgM beyond the first week of life is indicative of acute infection. However, up to 25% of infected newborns may be seronegative and have normal routine physical examinations. Thus assessment of the eye and the brain, with ophthalmologic testing, CSF evaluation, and radiologic studies, is important in establishing the diagnosis.

Ocular toxoplasmosis

The serum antibody titer may not correlate with the presence of active lesions in the fundus, particularly in cases of congenital toxoplasmosis. In general, a positive IgG titer (measured in undiluted serum if necessary) in conjunction with typical lesions establishes the diagnosis. Antibody production in ocular fluids, expressed in terms of the Goldmann-Witmer coefficient, can also be used for diagnosis of ocular disease. Confirmation of local specific antibody production in the eye indicates that the site of inflammatory activity is localized to this organ. However, two-thirds of patients without evidence of specific antibody production at initial clinical presentation later develop a detectable titer. If lesions are atypical and the titer is in the low-positive range, the diagnosis is presumptive. The parasitic antigen–specific polyclonal IgG assay as well as parasitic antigen–specific PCR may facilitate the diagnosis. Accordingly, the clinical diagnosis of ocular toxoplasmosis can be supported in 60–90% of cases by laboratory tests, depending on the time of anterior chamber puncture and the panel of antibody analyses used. In the remaining cases, the possibility of a falsely negative laboratory diagnosis or of an incorrect clinical diagnosis cannot be clarified further.

TREATMENT **Toxoplasmosis**

CONGENITAL INFECTION Congenitally infected neonates are treated with daily oral pyrimethamine (1 mg/kg) and sulfadiazine (100 mg/kg) with folinic acid for 1 year. Depending on the signs and symptoms, prednisone (1 mg/kg per day) may be used for congenital infection. Some U.S. states and some countries routinely screen pregnant women (France, Austria) and/or newborns (Denmark, Massachusetts). Management and treatment regimens vary with the country and the treatment center. Most experts use spiramycin to treat pregnant women who have acute toxoplasmosis early in pregnancy and use pyrimethamine/sulfadiazine/folinic acid to treat women who seroconvert after 18 weeks of pregnancy or in cases of documented fetal infection. This treatment is somewhat controversial: clinical studies, which have included few untreated women, have not proven the efficacy of such therapy in preventing

congenital toxoplasmosis. However, studies do suggest that treatment during pregnancy decreases the severity of infection. Many women who are infected in the first trimester elect termination of pregnancy. Those who do not terminate pregnancy are offered prenatal antibiotic therapy to reduce the frequency and severity of *Toxoplasma* infection in the infant.

INFECTION IN IMMUNOCOMPETENT PATIENTS

Immunologically competent adults and older children who have only lymphadenopathy do not require specific therapy unless they have persistent, severe symptoms. Patients with ocular toxoplasmosis are usually treated for 1 month with pyrimethamine plus either sulfadiazine or clindamycin and sometimes with prednisone. Treatment should be supervised by an ophthalmologist familiar with *Toxoplasma* disease. Ocular disease can be self-limited without treatment, but therapy is typically considered for lesions that are severe or close to the fovea or optic disc.

INFECTION IN IMMUNOCOMPROMISED PATIENTS

Primary Prophylaxis Patients with AIDS should be treated for acute toxoplasmosis; in immunocompromised patients, toxoplasmosis is rapidly fatal if untreated. Before the introduction of ART, the median survival time was >1 year for patients who could tolerate treatment for TE. Despite their toxicity, the drugs used to treat TE were required for survival prior to ART. The incidence of TE has declined as the survival of patients with HIV infection has increased through the use of ART.

In Africa, many patients are diagnosed with HIV infection only after developing opportunistic infections such as TE. Hence, the optimal management of these opportunistic infections is important if the benefits of subsequent ART are to be realized. AIDS patients who are seropositive for *T. gondii* and who have a CD4+ T lymphocyte count of <100/μL should receive prophylaxis against TE.

Of the currently available agents, trimethoprim-sulfamethoxazole (TMP-SMX) appears to be an effective alternative for treatment of TE in resource-poor settings where the preferred combination of pyrimethamine plus sulfadiazine is not available. The daily dose of TMP-SMX recommended as the preferred regimen for PcP prophylaxis (one double-strength tablet) is effective against TE. If patients cannot tolerate TMP-SMX, the recommended alternative is dapsone-pyrimethamine, which is also effective against PcP. Atovaquone with or without pyrimethamine also can be considered. Prophylactic monotherapy with dapsone, pyrimethamine, azithromycin, clarithromycin, or aerosolized pentamidine is probably insufficient. AIDS patients who are seronegative for *Toxoplasma* and are not receiving prophylaxis for PcP should be retested for IgG antibody to *Toxoplasma* if their CD4+ T cell count drops to <100/μL. If seroconversion has taken place, then the patient should be given prophylaxis as described earlier.

Discontinuing Primary Prophylaxis Current studies indicate that prophylaxis against TE can be discontinued in patients who have responded to ART and whose CD4+ T lymphocyte count has been >200/μL for 3 months. Although patients with CD4+ T lymphocyte counts of <100/μL are at greatest risk for developing TE, the risk that this condition will develop when the count has increased to 100–200/μL has not been established. Thus, prophylaxis should be discontinued when the count has increased to >200/μL. Discontinuation of therapy reduces the pill burden; the potential for drug toxicity, drug interaction, or selection of drug-resistant pathogens; and cost. Prophylaxis should be recommenced if the CD4+ T lymphocyte count again decreases to <100–200/μL.

Individuals who have completed initial therapy for TE should receive treatment indefinitely unless immune reconstitution, with a CD4+ T cell count of >200/μL, occurs as a consequence of ART. Combination therapy with pyrimethamine plus sulfadiazine plus leucovorin is effective for this purpose. An alternative to sulfadiazine in this regimen is clindamycin.

Discontinuing Secondary Prophylaxis (Long-Term Maintenance Therapy) Patients receiving secondary prophylaxis for TE are at low risk for recurrence when they have completed initial therapy for TE, remain asymptomatic, and have a CD4+ T lymphocyte count of >200/μL for at least 6 months after ART. This recommendation is based on recent observations in a large cohort (381 patients) and is consistent with more extensive data indicating the safety of discontinuing secondary prophylaxis for other opportunistic infections during advanced HIV disease. Discontinuation of long-term maintenance therapy among these patients appears reasonable. A repeat MRI brain scan is recommended. Secondary prophylaxis should be reintroduced if the CD4+ T lymphocyte count decreases to <200/μL.

PREVENTION

All HIV-infected persons, including those who lack IgG antibody to *Toxoplasma*, should be counseled regarding sources of *Toxoplasma* infection. The chances of primary infection with *Toxoplasma* can be reduced by not eating undercooked meat and by avoiding oocyst-contaminated material (i.e., a cat's litter box). Specifically, lamb, beef, and pork should be cooked to an internal temperature of 165°–170°F; from a more practical perspective, meat cooked until it is no longer pink inside usually satisfies this requirement. Hands should be washed thoroughly after work in the garden, and all fruits and vegetables should be washed. Ingestion of raw shellfish is a risk factor for toxoplasmosis, given that the filter-feeding mechanism of clams and mussels concentrates oocysts.

If the patient owns a cat, the litter box should be cleaned or changed daily, preferably by an HIV-negative, nonpregnant person; alternatively, patients should wash their hands thoroughly after changing the litter box. Litter boxes should be changed daily if possible, as freshly excreted oocysts will not

have sporulated and will not be infectious. Patients should be encouraged to keep their cats inside and not to adopt or handle stray cats. Cats should be fed only canned or dried commercial food or well-cooked table food, not raw or undercooked meats. Patients need not be advised to part with their cats or to have their cats tested for toxoplasmosis. Blood intended for transfusion into *Toxoplasma*-seronegative immunocompromised individuals should be screened for antibody to *T. gondii*. Although such serologic screening is not routinely performed, seronegative women should be screened for evidence of infection several times during pregnancy if they are exposed to environmental conditions that put them at risk for infection with *T. gondii*. HIV-positive individuals should adhere closely to these preventive measures.

CHAPTER 125

PROTOZOAL INTESTINAL INFECTIONS AND TRICHOMONIASIS

Peter F. Weller

PROTOZOAL INFECTIONS

GIARDIASIS

Giardia intestinalis (also known as *G. lamblia* or *G. duodenalis*) is a cosmopolitan protozoal parasite that inhabits the small intestines of humans and other mammals. Giardiasis is one of the most common parasitic diseases in both developed and developing countries worldwide, causing both endemic and epidemic intestinal disease and diarrhea.

Life cycle and epidemiology

(Fig. 125-1) Infection follows the ingestion of environmentally hardy cysts, which excyst in the small intestine, releasing flagellated trophozoites **(Fig. 125-2)** that multiply by binary fission. *Giardia* remains a pathogen of the proximal small bowel and does not disseminate hematogenously. Trophozoites remain free in the lumen or attach to the mucosal epithelium by means of a ventral sucking disk. As a trophozoite encounters altered conditions, it forms a morphologically distinct cyst, which is the stage of the parasite usually found in the feces. Trophozoites may be present and even predominate in loose or watery stools, but it is the resistant cyst that survives outside the body and is responsible for transmission. Cysts do not tolerate heating, desiccation, or continued exposure to feces but do remain viable for months in cold fresh water. The number of cysts excreted varies widely but can approach 10^7 per gram of stool.

Ingestion of as few as 10 cysts is sufficient to cause infection in humans. Because cysts are infectious when excreted, person-to-person transmission occurs where fecal hygiene is poor. Giardiasis (symptomatic or asymptomatic) is especially prevalent in day-care centers; person-to-person spread also takes place in other institutional settings with poor fecal hygiene and during anal-oral contact. If food is contaminated with *Giardia* cysts after cooking or preparation, food-borne transmission can occur. Waterborne transmission accounts for episodic infections (e.g., in campers and travelers) and for major epidemics in metropolitan areas. Surface water, ranging from mountain streams to large municipal reservoirs, can become contaminated with fecally derived *Giardia* cysts; outmoded water systems are subject to cross-contamination from leaking sewer lines. The efficacy of water as a means of transmission is enhanced by the small infectious inoculum of *Giardia*, the prolonged survival of cysts in cold water, and the resistance of cysts to killing by routine chlorination methods that are adequate for controlling bacteria. Viable cysts can be eradicated from water by either boiling or filtration. In the United States, *Giardia* (like *Cryptosporidium*; see following) is a common cause of waterborne epidemics of gastroenteritis.

Giardia is common in developing countries, and infections may be acquired by travelers.

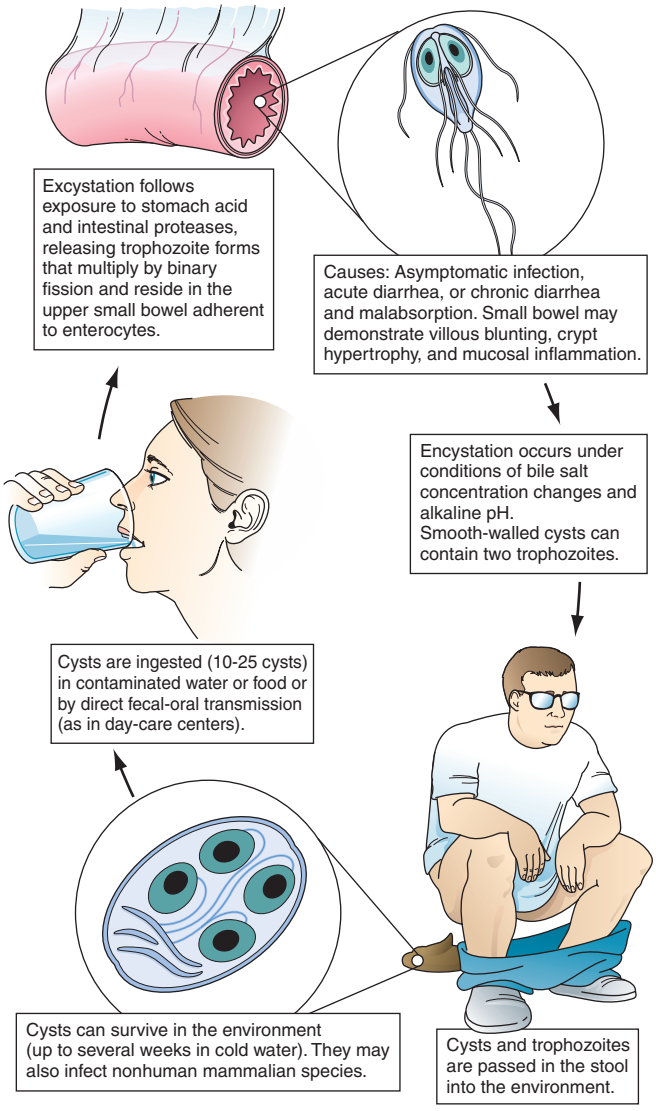


FIGURE 125-1
Life cycle of *Giardia*. (*Reprinted from RL Guerrant et al: Tropical Infectious Disease: Principles, Pathogens and Practice, 2nd ed, 2006, p 987, with permission from Elsevier Science.*)

Giardia parasites genotypically similar to those in humans are found in many mammals, including beavers from reservoirs implicated in epidemics. The importance of dogs and cats as sources of infection for humans is unclear.

Giardiasis, like cryptosporidiosis, creates a significant economic burden because of the costs incurred in the installation of water filtration systems required to prevent waterborne epidemics, in the management of epidemics that involve large communities, and in the evaluation and treatment of endemic infections.

Pathophysiology

The reasons that some, but not all, infected patients develop clinical manifestations and the mechanisms by which *Giardia* causes alterations in small-bowel function are largely unknown. Although trophozoites adhere to the epithelium, they do not cause invasive or locally destructive alterations. The lactose intolerance and, in a minority of infected adults and children, significant malabsorption that develop are clinical signs of the loss of brush-border enzyme activities. In most infections, the morphology of the bowel is unaltered; however, in a few cases (usually in chronically infected, symptomatic patients), the histopathologic findings (including flattened villi) and the clinical manifestations resemble those of tropical sprue and gluten-sensitive enteropathy. The pathogenesis of diarrhea in giardiasis is not known.

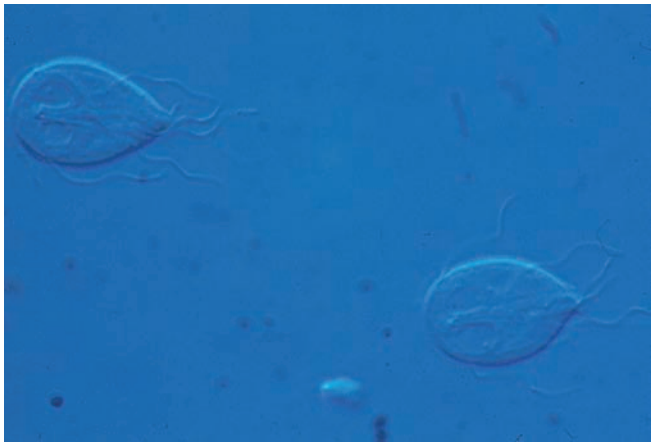


FIGURE 125-2
Flagellated, binucleate ***Giardia* trophozoites.**

The natural history of *Giardia* infection varies markedly. Infections may be aborted, transient, recurrent, or chronic. Parasite as well as host factors may be important in determining the course of infection and disease. Both cellular and humoral responses develop in human infections, but their precise roles in the control of infection and/or disease are unknown. Because patients with hypogammaglobulinemia suffer from prolonged, severe infections that are poorly responsive to treatment, humoral immune responses appear to be important. The greater susceptibility of the young than of the old and of newly exposed persons than of chronically exposed populations suggests that at least partial protective immunity may develop. *Giardia* isolates vary genotypically, biochemically, and biologically, and variations among isolates may contribute to different courses of infection.

Clinical manifestations

Disease manifestations of giardiasis range from asymptomatic carriage to fulminant diarrhea and malabsorption. Most infected persons are asymptomatic, but in epidemics the proportion of symptomatic cases may be higher. Symptoms may develop suddenly or gradually. In persons with acute giardiasis, symptoms develop after an incubation period that lasts at least 5–6 days and usually 1–3 weeks. Prominent early symptoms include diarrhea, abdominal pain, bloating, belching, flatus, nausea, and vomiting. Although diarrhea is common, upper intestinal manifestations such as nausea, vomiting, bloating, and abdominal pain may predominate. The duration of acute giardiasis is usually >1 week, although diarrhea often subsides. Individuals with chronic giardiasis may present with or without

having experienced an antecedent acute symptomatic episode. Diarrhea is not necessarily prominent, but increased flatus, loose stools, sulfurous belching, and (in some instances) weight loss occur. Symptoms may be continual or episodic and can persist for years. Some persons who have relatively mild symptoms for long periods recognize the extent of their discomfort only in retrospect. Fever, the presence of blood and/or mucus in the stools, and other signs and symptoms of colitis are uncommon and suggest a different diagnosis or a concomitant illness. Symptoms tend to be intermittent yet recurring and gradually debilitating, in contrast with the acute disabling symptoms associated with many enteric bacterial infections. Because of the less severe illness and the propensity for chronic infections, patients may seek medical advice late in the course of the illness; however, disease can be severe, resulting in malabsorption, weight loss, growth retardation, and dehydration. A number of extraintestinal manifestations have been described, such as urticaria, anterior uveitis, and arthritis; whether these are caused by giardiasis or concomitant processes is unclear.

Giardiasis can be severe in patients with hypogammaglobulinemia and can complicate other preexisting intestinal diseases, such as that occurring in cystic fibrosis. In patients with AIDS, *Giardia* can cause enteric illness that is refractory to treatment.

Diagnosis

(Table 125-1) Giardiasis is diagnosed by detection of parasite antigens in the feces or by identification of cysts in the feces or of trophozoites in the feces or small intestines. Cysts are oval, measure 8–12 μm × 7–10 μm, and characteristically contain four nuclei. Trophozoites are pear-shaped, dorsally convex, flattened parasites with two nuclei and four pairs of flagella (Fig. 125-2). The diagnosis is sometimes difficult to establish. Direct examination of fresh or properly preserved stools as well as concentration methods should be used. Because cyst excretion is variable and may be undetectable at times, repeated examination of stool, sampling of duodenal fluid, and biopsy of the small intestine may be required to detect the parasite. Tests for parasitic antigens in stool are at least as sensitive and specific as good microscopic examinations and are easier to perform. All of these methods occasionally yield false-negative results.

TABLE 125-1

DIAGNOSIS OF INTESTINAL PROTOZOAL INFECTIONS

PARASITE	STOOL O+P[a]	FECAL ACID-FAST STAIN	STOOL ANTIGEN IMMUNOASSAYS	OTHER
Giardia	+		+	
Cryptosporidium	–	+	+	
Isospora	–	+		
Cyclospora	–	+		
Microsporidia	–			Special fecal stains, tissue biopsies

[a]O+P, ova and parasites.

TREATMENT Giardiasis

Cure rates with metronidazole (250 mg thrice daily for 5 days) are usually >90%. Tinidazole (2 g once by mouth) is reportedly more effective than metronidazole. Nitazoxanide (500 mg twice daily for 3 days) is an alternative agent for treatment of giardiasis. Paromomycin, an oral aminoglycoside that is not well absorbed, can be given to symptomatic pregnant patients, although information is limited on how effectively this agent eradicates infection.

Almost all patients respond to therapy and are cured, although some with chronic giardiasis experience delayed resolution of symptoms after eradication of *Giardia*. For many of the latter patients, residual symptoms probably reflect delayed regeneration of intestinal brush-border enzymes. Continued infection should be documented by stool examinations before treatment is repeated. Patients who remain infected after repeated treatments should be evaluated for reinfection through family members, close personal contacts, and environmental sources as well as for hypogammaglobulinemia. In cases refractory to multiple treatment courses, prolonged therapy with metronidazole (750 mg thrice daily for 21 days) has been successful.

Prevention

Although giardiasis is extremely infectious, disease can be prevented by consumption of noncontaminated food and water and by personal hygiene when caring for infected children. Boiling or filtering potentially contaminated water prevents infection.

CRYPTOSPORIDIOSIS

The coccidian parasite *Cryptosporidium* causes diarrheal disease that is self-limited in immunocompetent human hosts but can be severe in persons with AIDS or other forms of immunodeficiency. Two species of *Cryptosporidium*, *C. hominis* and *C. parvum*, cause most human infections.

Life cycle and epidemiology

Cryptosporidium species are widely distributed in the world. Cryptosporidiosis is acquired by the consumption of oocysts (50% infectious dose: ~132 oocysts in nonimmune individuals), which excyst to liberate sporozoites that in turn enter and infect intestinal epithelial cells. The parasite's further development involves both asexual and sexual cycles, which produce forms

capable of infecting other epithelial cells and of generating oocysts that are passed in the feces. *Cryptosporidium* species infect a number of animals, and *C. parvum* can spread from infected animals to humans. Since oocysts are immediately infectious when passed in feces, person-to-person transmission takes place in day-care centers and among household contacts and medical providers. Waterborne transmission (especially that of *C. hominis*) accounts for infections in travelers and for common-source epidemics. Oocysts are quite hardy and resist killing by routine chlorination. Both drinking water and recreational water (e.g., pools, waterslides) have been increasingly recognized as sources of infection.

Pathophysiology

Although intestinal epithelial cells harbor cryptosporidia in an intracellular vacuole, the means by which secretory diarrhea is elicited remain uncertain. No characteristic pathologic changes are found by biopsy. The distribution of infection can be spotty within the principal site of infection, the small bowel. Cryptosporidia are found in the pharynx, stomach, and large bowel of some patients and at times in the respiratory tract. Especially in patients with AIDS, involvement of the biliary tract can cause papillary stenosis, sclerosing cholangitis, or cholecystitis.

Clinical manifestations

Asymptomatic infections can occur in both immunocompetent and immunocompromised hosts. In immunocompetent persons, symptoms develop after an incubation period of ~1 week and consist principally of watery nonbloody diarrhea, sometimes in conjunction with abdominal pain, nausea, anorexia, fever, and/or weight loss. In these hosts, the illness usually subsides after 1–2 weeks. In contrast, in immunocompromised hosts (especially those with AIDS and CD4+ T cell counts <100/μL), diarrhea can be chronic, persistent, and remarkably profuse, causing clinically significant fluid and electrolyte depletion. Stool volumes may range from 1 to 25 L/d. Weight loss, wasting, and abdominal pain may be severe. Biliary tract involvement can manifest as midepigastric or right-upper-quadrant pain.

Diagnosis

(Table 125-1) Evaluation starts with fecal examination for small oocysts, which are smaller (4–5 μm in diameter) than the fecal stages of most other parasites. Because conventional stool examination for ova and parasites does not detect *Cryptosporidium*, specific testing must be requested. Detection is enhanced by evaluation of stools (obtained on multiple days) by several techniques, including modified acid-fast and direct immunofluorescent stains and enzyme immunoassays. Cryptosporidia can also be identified by light and electron microscopy at the apical surfaces of intestinal epithelium from biopsy specimens of the small bowel and, less frequently, the large bowel.

TREATMENT **Cryptosporidiosis**

Nitazoxanide is approved by the U.S. Food and Drug Administration for the treatment of cryptosporidiosis and is available in tablet form for adults (500 mg twice daily for 3 days) and as an elixir for children. To date, however, this agent has not been effective for the treatment of HIV-infected patients, in whom improved immune status due to antiretroviral therapy can lead to amelioration of cryptosporidiosis. Otherwise, treatment includes supportive care with replacement of fluids and electrolytes and administration of antidiarrheal agents. Biliary tract obstruction may require papillotomy or T-tube placement. Prevention requires minimizing exposure to infectious oocysts in human or animal feces. Use of submicron water filters may minimize acquisition of infection from drinking water.

ISOSPORIASIS

The coccidian parasite *Isospora belli* causes human intestinal disease. Infection is acquired by the consumption of oocysts, after which the parasite invades intestinal epithelial cells and undergoes both sexual and asexual cycles of development. Oocysts excreted in stool are not immediately infectious but must undergo further maturation.

Although *I. belli* infects many animals, little is known about the epidemiology or prevalence of this parasite in humans. It appears to be most common in tropical and subtropical countries. Acute infections can begin abruptly with fever, abdominal pain, and watery nonbloody diarrhea and can last for weeks or months. In patients who have AIDS or are immunocompromised for other reasons, infections often are not self-limited but rather resemble cryptosporidiosis, with chronic, profuse watery diarrhea. Eosinophilia, which is not found in other enteric protozoan infections, may be detectable. The diagnosis (Table 125-1) is usually made by detection of the large (~25-μm) oocysts in stool by modified acid-fast staining. Oocyst excretion may be low-level and intermittent; if repeated stool examinations are unrevealing, sampling of duodenal contents by aspiration or small-bowel biopsy (often with electron-microscopic examination) may be necessary.

TREATMENT **Isosporiasis**

Trimethoprim-sulfamethoxazole (TMP-SMX, 160/800 mg four times daily for 10 days; and for HIV-infected patients, then three times daily for 3 weeks) is effective. For patients intolerant of sulfonamides, pyrimethamine (50–75 mg/d) can be used. Relapses can occur in persons with AIDS and necessitate maintenance therapy with TMP-SMX (160/800 mg three times per week).

CYCLOSPORIASIS

Cyclospora cayetanensis, a cause of diarrheal illness, is globally distributed: illness due to *C. cayetanensis* has been reported in the United States, Asia, Africa, Latin America, and Europe. The epidemiology of this parasite has not yet been fully defined, but waterborne transmission and food-borne transmission by basil and imported raspberries have been recognized. The full spectrum of illness attributable to *Cyclospora* has not been delineated. Some patients may harbor the infection without symptoms, but many have diarrhea, flulike symptoms, and flatulence and belching. The illness can be self-limited, can wax and wane, or in many cases can involve prolonged diarrhea, anorexia, and upper gastrointestinal symptoms, with sustained fatigue and weight loss in some instances. Diarrheal illness may persist for >1 month. *Cyclospora* can cause enteric illness in patients infected with HIV.

The parasite is detectable in epithelial cells of small-bowel biopsy samples and elicits secretory diarrhea by unknown means. The absence of fecal blood and leukocytes indicates that disease due to *Cyclospora* is not caused by destruction of the small-bowel mucosa. The diagnosis (Table 125-1) can be made by detection of spherical 8- to 10-μm oocysts in the stool, although routine stool ova andparasite (O+P) examinations are not sufficient. Specific fecal examinations must be requested to detect the oocysts, which are variably acid-fast and are fluorescent when viewed with ultraviolet light microscopy. Cyclosporiasis should be considered in the differential diagnosis of prolonged diarrhea, with or without a history of travel by the patient to other countries.

TREATMENT Cyclosporiasis

Cyclosporiasis is treated with TMP-SMX (160/800 mg twice daily for 7 days). HIV-infected patients may experience relapses after such treatment and thus may require longer-term suppressive maintenance therapy.

MICROSPORIDIOSIS

Microsporidia are obligate intracellular spore-forming protozoa that infect many animals and cause disease in humans, especially as opportunistic pathogens in AIDS. Microsporidia are members of a distinct phylum, Microspora, which contains dozens of genera and hundreds of species. The various microsporidia are differentiated by their developmental life cycles, ultrastructural features, and molecular taxonomy based on ribosomal RNA. The complex life cycles of the organisms result in the production of infectious spores **(Fig. 125-3)**. Currently, eight genera of microsporidia—*Encephalitozoon*, *Pleistophora*, *Nosema*, *Vittaforma*, *Trachipleistophora*, *Brachiola*, *Microsporidium*, and *Enterocytozoon*—are recognized as causes of human disease. Although some microsporidia are probably prevalent causes of self-limited or asymptomatic infections in immunocompetent patients, little is known about how microsporidiosis is acquired.

Microsporidiosis is most common among patients with AIDS, less common among patients with other types of immunocompromise, and rare among immunocompetent hosts. In patients with AIDS, intestinal infections with *Enterocytozoon bieneusi* and *Encephalitozoon* (formerly *Septata*) *intestinalis* are recognized to contribute to chronic diarrhea and wasting; these infections are found in 10–40% of patients with chronic diarrhea. Both organisms have been found in the biliary tracts of patients with cholecystitis. *E. intestinalis* may also disseminate to cause fever, diarrhea, sinusitis, cholangitis, and bronchiolitis. In patients with AIDS, *Encephalitozoon hellem* has caused superficial keratoconjunctivitis as well as sinusitis, respiratory tract disease, and disseminated infection. Myositis due to *Pleistophora* has been documented. *Nosema*, *Vittaforma*, and *Microsporidium* have caused stromal keratitis associated with trauma in immunocompetent patients.

Microsporidia are small gram-positive organisms with mature spores measuring 0.5–2 μm × 1–4 μm. Diagnosis of microsporidial infections in tissue often requires electron microscopy, although intracellular spores can be visualized by light microscopy with hematoxylin and eosin, Giemsa, or tissue Gram's stain. For the diagnosis of intestinal microsporidiosis, modified trichrome or chromotrope 2R-based staining and Uvitex 2B or calcofluor fluorescent staining reveal spores in smears of feces or duodenal aspirates. Definitive therapies for microsporidial infections remain to be established. For superficial keratoconjunctivitis due to *E. hellem*, topical therapy with fumagillin suspension has shown promise (Chap. 116). For enteric infections with *E. bieneusi* and *E. intestinalis* in HIV-infected patients, therapy with albendazole may be efficacious (Chap. 116).

OTHER INTESTINAL PROTOZOA

Balantidiasis

Balantidium coli is a large ciliated protozoal parasite that can produce a spectrum of large-intestinal disease analogous to amebiasis. The parasite is widely distributed in the world. Since it infects pigs, cases in humans are more common where pigs are raised. Infective cysts can be transmitted from person to person and through water, but many cases are due to the ingestion of cysts derived from porcine feces in association with slaughtering, with use of pig feces for fertilizer, or with contamination of water supplies by pig feces.

Ingested cysts liberate trophozoites, which reside and replicate in the large bowel. Many patients remain asymptomatic, but some have persisting intermittent diarrhea, and a few develop more fulminant dysentery. In symptomatic individuals, the pathology in the bowel—both gross and microscopic—is similar to that seen in amebiasis, with varying degrees of mucosal invasion, focal necrosis, and ulceration. Balantidiasis, unlike amebiasis, does not spread hematogenously to

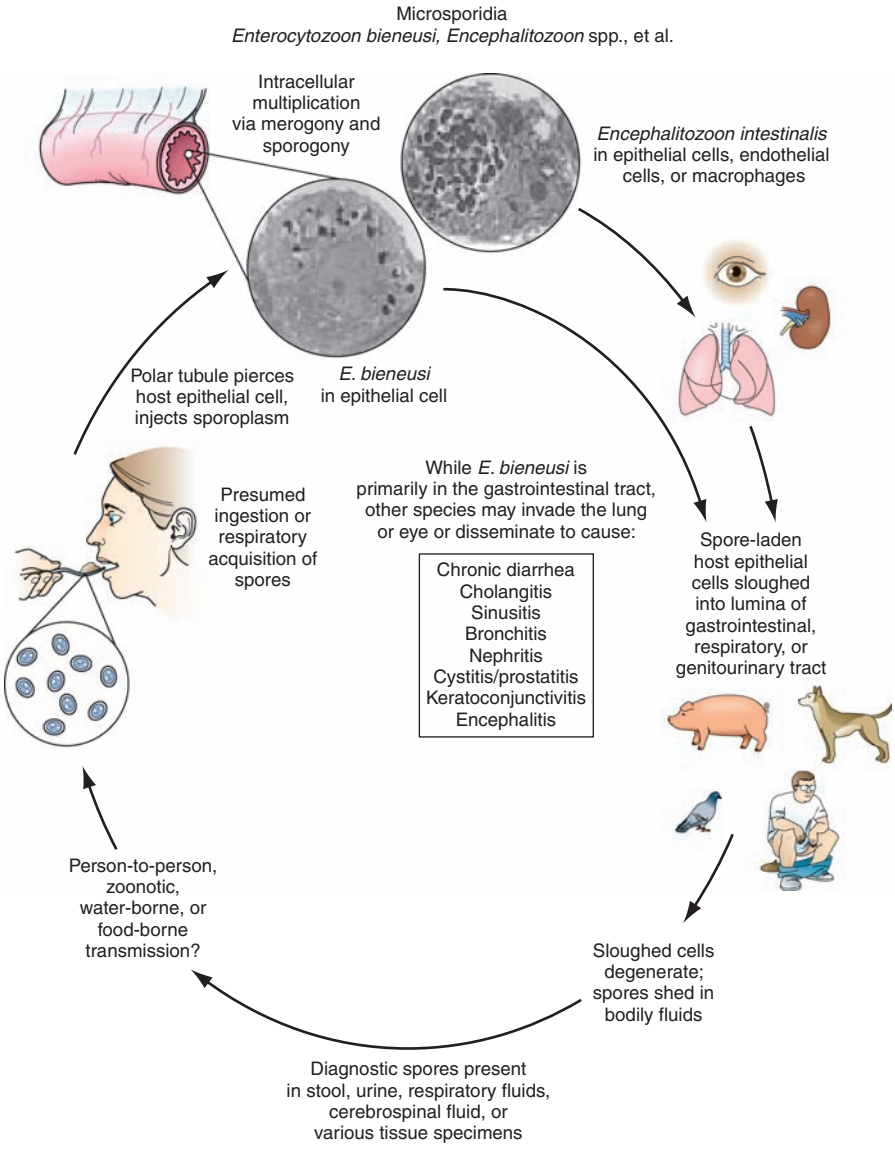


FIGURE 125-3
Life cycle of microsporidia. (*Reprinted from RL Guerrant et al: Tropical Infectious Disease: Principles, Pathogens and Practice, 2nd ed, 2006, p 1128, with permission from Elsevier Science.*)

other organs. The diagnosis is made by detection of the trophozoite stage in stool or sampled colonic tissue. Tetracycline (500 mg four times daily for 10 days) is an effective therapeutic agent.

Blastocystis hominis infection

B. hominis, while believed by some to be a protozoan capable of causing intestinal disease, remains an organism of uncertain pathogenicity. Some patients who pass *B. hominis* in their stools are asymptomatic, whereas others have diarrhea and associated intestinal symptoms. Diligent evaluation reveals other potential bacterial, viral, or protozoal causes of diarrhea in some but not all patients with symptoms. Because the pathogenicity of *B. hominis* is uncertain and because therapy for *Blastocystis* infection is neither specific nor uniformly effective, patients with prominent intestinal symptoms should be fully evaluated for other infectious causes of diarrhea. If diarrheal symptoms associated with *Blastocystis* are prominent, either metronidazole (750 mg thrice daily for 10 days) or TMP-SMX (160 mg/800 mg twice daily for 7 days) can be used.

Dientamoeba fragilis infection

D. fragilis is unique among intestinal protozoa in that it has a trophozoite stage but not a cyst stage. How trophozoites survive to transmit infection is not known. When symptoms develop in patients with *D. fragilis* infection,

they are generally mild and include intermittent diarrhea, abdominal pain, and anorexia. The diagnosis is made by the detection of trophozoites in stool; the lability of these forms accounts for the greater yield when fecal samples are preserved immediately after collection. Since fecal excretion rates vary, examination of several samples obtained on alternate days increases the rate of detection. Iodoquinol (650 mg three times daily for 20 days), paromomycin (25–35 mg/kg per day in three doses for 7 days), metronidazole (500–750 mg three times daily for 10 days), or tetracycline (500 mg four times daily for 10 days) is appropriate for treatment.

TRICHOMONIASIS

Various species of trichomonads can be found in the mouth (in association with periodontitis) and occasionally in the gastrointestinal tract. *Trichomonas vaginalis*—one of the most prevalent protozoal parasites in the United States—is a pathogen of the genitourinary tract and a major cause of symptomatic vaginitis.

LIFE CYCLE AND EPIDEMIOLOGY

T. vaginalis is a pear-shaped, actively motile organism that measures about 10 × 7 μm, replicates by binary fission, and inhabits the lower genital tract of females and the urethra and prostate of males. In the United States, it accounts for ~3 million infections per year in women. While the organism can survive for a few hours in moist environments and could be acquired by direct contact, person-to-person venereal transmission accounts for virtually all cases of trichomoniasis. Its prevalence is greatest among persons with multiple sexual partners and among those with other sexually transmitted diseases (Chap. 30).

CLINICAL MANIFESTATIONS

Many men infected with *T. vaginalis* are asymptomatic, although some develop urethritis and a few have epididymitis or prostatitis. In contrast, infection in women, which has an incubation period of 5–28 days, is usually symptomatic and manifests with malodorous vaginal discharge (often yellow), vulvar erythema and itching, dysuria or urinary frequency (in 30–50% of patients), and dyspareunia. These manifestations, however, do not clearly distinguish trichomoniasis from other types of infectious vaginitis.

DIAGNOSIS

Detection of motile trichomonads by microscopic examination of wet mounts of vaginal or prostatic secretions has been the conventional means of diagnosis. Although this approach provides an immediate diagnosis, its sensitivity for the detection of *T. vaginalis* is only ~50–60% in routine evaluations of vaginal secretions. Direct immunofluorescent antibody staining is more sensitive (70–90%) than wet-mount examinations. *T. vaginalis* can be recovered from the urethra of both males and females and is detectable in males after prostatic massage. Culture of the parasite is the most sensitive means of detection; however, facilities for culture are not generally available, and detection of the organism takes 3–7 days.

TREATMENT Trichomoniasis

Metronidazole, given either as a single 2-g dose or in 500-mg doses twice daily for 7 days, is usually effective. Tinidazole (a single 2-g dose) is also effective. All sexual partners must be treated concurrently to prevent reinfection, especially from asymptomatic males. In males with persistent symptomatic urethritis after therapy for nongonococcal urethritis, metronidazole therapy should be considered for possible trichomoniasis. Alternatives to metronidazole for treatment during pregnancy are not readily available, although use of 100-mg clotrimazole vaginal suppositories nightly for 2 weeks may cure some infections in pregnant women. Reinfection often accounts for apparent treatment failures, but strains of *T. vaginalis* exhibiting high-level resistance to metronidazole have been encountered. Treatment of these resistant infections with higher oral doses, parenteral doses, or concurrent oral and vaginal doses of metronidazole or with tinidazole has been successful.

CHAPTER 126

TRICHINELLOSIS AND OTHER TISSUE NEMATODE INFECTIONS

Peter F. Weller

Nematodes are elongated, symmetric roundworms. Parasitic nematodes of medical significance may be broadly classified as either predominantly intestinal or tissue nematodes. This chapter covers the tissue nematodes that cause trichinellosis, visceral and ocular larva migrans, cutaneous larva migrans, cerebral angiostrongyliasis, and gnathostomiasis. All of these zoonotic infections result from incidental exposure to infectious nematodes. The clinical symptoms of these infections are due largely to invasive larval stages that (except in the case of *Trichinella*) do not reach maturity in humans.

TRICHINELLOSIS

Trichinellosis develops after the ingestion of meat containing cysts of *Trichinella* (e.g., pork or other meat from a carnivore). Although most infections are mild and asymptomatic, heavy infections can cause severe enteritis, periorbital edema, myositis, and (infrequently) death.

Life cycle and epidemiology

Eight species of *Trichinella* are recognized as causes of infection in humans. Two species are distributed worldwide: *T. spiralis*, which is found in a great variety of carnivorous and omnivorous animals, and *T. pseudospiralis*, which is found in mammals and birds. *T. nativa* is present in Arctic regions and infects bears; *T. nelsoni* is found in equatorial eastern Africa, where it is common among felid predators and scavengers such as hyenas and bush pigs; and *T. britovi* is found in Europe, western Africa, and western Asia among carnivores but not among domestic swine. *T. murrelli* is present in North American game animals.

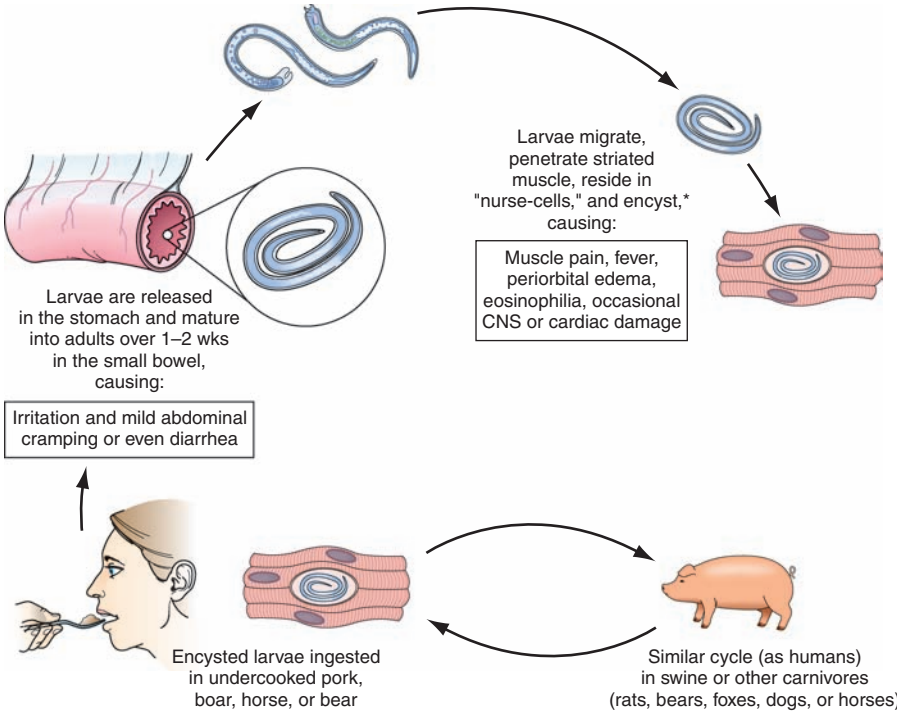
After human consumption of trichinous meat, encysted larvae are liberated by digestive acid and proteases **(Fig. 126-1)**. The larvae invade the small-bowel mucosa and mature into adult worms. After ~1 week, female worms release newborn larvae that migrate via the circulation to striated muscle. The larvae of all species except *T. pseudospiralis*, *T. papuae*, and *T. zimbabwensis* then encyst by inducing a radical transformation in the muscle cell architecture. Although host immune responses may help to expel intestinal adult worms, they have little effect on muscle-dwelling larvae.

Human trichinellosis is often caused by the ingestion of infected pork products and thus can occur in almost any location where the meat of domestic or wild swine is eaten. Human trichinellosis also may be acquired from the meat of other animals, including dogs (in parts of Asia and Africa), horses (in Italy and France), and bears and walruses (in northern regions). Although cattle (being herbivores) are not natural hosts of *Trichinella*, beef has been implicated in outbreaks when contaminated or adulterated with trichinous pork. Laws that prohibit the feeding of uncooked garbage to pigs have greatly reduced the transmission of trichinellosis in the United States. About 12 cases of trichinellosis are reported annually in this country, but most mild cases probably remain undiagnosed. Recent U.S. and Canadian outbreaks have been attributable to consumption of wild game (especially bear meat) and, less frequently, of pork.

Pathogenesis and clinical features

Clinical symptoms of trichinellosis arise from the successive phases of parasite enteric invasion, larval migration, and muscle encystment (Fig. 126-1). Most light infections (those with <10 larvae per gram of muscle) are asymptomatic, whereas heavy infections (which can involve >50 larvae per gram of muscle) can be life-threatening. Invasion of the gut by large numbers of parasites occasionally provokes diarrhea during the first week after infection. Abdominal pain, constipation, nausea, or vomiting also may be prominent.

Symptoms due to larval migration and muscle invasion begin to appear in the second week after infection.



T. papuae, T. zimbabwensis, and *T. pseudospiralis* do not encyst.

FIGURE 126-1
Life cycle of *Trichinella* *spiralis* (cosmopolitan); *nelsoni* (equatorial Africa); *britovi* (Europe, western Africa, western Asia); *nativa* (Arctic); *murrelli* (North America); *papuae* (Papua New Guinea); *zimbabwensis* (Tanzania); and *pseudospiralis* (cosmopolitan). CNS, central nervous system. (*Reprinted from Guerrant RL et al [eds]: Tropical Infectious Diseases: Principles, Pathogens and Practice, 2nd ed, p 1218. © 2006, with permission from Elsevier Science.*)

The migrating *Trichinella* larvae provoke a marked local and systemic hypersensitivity reaction, with fever and hypereosinophilia. Periorbital and facial edema is common, as are hemorrhages in the subconjunctivae, retina, and nail beds ("splinter" hemorrhages). A maculopapular rash, headache, cough, dyspnea, or dysphagia sometimes develops. Myocarditis with tachyarrhythmias or heart failure—and, less commonly, encephalitis or pneumonitis—may develop and accounts for most deaths of patients with trichinellosis.

Upon onset of larval encystment in muscle 2–3 weeks after infection, symptoms of myositis with myalgias, muscle edema, and weakness develop, usually overlapping with the inflammatory reactions to migrating larvae. The most commonly involved muscle groups include the extraocular muscles; the biceps; and the muscles of the jaw, neck, lower back, and diaphragm. Peaking ~3 weeks after infection, symptoms subside only gradually during a prolonged convalescence. Uncommon infections with *T. pseudospiralis*, whose larvae do not encapsulate in muscles, elicit prolonged polymyositis-like illness.

Laboratory findings and diagnosis

Blood eosinophilia develops in >90% of patients with symptomatic trichinellosis and may peak at a level of >50% 2–4 weeks after infection. Serum levels of muscle enzymes, including creatine phosphokinase, are elevated in most symptomatic patients. Patients should be questioned thoroughly about their consumption of pork or wild animal meat and about illness in other individuals who ate the same meat. A presumptive clinical diagnosis can be based on fevers, eosinophilia, periorbital edema, and myalgias after a suspect meal. A rise in the titer of parasite-specific antibody, which usually does not occur until after the third week of infection, confirms the diagnosis. Alternatively, a definitive diagnosis requires surgical biopsy of at least 1 g of involved muscle; the yields are highest near tendon insertions. The fresh muscle tissue should be compressed between glass slides and examined microscopically **(Fig. 126-2)**, because larvae may be missed by examination of routine histopathologic sections alone.

TREATMENT **Trichinellosis**

Most lightly infected patients recover uneventfully with bed rest, antipyretics, and analgesics. Glucocorticoids like prednisone **(Table 126-1)** are beneficial for severe myositis and myocarditis. Mebendazole and albendazole are active against enteric stages of the parasite, but their efficacy against encysted larvae has not been conclusively demonstrated.

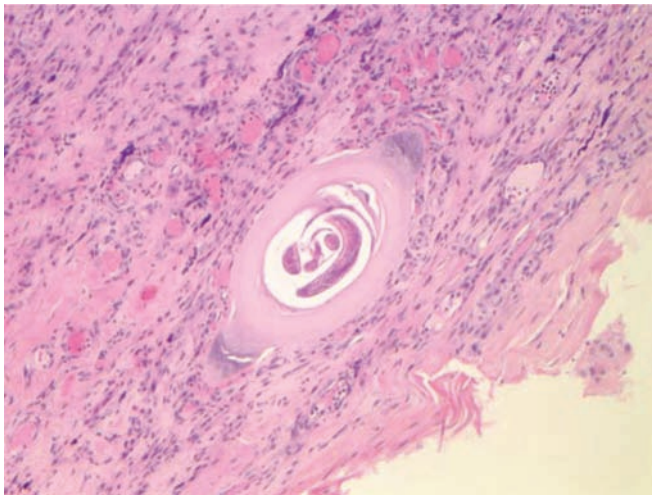


FIGURE 126-2
***Trichinella* larva** encysted in a characteristic hyalinized capsule in striated muscle tissue. *(Photo/Wadsworth Center, New York State Department of Health. Reprinted from MMWR 53:606, 2004; public domain.)*

Prevention

Larvae may be killed by cooking pork until it is no longer pink or by freezing it at −15°C for 3 weeks. However, Arctic *T. nativa* larvae in walrus or bear meat are relatively resistant and may remain viable despite freezing.

VISCERAL AND OCULAR LARVA MIGRANS

Visceral larva migrans is a syndrome caused by nematodes that are normally parasitic for nonhuman host species. In humans, these nematode larvae do not develop into adult worms but instead migrate through host tissues and elicit eosinophilic inflammation. The most common form of visceral larva migrans is toxocariasis due to larvae of the canine ascarid *Toxocara canis*; the syndrome is due less commonly to the feline ascarid *T. cati* and even less commonly to the pig ascarid *Ascaris suum*. Rare cases with eosinophilic meningoencephalitis have been caused by the raccoon ascarid *Baylisascaris procyonis*.

Life cycle and epidemiology

The canine roundworm *T. canis* is distributed among dogs worldwide. Ingestion of infective eggs by dogs is followed by liberation of *Toxocara* larvae, which penetrate the gut wall and migrate intravascularly into canine tissues, where most remain in a developmentally arrested state. During pregnancy, some larvae resume migration in bitches and infect puppies prenatally (through transplacental transmission) or after birth (through suckling). Thus, in lactating bitches and puppies, larvae return to the intestinal tract and develop into adult worms, which produce eggs that are released in the feces.

TABLE 126-1
THERAPY FOR TISSUE NEMATODE INFECTIONS

INFECTION	SEVERITY	TREATMENT
Trichinellosis	Mild	Supportive
	Moderate	Albendazole (400 mg bid × 8–14 days) or Mebendazole (200–400 mg tid × 3 days, then 400 mg tid × 8–14 days)
	Severe	Add glucocorticoids (e.g., prednisone, 1 mg/kg qd × 5 days)
Visceral larva migrans	Mild to moderate	Supportive
	Severe	Glucocorticoids (as above)
	Ocular	Not fully defined; albendazole (800 mg bid for adults, 400 mg bid for children) with glucocorticoids × 5–20 days has been effective
Cutaneous larva migrans		Ivermectin (single dose, 200 µg/kg) or Albendazole (200 mg bid × 3 days)
Angiostrongyliasis	Mild to moderate	Supportive
	Severe	Glucocorticoids (as above)
Gnathostomiasis		Ivermectin (200 µg/kg per day × 2 days) or Albendazole (400 mg bid × 21 days)

Eggs must undergo embryonation over several weeks to become infectious. Humans acquire toxocariasis mainly by eating soil contaminated by puppy feces that contains infective *T. canis* eggs. Visceral larva migrans is most common among children who habitually eat dirt.

Pathogenesis and clinical features

Clinical disease most commonly afflicts preschool children. After humans ingest *Toxocara* eggs, the larvae hatch and penetrate the intestinal mucosa, from which they are carried by the circulation to a wide variety of organs and tissues. The larvae invade the liver, lungs, central nervous system (CNS), and other sites, provoking intense local eosinophilic granulomatous responses. The degree of clinical illness depends on larval number and tissue distribution, reinfection, and host immune responses. Most light infections are asymptomatic and may be manifest only by blood eosinophilia. Characteristic symptoms of

visceral larva migrans include fever, malaise, anorexia and weight loss, cough, wheezing, and rashes. Hepatosplenomegaly is common. These features are often accompanied by extraordinary peripheral eosinophilia, which may approach 90%. Uncommonly, seizures or behavioral disorders develop. Rare deaths are due to severe neurologic, pneumonic, or myocardial involvement.

The ocular form of the larva migrans syndrome occurs when *Toxocara* larvae invade the eye. An eosinophilic granulomatous mass, most commonly in the posterior pole of the retina, develops around the entrapped larva. The retinal lesion can mimic retinoblastoma in appearance, and mistaken diagnosis of the latter condition can lead to unnecessary enucleation. The spectrum of eye involvement also includes endophthalmitis, uveitis, and chorioretinitis. Unilateral visual disturbances, strabismus, and eye pain are the most common presenting symptoms. In contrast to visceral larva migrans, ocular toxocariasis usually develops in older children or young adults with no history of pica; these patients seldom have eosinophilia or visceral manifestations.

Diagnosis

In addition to eosinophilia, leukocytosis and hypergammaglobulinemia may be evident. Transient pulmonary infiltrates are apparent on chest x-rays of about one-half of patients with symptoms of pneumonitis. The clinical diagnosis can be confirmed by an enzyme-linked immunosorbent assay for toxocaral antibodies. Stool examination for parasite eggs, while important in the evaluation of unexplained eosinophilia, is worthless for toxocariasis, since the larvae do not develop into egg-producing adults in humans.

TREATMENT **Visceral and Ocular Larva Migrans**

The vast majority of *Toxocara* infections are self-limited and resolve without specific therapy. In patients with severe myocardial, CNS, or pulmonary involvement, glucocorticoids may be employed to reduce inflammatory complications. Available antihelminthic drugs, including mebendazole and albendazole, have not been shown conclusively to alter the course of larva migrans. Control measures include prohibiting dog excreta in public parks and playgrounds, deworming dogs, and preventing pica in children. Treatment of ocular disease is not fully defined, but the administration of albendazole in conjunction with glucocorticoids has been effective (Table 126-1).

CUTANEOUS LARVA MIGRANS

Cutaneous larva migrans ("creeping eruption") is a serpiginous skin eruption caused by burrowing larvae of animal hookworms, usually the dog and cat hookworm *Ancylostoma braziliense*. The larvae hatch from eggs passed in dog and cat feces and mature in the soil. Humans become infected after skin contact with soil in areas frequented by dogs and cats, such as areas underneath house porches. Cutaneous larva migrans is prevalent among children and travelers in regions with warm humid climates, including the southeastern United States.

After larvae penetrate the skin, erythematous lesions form along the tortuous tracks of their migration through the dermal-epidermal junction; the larvae advance several centimeters in a day. The intensely pruritic lesions may occur anywhere on the body and can be numerous if the patient has lain on the ground. Vesicles and bullae may form later. The animal hookworm larvae do not mature in humans and, without treatment, will die after an interval ranging from weeks to a couple of months, with resolution of skin lesions. The diagnosis is made on clinical grounds. Skin biopsies only rarely detect diagnostic larvae. Symptoms can be alleviated by ivermectin or albendazole (Table 126-1).

ANGIOSTRONGYLIASIS

Angiostrongylus cantonensis, the rat lungworm, is the most common cause of human eosinophilic meningitis **(Fig. 126-3)**.

Life cycle and epidemiology

This infection occurs principally in Southeast Asia and the Pacific Basin but has spread to other areas of the world. *A. cantonensis* larvae produced by adult worms in the rat lung migrate to the gastrointestinal tract and are expelled with the feces. They develop into infective larvae in land snails and slugs. Humans acquire the infection by ingesting raw infected mollusks; vegetables contaminated by mollusk slime; or crabs, freshwater shrimp, and certain marine fish that have themselves eaten infected mollusks. The larvae then migrate to the brain.

Pathogenesis and clinical features

The parasites eventually die in the CNS, but not before initiating pathologic consequences that, in heavy infections, can result in permanent neurologic sequelae or death. Migrating larvae cause marked local eosinophilic inflammation and hemorrhage, with subsequent necrosis and granuloma formation around dying worms. Clinical symptoms develop 2–35 days after the ingestion of larvae. Patients usually present with an insidious or abrupt excruciating frontal, occipital, or bitemporal headache. Neck stiffness, nausea and vomiting, and paresthesias are also common. Fever, cranial and extraocular nerve palsies, seizures, paralysis, and lethargy are uncommon.

Laboratory findings

Examination of cerebrospinal fluid (CSF) is mandatory in suspected cases and usually reveals an elevated opening pressure, a white blood cell count of 150–2000/μL, and an eosinophilic pleocytosis of >20%. The protein concentration is usually elevated and the glucose level

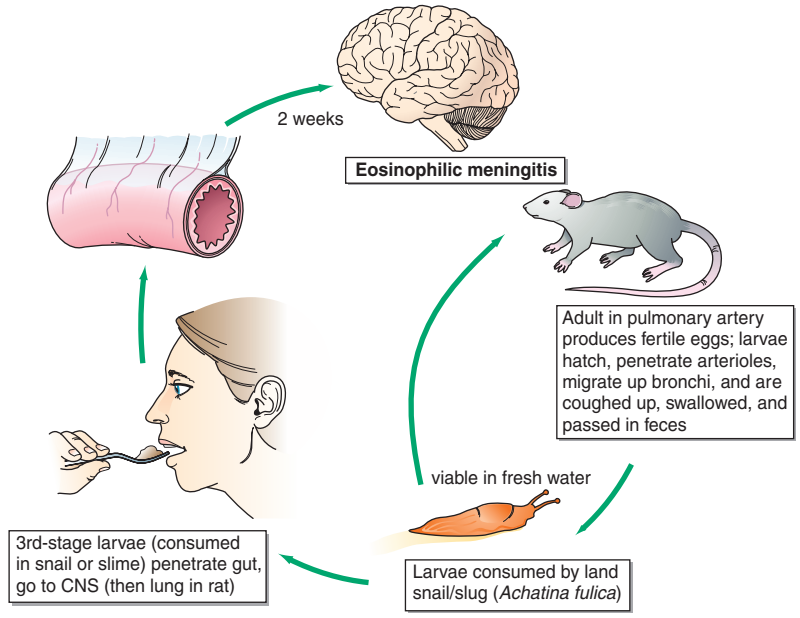


FIGURE 126-3
Life cycle of *Angiostrongylus cantonensis* (rat lung worm), found in Southeast Asia, Pacific Islands, Cuba, Australia, Japan, China, Mauritius, and U.S. ports. CNS, central nervous system. (*Reprinted from Guerrant RL et al (eds): Tropical Infectious Diseases: Principles, Pathogens and Practice, 2nd ed, p 1225. © 2006, with permission from Elsevier Science.*)

normal. The larvae of *A. cantonensis* are only rarely seen in CSF. Peripheral-blood eosinophilia may be mild. The diagnosis is generally based on the clinical presentation of eosinophilic meningitis together with a compatible epidemiologic history.

TREATMENT **Angiostrongyliasis**

Specific chemotherapy is not of benefit in angiostrongyliasis; larvicidal agents may exacerbate inflammatory brain lesions. Management consists of supportive measures, including the administration of analgesics, sedatives, and—in severe cases—glucocorticoids (Table 126-1). Repeated lumbar punctures with removal of CSF can relieve symptoms. In most patients, cerebral angiostrongyliasis has a self-limited course, and recovery is complete. The infection may be prevented by adequately cooking snails, crabs, and prawns and inspecting vegetables for mollusk infestation. Other parasitic or fungal causes of eosinophilic meningitis in endemic areas may include gnathostomiasis (see next), paragonimiasis (Chap. 129), schistosomiasis (Chap. 129), neurocysticercosis (Chap. 130), and coccidioidomycosis (Chap. 107).

GNATHOSTOMIASIS

Infection of human tissues with larvae of *Gnathostoma spinigerum* can cause eosinophilic meningoencephalitis, migratory cutaneous swellings, or invasive masses of the eye and visceral organs.

Life cycle and epidemiology

Human gnathostomiasis occurs in many countries and is notably endemic in Southeast Asia and parts of China and Japan. In nature, the mature adult worms parasitize the gastrointestinal tract of dogs and cats. First-stage larvae hatch from eggs passed into water and are ingested by *Cyclops* species (water fleas). Infective third-stage larvae develop in the flesh of many animal species (including fish, frogs, eels, snakes, chickens, and ducks) that have eaten either infected *Cyclops* or another infected second intermediate host. Humans typically acquire the infection by eating raw or undercooked fish or poultry. Raw fish dishes, such as *som fak* in Thailand and *sashimi* in Japan, account for many cases of human gnathostomiasis. Some cases in Thailand result from the local practice of applying frog or snake flesh as a poultice.

Pathogenesis and clinical features

Clinical symptoms are due to the aberrant migration of a single larva into cutaneous, visceral, neural, or ocular tissues. After invasion, larval migration may cause local inflammation, with pain, cough, or hematuria accompanied by fever and eosinophilia. Painful, itchy, migratory swellings may develop in the skin, particularly in the distal extremities or periorbital area. Cutaneous swellings usually last ~1 week, but often recur intermittently over many years. Larval invasion of the eye can provoke a sight-threatening inflammatory response. Invasion of the CNS results in eosinophilic meningitis

with myeloencephalitis, a serious complication due to ascending larval migration along a large nerve track. Patients characteristically present with agonizing radicular pain and paresthesias in the trunk or a limb, which are followed shortly by paraplegia. Cerebral involvement, with focal hemorrhages and tissue destruction, is often fatal.

Diagnosis and treatment

Cutaneous migratory swellings with marked peripheral eosinophilia, supported by an appropriate geographic and dietary history, generally constitute an adequate basis for a clinical diagnosis of gnathostomiasis. However, patients may present with ocular or cerebrospinal involvement without antecedent cutaneous swellings. In the latter case, eosinophilic pleocytosis is demonstrable (usually along with hemorrhagic or xanthochromic CSF), but worms are almost never recovered from CSF. Surgical removal of the parasite from subcutaneous or ocular tissue, though rarely feasible, is both diagnostic and therapeutic. Albendazole or ivermectin may be helpful (Table 126-1). At present, cerebrospinal involvement is managed with supportive measures and generally with a course of glucocorticoids. Gnathostomiasis can be prevented by adequate cooking of fish and poultry in endemic areas.

CHAPTER 127

INTESTINAL NEMATODE INFECTIONS

Peter F. Weller ■ Thomas B. Nutman

More than a billion persons worldwide are infected with one or more species of intestinal nematodes. Table 127-1 summarizes biologic and clinical features of infections due to the major intestinal parasitic nematodes. These parasites are most common in regions with poor fecal sanitation, particularly in resource-poor countries in the tropics and subtropics, but they have also been seen with increasing frequency among immigrants and refugees to resource-rich countries. Although nematode infections are not usually fatal, they contribute to malnutrition and diminished work capacity. It is interesting that these helminth infections may protect some individuals from allergic disease. Humans may on occasion be infected with nematode parasites that ordinarily infect animals; these zoonotic infections produce diseases such as trichostrongyliasis, anisakiasis, capillariasis, and abdominal angiostrongyliasis.

Intestinal nematodes are roundworms; they range in length from 1 mm to many centimeters when mature (Table 127-1). Their life cycles are complex and highly varied; some species, including *Strongyloides stercoralis* and *Enterobius vermicularis*, can be transmitted directly from person to person, while others, such as *Ascaris lumbricoides*, *Necator americanus*, and *Ancylostoma duodenale*, require a soil phase for development. Because most helminth parasites do not self-replicate, the acquisition of a heavy burden of adult worms requires repeated exposure to the parasite in its infectious stage, whether larval or egg. Hence, clinical disease, as opposed to asymptomatic infection, generally develops only with prolonged residence in an endemic area and is typically related to infection intensity. In persons with marginal nutrition, intestinal helminth infections may impair growth and development. Eosinophilia and elevated serum IgE levels are features of many helminth infections and, when unexplained, should always prompt a search for intestinal helminths. Significant protective immunity to intestinal nematodes appears not to develop in humans, although mechanisms of parasite immune evasion and host immune responses to these infections have not been elucidated in detail.

ASCARIASIS

A. lumbricoides is the largest intestinal nematode parasite of humans, reaching up to 40 cm in length. Most infected individuals have low worm burdens and are asymptomatic. Clinical disease arises from larval migration in the lungs or effects of the adult worms in the intestines.

TABLE 127-1

MAJOR HUMAN INTESTINAL PARASITIC NEMATODES

FEATURE	PARASITIC NEMATODE				
	***ASCARIS LUMBRICOIDES* (ROUNDWORM)**	***NECATOR AMERICANUS, ANCYLOSTOMA DUODENALE* (HOOKWORM)**	***STRONGYLOIDES STERCORALIS***	***TRICHURIS TRICHIURA* (WHIPWORM)**	***ENTEROBIUS VERMICULARIS* (PINWORM)**
Global prevalence in humans (millions)	807	576	100	604	209
Endemic areas	Worldwide	Hot, humid regions	Hot, humid regions	Worldwide	Worldwide
Infective stage	Egg	Filariform larva	Filariform larva	Egg	Egg
Route of infection	Oral	Percutaneous	Percutaneous or autoinfection	Oral	Oral
Gastrointestinal location of worms	Jejunal lumen	Jejunal mucosa	Small-bowel mucosa	Cecum, colonic mucosa	Cecum, appendix
Adult worm size	15–40 cm	7–12 mm	2 mm	30–50 mm	8–13 mm (female)
Pulmonary passage of larvae	Yes	Yes	Yes	No	No
Incubation period[a] (days)	60–75	40–100	17–28	70–90	35–45
Longevity	1 y	*N. americanus*: 2–5 y *A. duodenale*: 6–8 y	Decades (owing to autoinfection)	5 y	2 months
Fecundity (eggs/day/worm)	240,000	*N. americanus*: 4000–10,000 *A. duodenale*: 10,000–25,000	5000–10,000	3000–7000	2000
Principal symptoms	Rarely gastrointestinal or biliary obstruction	Iron-deficiency anemia in heavy infection	Gastrointestinal symptoms; malabsorption or sepsis in hyperinfection	Gastrointestinal symptoms, anemia	Perianal pruritus
Diagnostic stage	Eggs in stool	Eggs in fresh stool, larvae in old stool	Larvae in stool or duodenal aspirate; sputum in hyperinfection	Eggs in stool	Eggs from perianal skin on cellulose acetate tape
Treatment	Mebendazole Albendazole Pyrantel pamoate Ivermectin Nitazoxanide	Mebendazole Pyrantel pamoate Albendazole	1. Ivermectin 2. Albendazole	Mebendazole Albendazole Ivermectin	Mebendazole Pyrantel pamoate Albendazole

[a]Time from infection to egg production by mature female worm.

Life cycle

Adult worms live in the lumen of the small intestine. Mature female *Ascaris* worms are extraordinarily fecund, each producing up to 240,000 eggs a day, which pass with the feces. Ascarid eggs, which are remarkably resistant to environmental stresses, become infective after several weeks of maturation in the soil and can remain infective for years. After infective eggs are swallowed, larvae hatched in the intestine invade the mucosa, migrate through the circulation to the lungs, break into the alveoli, ascend the bronchial tree, and return—through swallowing—to the small intestine, where they develop into adult worms. Between 2 and

3 months elapse between initial infection and egg production. Adult worms live for 1–2 years.

Epidemiology

Ascaris is widely distributed in tropical and subtropical regions as well as in other humid areas, including the rural southeastern United States. Transmission typically occurs through fecally contaminated soil and is due either to a lack of sanitary facilities or to the use of human feces as fertilizer. With their propensity for hand-to-mouth fecal carriage, younger children are most affected. Infection outside endemic areas, though uncommon, can occur when eggs on transported vegetables are ingested.

Clinical features

During the lung phase of larval migration, ~9–12 days after egg ingestion, patients may develop an irritating nonproductive cough and burning substernal discomfort that is aggravated by coughing or deep inspiration. Dyspnea and blood-tinged sputum are less common. Fever is usually reported. Eosinophilia develops during this symptomatic phase and subsides slowly over weeks. Chest x-rays may reveal evidence of eosinophilic pneumonitis (Löffler's syndrome), with rounded infiltrates a few millimeters to several centimeters in size. These infiltrates may be transient and intermittent, clearing after several weeks. Where there is seasonal transmission of the parasite, seasonal pneumonitis with eosinophilia may develop in previously infected and sensitized hosts.

In established infections, adult worms in the small intestine usually cause no symptoms. In heavy infections, particularly in children, a large bolus of entangled worms can cause pain and small-bowel obstruction, sometimes complicated by perforation, intussusception, or volvulus. Single worms may cause disease when they migrate into aberrant sites. A large worm can enter and occlude the biliary tree, causing biliary colic, cholecystitis, cholangitis, pancreatitis, or (rarely) intrahepatic abscesses. Migration of an adult worm up the esophagus can provoke coughing and oral expulsion of the worm. In highly endemic areas, intestinal and biliary ascariasis can rival acute appendicitis and gallstones as causes of surgical acute abdomen.

Laboratory findings

Most cases of ascariasis can be diagnosed by microscopic detection of characteristic *Ascaris* eggs (65 by 45 μm) in fecal samples. Occasionally, patients present after passing an adult worm—identifiable by its large size and smooth cream-colored surface—in the stool or through the mouth or nose. During the early transpulmonary migratory phase, when eosinophilic pneumonitis occurs, larvae can be found in sputum or gastric aspirates before diagnostic eggs appear in the stool. The eosinophilia that is prominent during this early stage usually decreases to minimal levels in established infection. Adult worms may be visualized, occasionally serendipitously, on contrast studies of the gastrointestinal tract. A plain abdominal film may reveal masses of worms in gas-filled loops of bowel in patients with intestinal obstruction. Pancreaticobiliary worms can be detected by ultrasound and endoscopic retrograde cholangiopancreatography; the latter method also has been used to extract biliary *Ascaris* worms.

TREATMENT **Ascariasis**

Ascariasis should always be treated to prevent potentially serious complications. Albendazole (400 mg once), mebendazole (100 g twice daily for 3 days or 500 mg once), or ivermectin (150–200 μg/kg once) is effective. These medications are contraindicated in pregnancy, however. Pyrantel pamoate (11 mg/kg once; maximum, 1 g) is safe in pregnancy. Nitazoxanide (7.5 mg/kg once; maximum, 500 mg) has also been used in ascariasis. Mild diarrhea and abdominal pain are uncommon side effects of these agents. Partial intestinal obstruction should be managed with nasogastric suction, IV fluid administration, and instillation of piperazine through the nasogastric tube, but complete obstruction and its severe complications require immediate surgical intervention.

HOOKWORM

Two hookworm species (*A. duodenale* and *N. americanus*) are responsible for human infections. Most infected individuals are asymptomatic. Hookworm disease develops from a combination of factors—a heavy worm burden, a prolonged duration of infection, and an inadequate iron intake—and results in iron-deficiency anemia and, on occasion, hypoproteinemia.

Life cycle

Adult hookworms, which are ~1 cm long, use buccal teeth (*Ancylostoma*) or cutting plates (*Necator*) to attach to the small-bowel mucosa and suck blood (0.2 mL/d per *Ancylostoma* adult) and interstitial fluid. The adult hookworms produce thousands of eggs daily. The eggs are deposited with feces in soil, where rhabditiform larvae hatch and develop over a 1-week period into infectious filariform larvae. Infective larvae penetrate the skin and reach the lungs by way of the bloodstream. There they invade alveoli and ascend the airways before being swallowed and reaching the small intestine. The prepatent period from skin invasion to appearance of eggs in the feces is ~6–8 weeks, but it may be longer with *A. duodenale*. Larvae of *A. duodenale*, if swallowed, can survive and develop directly in the intestinal mucosa. Adult hookworms may survive over a decade but usually live ~6–8 years for *A. duodenale* and 2–5 years for *N. americanus*.

Epidemiology

A. duodenale is prevalent in southern Europe, North Africa, and northern Asia, and *N. americanus* is the predominant species in the Western Hemisphere

and equatorial Africa. The two species overlap in many tropical regions, particularly Southeast Asia. In most areas, older children have the highest incidence and greatest intensity of hookworm infection. In rural areas where fields are fertilized with human feces, older working adults also may be heavily infected.

Clinical features

Most hookworm infections are asymptomatic. Infective larvae may provoke pruritic maculopapular dermatitis ("ground itch") at the site of skin penetration as well as serpiginous tracks of subcutaneous migration (similar to those of cutaneous larva migrans; Chap. 126) in previously sensitized hosts. Larvae migrating through the lungs occasionally cause mild transient pneumonitis, but this condition develops less frequently in hookworm infection than in ascariasis. In the early intestinal phase, infected persons may develop epigastric pain (often with postprandial accentuation), inflammatory diarrhea, or other abdominal symptoms accompanied by eosinophilia. The major consequence of chronic hookworm infection is iron deficiency. Symptoms are minimal if iron intake is adequate, but marginally nourished individuals develop symptoms of progressive iron-deficiency anemia and hypoproteinemia, including weakness and shortness of breath.

Laboratory findings

The diagnosis is established by the finding of characteristic 40- by 60-μm oval hookworm eggs in the feces. Stool-concentration procedures may be required to detect light infections. Eggs of the two species are indistinguishable by light microscopy. In a stool sample that is not fresh, the eggs may have hatched to release rhabditiform larvae, which need to be differentiated from those of *S. stercoralis*. Hypochromic microcytic anemia, occasionally with eosinophilia or hypoalbuminemia, is characteristic of hookworm disease.

TREATMENT **Hookworm Infection**

Hookworm infection can be eradicated with several safe and highly effective antihelminthic drugs, including albendazole (400 mg once), mebendazole (500 mg once), and pyrantel pamoate (11 mg/kg for 3 days). Mild iron-deficiency anemia can often be treated with oral iron alone. Severe hookworm disease with protein loss and malabsorption necessitates nutritional support and oral iron replacement along with deworming. There is some concern that the benzimidazoles (mebendazole and albendazole) are becoming less effective against human hookworms than in the past.

Ancylostoma caninum and *Ancylostoma braziliense*

A. caninum, the canine hookworm, has been identified as a cause of human eosinophilic enteritis, especially in northeastern Australia. In this zoonotic infection, adult hookworms attach to the small intestine (where they may be visualized by endoscopy) and elicit abdominal pain and intense local eosinophilia. Treatment with mebendazole (100 mg twice daily for 3 days) or albendazole (400 mg once) or endoscopic removal is effective. Both of these animal hookworm species can cause cutaneous larva migrans ("creeping eruption"; Chap. 126).

STRONGYLOIDIASIS

S. stercoralis is distinguished by its ability—unique among helminths (except for *Capillaria*; see later)—to replicate in the human host. This capacity permits ongoing cycles of autoinfection as infective larvae are internally produced. Strongyloidiasis can thus persist for decades without further exposure of the host to exogenous infective larvae. In immunocompromised hosts, large numbers of invasive *Strongyloides* larvae can disseminate widely and can be fatal.

Life cycle

In addition to a parasitic cycle of development, *Strongyloides* can undergo a free-living cycle of development in the soil **(Fig. 127-1)**. This adaptability facilitates the parasite's survival in the absence of mammalian hosts. Rhabditiform larvae passed in feces can transform into infectious filariform larvae either directly or after a free-living phase of development. Humans acquire strongyloidiasis when filariform larvae in fecally contaminated soil penetrate the skin or mucous membranes. The larvae then travel through the bloodstream to the lungs, where they break into the alveolar spaces, ascend the bronchial tree, are swallowed, and thereby reach the small intestine. There the larvae mature into adult worms that penetrate the mucosa of the proximal small bowel. The minute (2-mm-long) parasitic adult female worms reproduce by parthenogenesis; adult males do not exist. Eggs hatch in the intestinal mucosa, releasing rhabditiform larvae that migrate to the lumen and pass with the feces into soil. Alternatively, rhabditiform larvae in the bowel can develop directly into filariform larvae that penetrate the colonic wall or perianal skin and enter the circulation to repeat the migration that establishes ongoing internal reinfection. This autoinfection cycle allows strongyloidiasis to persist for decades.

Epidemiology

S. stercoralis is spottily distributed in tropical areas and other hot, humid regions and is particularly common in Southeast Asia, sub-Saharan Africa, and Brazil. In the United States, the parasite is endemic in parts of the Southeast and is found in immigrants, refugees, travelers, and military personnel who have lived in endemic areas.

Clinical features

In uncomplicated strongyloidiasis, many patients are asymptomatic or have mild cutaneous and/or abdominal symptoms. Recurrent urticaria, often involving the

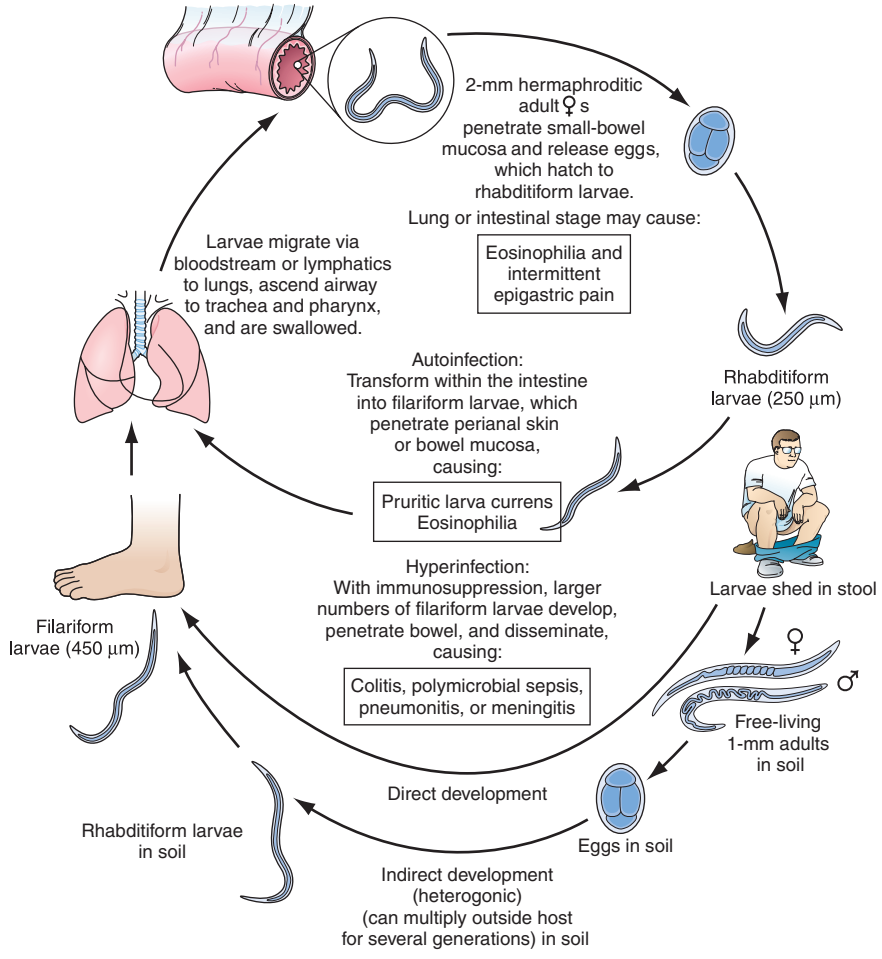


FIGURE 127-1
Life cycle of *Strongyloides stercoralis.* *(Adapted from Guerrant RL et al (eds): Tropical Infectious Diseases: Principles, Pathogens and Practice, 2nd ed, p 1276. © 2006, with permission from Elsevier Science.)*

buttocks and wrists, is the most common cutaneous manifestation. Migrating larvae can elicit a pathognomonic serpiginous eruption, *larva currens* ("running larva"). This pruritic, raised, erythematous lesion advances as rapidly as 10 cm/h along the course of larval migration. Adult parasites burrow into the duodenojejunal mucosa and can cause abdominal (usually midepigastric) pain, which resembles peptic ulcer pain except that it is aggravated by food ingestion. Nausea, diarrhea, gastrointestinal bleeding, mild chronic colitis, and weight loss can occur. Small-bowel obstruction may develop with early, heavy infection. Pulmonary symptoms are rare in uncomplicated strongyloidiasis. Eosinophilia is common, with levels fluctuating over time.

The ongoing autoinfection cycle of strongyloidiasis is normally constrained by unknown factors of the host's immune system. Abrogation of host immunity, especially with glucocorticoid therapy and much less commonly with other immunosuppressive medications, leads to hyperinfection, with the generation of large numbers of filariform larvae. Colitis, enteritis, or malabsorption may develop. In disseminated strongyloidiasis, larvae may invade not only gastrointestinal tissues and the lungs but also the central nervous system, peritoneum, liver, and kidneys. Moreover, bacteremia may develop because of the passage of enteric flora through disrupted mucosal barriers. Gram-negative sepsis, pneumonia, or meningitis may complicate or dominate the clinical course. Eosinophilia is often absent in severely infected patients. Disseminated strongyloidiasis, particularly in patients with unsuspected infection who are given glucocorticoids, can be fatal. Strongyloidiasis is a frequent complication of infection with human T cell lymphotropic virus type I, but disseminated strongyloidiasis is not common among patients infected with HIV-1.

Diagnosis

In uncomplicated strongyloidiasis, the finding of rhabditiform larvae in feces is diagnostic. Rhabditiform larvae are ~250 μm long, with a short buccal cavity that distinguishes them from hookworm larvae. In uncomplicated infections, few larvae are passed and single stool examinations detect only about one-third of cases. Serial examinations and the use of the agar plate detection method improve the sensitivity of stool diagnosis. In uncomplicated strongyloidiasis (but not in hyperinfection), stool examinations may be repeatedly negative.

Strongyloides larvae may also be found by sampling of the duodenojejunal contents by aspiration or biopsy. An enzyme-linked immunosorbent assay for serum antibodies to antigens of *Strongyloides* is a sensitive method of diagnosing uncomplicated infections. Such serologic testing should be performed for patients whose geographic histories indicate potential exposure, especially those who exhibit eosinophilia and/or are candidates for glucocorticoid treatment of other conditions. In disseminated strongyloidiasis, filariform larvae should be sought in stool as well as in samples obtained from sites of potential larval migration, including sputum, bronchoalveolar lavage fluid, or surgical drainage fluid.

TREATMENT Strongyloidiasis

Even in the asymptomatic state, strongyloidiasis must be treated because of the potential for subsequent fatal hyperinfection. Ivermectin (200 µg/kg daily for 2 days) is more effective than albendazole (400 mg daily for 3 days). For disseminated strongyloidiasis, treatment with ivermectin should be extended for at least 5–7 days or until the parasites are eradicated.

TRICHURIASIS

Most infections with *Trichuris trichiura* are asymptomatic, but heavy infections may cause gastrointestinal symptoms. Like the other soil-transmitted helminths, whipworm is distributed globally in the tropics and subtropics and is most common among poor children from resource-poor regions of the world.

Life cycle

Adult *Trichuris* worms reside in the colon and cecum, the anterior portions threaded into the superficial mucosa. Thousands of eggs laid daily by adult female worms pass with the feces and mature in the soil. After ingestion, infective eggs hatch in the duodenum, releasing larvae that mature before migrating to the large bowel. The entire cycle takes ~3 months, and adult worms may live for several years.

Clinical features

Tissue reactions to *Trichuris* are mild. Most infected individuals have no symptoms or eosinophilia. Heavy infections may result in abdominal pain, anorexia, and bloody or mucoid diarrhea resembling inflammatory bowel disease. Rectal prolapse can result from massive infections in children, who often suffer from malnourishment and other diarrheal illnesses. Moderately heavy *Trichuris* burdens also contribute to growth retardation.

Diagnosis and treatment

The characteristic 50- by 20-µm lemon-shaped *Trichuris* eggs are readily detected on stool examination. Adult worms, which are 3–5 cm long, are occasionally seen on proctoscopy. Mebendazole (500 mg once) or albendazole (400 mg daily for 3 doses) is safe and moderately effective for treatment, with cure rates of 70–90%. Ivermectin (200 µg/kg daily for 3 doses) is also safe but is not quite as efficacious as the benzimidazoles.

ENTEROBIASIS (PINWORM)

E. vermicularis is more common in temperate countries than in the tropics. In the United States, ~40 million persons are infected with pinworms, with a disproportionate number of cases among children.

Life cycle and epidemiology

Enterobius adult worms are ~1 cm long and dwell in the cecum. Gravid female worms migrate nocturnally into the perianal region and release up to 10,000 immature eggs each. The eggs become infective within hours and are transmitted by hand-to-mouth passage. From ingested eggs, larvae hatch and mature into adults. This life cycle takes ~1 month, and adult worms survive for ~2 months. Self-infection results from perianal scratching and transport of infective eggs on the hands or under the nails to the mouth. Because of the ease of person-to-person spread, pinworm infections are common among family members.

Clinical features

Most pinworm infections are asymptomatic. Perianal pruritus is the cardinal symptom. The itching, which is often worse at night as a result of the nocturnal migration of the female worms, may lead to excoriation and bacterial superinfection. Heavy infections have been claimed to cause abdominal pain and weight loss. On rare occasions, pinworms invade the female genital tract, causing vulvovaginitis and pelvic or peritoneal granulomas. Eosinophilia is uncommon.

Diagnosis

Since pinworm eggs are not released in feces, the diagnosis cannot be made by conventional fecal ova and parasite tests. Instead, eggs are detected by the application of clear cellulose acetate tape to the perianal region in the morning. After the tape is transferred to a slide, microscopic examination will detect pinworm eggs, which are oval, measure 55 by 25 µm, and are flattened along one side.

TREATMENT Enterobiasis

Infected children and adults should be treated with mebendazole (100 mg once), albendazole (400 mg once), or pyrantel pamoate (11 mg/kg once; maximum, 1 g), with the same treatment repeated after 2 weeks. Treatment of household members is advocated to eliminate asymptomatic reservoirs of potential reinfection.

TRICHOSTRONGYLIASIS

Trichostrongylus species, which are normally parasites of herbivorous animals, occasionally infect humans, particularly in Asia and Africa. Humans acquire the infection by accidentally ingesting *Trichostrongylus* larvae on contaminated leafy vegetables. The larvae do not migrate in humans but mature directly into adult worms in the small bowel. These worms ingest far less blood than hookworms; most infected persons are asymptomatic, but heavy infections may give rise to mild anemia and eosinophilia. *Trichostrongylus* eggs in stool examinations resemble those of hookworms but are larger (85 by 115 μm). Treatment consists of mebendazole or albendazole (Chap. 116).

ANISAKIASIS

Anisakiasis is a gastrointestinal infection caused by the accidental ingestion in uncooked saltwater fish of nematode larvae belonging to the family Anisakidae. The incidence of anisakiasis in the United States has increased as a result of the growing popularity of raw fish dishes. Most cases occur in Japan, the Netherlands, and Chile, where raw fish—sashimi, pickled green herring, and ceviche, respectively—are national culinary staples. Anisakid nematodes parasitize large sea mammals such as whales, dolphins, and seals. As part of a complex parasitic life cycle involving marine food chains, infectious larvae migrate to the musculature of a variety of fish. Both *Anisakis simplex* and *Pseudoterranova decipiens* have been implicated in human anisakiasis, but an identical gastric syndrome may be caused by the red larvae of eustrongylid parasites of fish-eating birds.

When humans consume infected raw fish, live larvae may be coughed up within 48 h. Alternatively, larvae may immediately penetrate the mucosa of the stomach. Within hours, violent upper abdominal pain accompanied by nausea and occasionally vomiting ensues, mimicking an acute abdomen. The diagnosis can be established by direct visualization on upper endoscopy, outlining of the worm by contrast radiographic studies, or histopathologic examination of extracted tissue. Extraction of the burrowing larvae during endoscopy is curative. In addition, larvae may pass to the small bowel, where they penetrate the mucosa and provoke a vigorous eosinophilic granulomatous response. Symptoms may appear 1–2 weeks after the infective meal, with intermittent abdominal pain, diarrhea, nausea, and fever resembling the manifestations of Crohn's disease. The diagnosis may be suggested by barium studies and confirmed by curative surgical resection of a granuloma in which the worm is embedded. Anisakid eggs are not found in the stool, since the larvae do not mature in humans. Serologic tests have been developed but are not widely available.

Anisakid larvae in saltwater fish are killed by cooking to 60°C, freezing at –20°C for 3 days, or commercial blast freezing, but not usually by salting, marinating, or cold smoking. No medical treatment is available; surgical or endoscopic removal should be undertaken.

CAPILLARIASIS

Intestinal capillariasis is caused by ingestion of raw fish infected with *Capillaria philippinensis*. Subsequent autoinfection can lead to a severe wasting syndrome. The disease occurs in the Philippines and Thailand and, on occasion, elsewhere in Asia. The natural cycle of *C. philippinensis* involves fish from fresh and brackish water. When humans eat infected raw fish, the larvae mature in the intestine into adult worms, which produce invasive larvae that cause intestinal inflammation and villus loss. Capillariasis has an insidious onset with nonspecific abdominal pain and watery diarrhea. If untreated, progressive autoinfection can lead to protein-losing enteropathy, severe malabsorption, and ultimately death from cachexia, cardiac failure, or superinfection. The diagnosis is established by identification of the characteristic peanut-shaped (20- by 40-μm) eggs on stool examination. Severely ill patients require hospitalization and supportive therapy in addition to prolonged antihelminthic treatment with albendazole (200 mg twice daily for 10 days; Chap. 116).

ABDOMINAL ANGIOSTRONGYLIASIS

Abdominal angiostrongyliasis is found in Latin America and Africa. The zoonotic parasite *Angiostrongylus costaricensis* causes eosinophilic ileocolitis after the ingestion of contaminated vegetation. *A. costaricensis* normally parasitizes the cotton rat and other rodents, with slugs and snails serving as intermediate hosts. Humans become infected by accidentally ingesting infective larvae in mollusk slime deposited on fruits and vegetables; children are at highest risk. The larvae penetrate the gut wall and migrate to the mesenteric artery, where they develop into adult worms. Eggs deposited in the gut wall provoke an intense eosinophilic granulomatous reaction, and adult worms may cause mesenteric arteritis, thrombosis, or frank bowel infarction. Symptoms may mimic those of appendicitis, including abdominal pain and tenderness, fever, vomiting, and a palpable mass in the right iliac fossa. Leukocytosis and eosinophilia are prominent. CT with contrast medium typically shows inflamed bowel, often with concomitant obstruction, but a definitive diagnosis is usually made surgically with partial bowel resection. Pathologic study reveals a thickened bowel wall with eosinophilic granulomas surrounding the *Angiostrongylus* eggs. In nonsurgical cases, the diagnosis rests solely on clinical grounds because larvae and eggs cannot be detected in the stool. Medical therapy for abdominal angiostrongyliasis is of uncertain efficacy. Careful observation and surgical resection for severe symptoms are the mainstays of treatment.

CHAPTER 128

FILARIAL AND RELATED INFECTIONS

Thomas B. Nutman ■ Peter F. Weller

Filarial worms are nematodes that dwell in the subcutaneous tissues and the lymphatics. Eight filarial species infect humans **(Table 128-1)**; of these, four—*Wuchereria bancrofti*, *Brugia malayi*, *Onchocerca volvulus*, and *Loa loa*—are responsible for most serious filarial infections. Filarial parasites, which infect an estimated 170 million persons worldwide, are transmitted by specific species of mosquitoes or other arthropods and have a complex life cycle, including infective larval stages carried by insects and adult worms that reside in either lymphatic or subcutaneous tissues of humans. The offspring of adults are microfilariae, which, depending on their species, are 200–250 μm long and 5–7 μm wide, may or may not be enveloped in a loose sheath, and either circulate in the blood or migrate through the skin (Table 128-1). To complete the life cycle, microfilariae are ingested by the arthropod vector and develop over 1–2 weeks into new infective larvae. Adult worms live for many years, whereas microfilariae survive for 3–36 months. The *Rickettsia*-like endosymbiont *Wolbachia* has been found intracellularly in all stages of *Brugia*, *Wuchereria*, *Mansonella*, and *Onchocerca* and has become a target for antifilarial chemotherapy.

Usually, infection is established only with repeated, prolonged exposures to infective larvae. Since the clinical manifestations of filarial diseases develop relatively slowly, these infections should be considered to induce chronic diseases with possible long-term debilitating effects. In terms of the nature, severity, and timing of clinical manifestations, patients with filarial infections who are native to endemic areas and have lifelong exposure may differ significantly from those who are travelers or who have recently moved to these areas. Characteristically, filarial disease is more acute and intense in newly exposed individuals than in natives of endemic areas.

LYMPHATIC FILARIASIS

Lymphatic filariasis is caused by *W. bancrofti*, *B. malayi*, or *B. timori*. The threadlike adult parasites reside in lymphatic channels or lymph nodes, where they may remain viable for more than two decades.

EPIDEMIOLOGY

W. bancrofti, the most widely distributed filarial parasite of humans, affects an estimated 110 million people and is found throughout the tropics and subtropics, including Asia and the Pacific Islands, Africa, areas of South America, and the Caribbean basin. Humans are the only definitive host for the parasite. Generally, the subperiodic form is found only in the Pacific Islands; elsewhere, *W. bancrofti* is nocturnally periodic. (Nocturnally periodic forms of microfilariae are scarce in peripheral blood by day and increase at night, whereas subperiodic forms are present in peripheral blood at all times and reach maximal levels in the afternoon.) Natural vectors for *W. bancrofti* are *Culex fatigans* mosquitoes in urban settings and anopheline or aedean mosquitoes in rural areas.

Brugian filariasis due to *B. malayi* occurs primarily in eastern India, Indonesia, Malaysia, and the Philippines. *B. malayi* also has two forms distinguished by the periodicity of microfilaremia. The more common nocturnal form is transmitted in areas of coastal rice fields, while the subperiodic form is found in forests. *B. malayi* naturally infects cats as well as humans. The distribution of *B. timori* is limited to the islands of southeastern Indonesia.

PATHOLOGY

The principal pathologic changes result from inflammatory damage to the lymphatics, which is typically caused by adult worms and not by microfilariae. Adult worms live in afferent lymphatics or sinuses of lymph nodes and cause lymphatic dilatation and thickening of the vessel walls. The infiltration of plasma cells, eosinophils, and macrophages in and around the infected vessels, along with endothelial and connective tissue proliferation, leads to tortuosity of the lymphatics and damaged or incompetent lymph valves. Lymphedema and chronic stasis changes with hard or brawny edema develop in the overlying skin. These consequences of

TABLE 128-1

CHARACTERISTICS OF THE FILARIAE

ORGANISM	PERIODICITY	DISTRIBUTION	VECTOR	LOCATION OF ADULT	MICROFILARIAL LOCATION	SHEATH
Wuchereria bancrofti	Nocturnal	Cosmopolitan areas worldwide, including South America, Africa, southern Asia, Papua New Guinea, China, Indonesia	*Culex, Anopheles* (mosquitoes)	Lymphatic tissue	Blood	+
	Subperiodic	Eastern Pacific	*Aedes* (mosquitoes)	Lymphatic tissue	Blood	+
Brugia malayi	Nocturnal	Southeast Asia, Indonesia, India	*Mansonia*, *Anopheles* (mosquitoes)	Lymphatic tissue	Blood	+
	Subperiodic	Indonesia, Southeast Asia	*Coquillettidia*, *Mansonia* (mosquitoes)	Lymphatic tissue	Blood	+
B. timori	Nocturnal	Indonesia	*Anopheles* (mosquitoes)	Lymphatic tissue	Blood	+
Loa loa	Diurnal	West and Central Africa	*Chrysops* (deerflies)	Subcutaneous tissue	Blood	+
Onchocerca volvulus	None	South and Central America, Africa	*Simulium* (blackflies)	Subcutaneous tissue	Skin, eye	–
Mansonella ozzardi	None	South and Central America Caribbean	*Culicoides* (midges) *Simulium* (blackflies)	Undetermined site	Blood	–
M. perstans	None	South and Central America, Africa	*Culicoides* (midges)	Body cavities, mesentery, perirenal tissue	Blood	–
M. streptocerca	None	West and Central Africa	*Culicoides* (midges)	Subcutaneous tissue	Skin	–

filarial infection are due both to the direct effects of the worms and to the host's inflammatory response to the parasite. Inflammatory responses are believed to cause the granulomatous and proliferative processes that precede total lymphatic obstruction. It is thought that the lymphatic vessel remains patent as long as the worm remains viable and that the death of the worm leads to enhanced granulomatous reaction and fibrosis. Lymphatic obstruction results, and, despite collateralization of the lymphatics, lymphatic function is compromised.

CLINICAL FEATURES

The most common presentations of the lymphatic filariases are asymptomatic (or subclinical) microfilaremia, hydrocele **(Fig. 128-1)**, acute adenolymphangitis (ADL), and chronic lymphatic disease. In areas where *W. bancrofti* or *B. malayi* is endemic, the overwhelming majority of infected individuals have few overt clinical manifestations of filarial infection despite large numbers of circulating microfilariae in the peripheral blood. Although they may be clinically asymptomatic, virtually all persons with *W. bancrofti* or *B. malayi* microfilaremia have some degree of subclinical disease that includes microscopic hematuria and/or proteinuria, dilated (and tortuous) lymphatics (visualized by imaging), and—in men with *W. bancrofti* infection—scrotal lymphangiectasia (detectable by ultrasound). In spite of these findings, the majority of individuals appear to remain clinically asymptomatic for years; in relatively few does the infection progress to either acute or chronic disease.

ADL is characterized by high fever, lymphatic inflammation (lymphangitis and lymphadenitis), and transient local edema. The lymphangitis is retrograde,

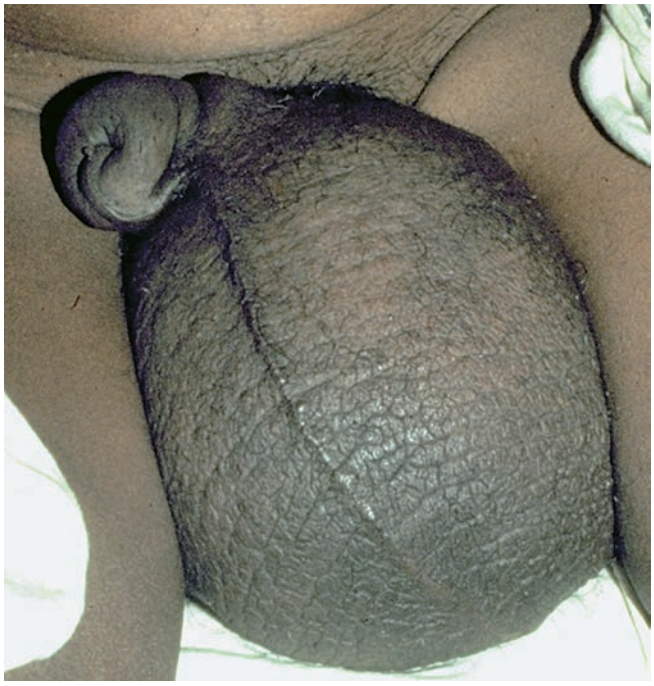


FIGURE 128-1
Hydrocele associated with *Wuchereria bancrofti* infection.

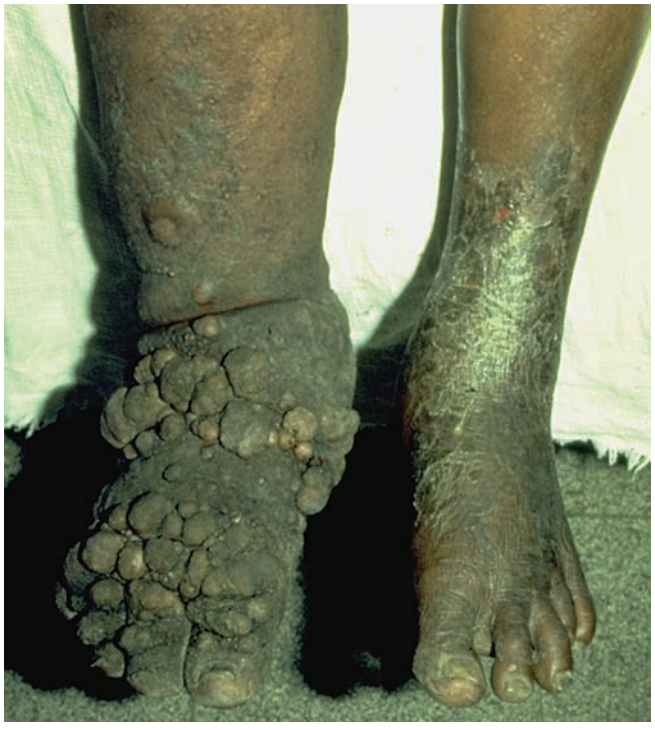


FIGURE 128-2
Elephantiasis of the lower extremity associated with *Wuchereria bancrofti* infection.

extending peripherally from the lymph node draining the area where the adult parasites reside. Regional lymph nodes are often enlarged, and the entire lymphatic channel can become indurated and inflamed. Concomitant local thrombophlebitis can occur as well. In brugian filariasis, a single local abscess may form along the involved lymphatic tract and subsequently rupture to the surface. The lymphadenitis and lymphangitis can involve both the upper and lower extremities in both bancroftian and brugian filariasis, but involvement of the genital lymphatics occurs almost exclusively with *W. bancrofti* infection. This genital involvement can be manifested by funiculitis, epididymitis, and scrotal pain and tenderness. In endemic areas, another type of acute disease—dermatolymphangioadenitis (DLA)—is recognized as a syndrome that includes high fever, chills, myalgias, and headache. Edematous inflammatory plaques clearly demarcated from normal skin are seen. Vesicles, ulcers, and hyperpigmentation may also be noted. There is often a history of trauma, burns, radiation, insect bites, punctiform lesions, or chemical injury. Entry lesions, especially in the interdigital area, are common. DLA is often diagnosed as cellulitis.

If lymphatic damage progresses, transient lymphedema can develop into lymphatic obstruction and the permanent changes associated with elephantiasis **(Fig. 128-2)**. Brawny edema follows early pitting edema, and thickening of the subcutaneous tissues and hyperkeratosis occur. Fissuring of the skin develops, as do hyperplastic changes. Superinfection of these poorly vascularized tissues becomes a problem. In bancroftian filariasis, in which genital involvement is common, hydroceles may develop (Fig. 128-1); in advanced stages, this condition may evolve into scrotal lymphedema and scrotal elephantiasis. Furthermore, if there is obstruction of the retroperitoneal lymphatics, increased renal lymphatic pressure leads to rupture of the renal lymphatics and the development of chyluria, which is usually intermittent and most prominent in the morning.

The clinical manifestations of filarial infections in travelers or transmigrants who have recently entered an endemic region are distinctive. Given a sufficient number of bites by infected vectors, usually over a 3- to 6-month period, recently exposed patients can develop acute lymphatic or scrotal inflammation with or without urticaria and localized angioedema. Lymphadenitis of epitrochlear, axillary, femoral, or inguinal lymph nodes is often followed by retrogradely evolving lymphangitis. Acute attacks are short-lived and are not usually accompanied by fever. With prolonged exposure to infected mosquitoes, these attacks, if untreated, become more severe and lead to permanent lymphatic inflammation and obstruction.

DIAGNOSIS

A definitive diagnosis can be made only by detection of the parasites and hence can be difficult. Adult worms localized in lymphatic vessels or nodes are

largely inaccessible. Microfilariae can be found in blood, in hydrocele fluid, or (occasionally) in other body fluids. Such fluids can be examined microscopically, either directly or—for greater sensitivity—after concentration of the parasites by the passage of fluid through a polycarbonate cylindrical-pore filter (pore size, 3 μm) or by the centrifugation of fluid fixed in 2% formalin (Knott's concentration technique). The timing of blood collection is critical and should be based on the periodicity of the microfilariae in the endemic region involved. Many infected individuals do not have microfilaremia, and definitive diagnosis in such cases can be difficult. Assays for circulating antigens of *W. bancrofti* permit the diagnosis of microfilaremic and cryptic (amicrofilaremic) infection. Two tests are commercially available: an enzyme-linked immunosorbent assay (ELISA) and a rapid-format immunochromatographic card test. Both assays have sensitivities of 93–100% and specificities approaching 100%. There are currently no tests for circulating antigens in brugian filariasis.

Polymerase chain reaction (PCR)-based assays for DNA of *W. bancrofti* and *B. malayi* in blood have been developed. A number of studies indicate that the sensitivity of this diagnostic method is equivalent to or greater than that of parasitologic methods.

In cases of suspected lymphatic filariasis, examination of the scrotum, the lymph nodes, or (in female patients) the breast by means of high-frequency ultrasound in conjunction with Doppler techniques may result in the identification of motile adult worms within dilated lymphatics. Worms may be visualized in the lymphatics of the spermatic cord in up to 80% of men infected with *W. bancrofti*. Live adult worms have a distinctive pattern of movement within the lymphatic vessels (termed the *filaria dance sign*). Radionuclide lymphoscintigraphic imaging of the limbs reliably demonstrates widespread lymphatic abnormalities in both subclinical microfilaremic persons and those with clinical manifestations of lymphatic pathology. While of potential utility in the delineation of anatomic changes associated with infection, lymphoscintigraphy is unlikely to assume primacy in the diagnostic evaluation of individuals with suspected infection; it is principally a research tool, although it has been used more widely for assessment of lymphedema of any cause. Eosinophilia and elevated serum concentrations of IgE and antifilarial antibody support the diagnosis of lymphatic filariasis. There is, however, extensive cross-reactivity between filarial antigens and antigens of other helminths, including the common intestinal roundworms; thus, interpretations of serologic findings can be difficult. In addition, residents of endemic areas can become sensitized to filarial antigens (and thus be serologically positive) through exposure to infected mosquitoes without having patent filarial infections.

The ADL associated with lymphatic filariasis must be distinguished from thrombophlebitis, infection, and trauma. Retrograde evolution is a characteristic feature that helps distinguish filarial lymphangitis from ascending bacterial lymphangitis. Chronic filarial lymphedema must also be distinguished from the lymphedema of malignancy, postoperative scarring, trauma, chronic edematous states, and congenital lymphatic system abnormalities.

TREATMENT Lymphatic Filariasis

With newer definitions of clinical syndromes in lymphatic filariasis and new tools to assess clinical status (e.g., ultrasound, lymphoscintigraphy, circulating filarial antigen assays, PCR), approaches to treatment based on infection status can be considered.

Diethylcarbamazine [(DEC), 6 mg/kg daily for 12 days], which has both macro- and microfilaricidal properties, remains the drug of choice for the treatment of active lymphatic filariasis (defined by microfilaremia, antigen positivity, or adult worms on ultrasound), although albendazole (400 mg twice daily for 21 days) has also demonstrated macrofilaricidal efficacy. A 4- to 6-week course of doxycycline (targeting the intracellular *Wolbachia*) also has significant macrofilaricidal activity, as has DEC/albendazole used daily for 7 days. The addition of DEC to a 3-week course of doxycycline has recently been shown to be efficacious in lymphatic filariasis.

Regimens that combine single doses of albendazole (400 mg) with either DEC (6 mg/kg) or ivermectin (200 μg/kg) all have a sustained microfilaricidal effect and are the mainstay of programs for the eradication of lymphatic filariasis in Africa (albendazole/ivermectin) and elsewhere (albendazole/DEC) (see "Prevention and Control").

As has already been mentioned, a growing body of evidence indicates that, although they may be asymptomatic, virtually all persons with *W. bancrofti* or *B. malayi* microfilaremia have some degree of subclinical disease (hematuria, proteinuria, abnormalities on lymphoscintigraphy). Thus, early treatment of asymptomatic persons is recommended to prevent further lymphatic damage. For ADL, supportive treatment (including the administration of antipyretics and analgesics) is recommended, as is antibiotic therapy if secondary bacterial infection is likely. Similarly, because lymphatic disease is associated with the presence of adult worms, treatment with DEC is recommended for microfilaria-negative carriers of adult worms.

In persons with chronic manifestations of lymphatic filariasis, treatment regimens that emphasize hygiene, prevention of secondary bacterial infections, and physiotherapy have gained wide acceptance for morbidity control. These regimens are similar to those recommended for lymphedema of most nonfilarial causes and known by a variety of names, including *complex decongestive physiotherapy* and *complex lymphedema therapy*. Hydroceles (Fig. 128-1) can be managed surgically. With chronic manifestations of lymphatic filariasis, drug treatment should be reserved for individuals with evidence of active infection.

Side effects of DEC treatment include fever, chills, arthralgias, headaches, nausea, and vomiting. Both the development and the severity of these reactions are directly related to the number of microfilariae circulating in the bloodstream. The adverse reactions may represent either an acute hypersensitivity reaction to the antigens being released by dead and dying parasites or an inflammatory reaction induced by the intracellular *Wolbachia* endosymbionts freed from their intracellular niche.

Ivermectin has a side effect profile similar to that of DEC when used in lymphatic filariasis. In patients infected with *L. loa*, who have high levels of *Loa* microfilaremia, DEC—like ivermectin (see "Loiasis," later in the chapter)—can elicit severe encephalopathic complications. When used in single-dose regimens for the treatment of lymphatic filariasis, albendazole is associated with relatively few side effects.

PREVENTION AND CONTROL

To protect themselves against filarial infection, individuals must avoid contact with infected mosquitoes by using personal protective measures including bed nets, particularly those impregnated with insecticides such as permethrin. Community-based intervention is the current approach to elimination of lymphatic filariasis as a public health problem. The underlying tenet of this approach is that mass annual distribution of antimicrofilarial chemotherapy—albendazole with either DEC (for all areas except those where onchocerciasis is coendemic; see section on onchocerciasis treatment, later in the chapter) or ivermectin—will profoundly suppress microfilaremia. If the suppression is sustained, then transmission can be interrupted.

Created by the World Health Organization in 1997, the Global Programme to Eliminate Lymphatic Filariasis is based on mass administration of single annual doses of DEC plus albendazole in non-African regions and of albendazole plus ivermectin in Africa. Available information at the end of 2008 indicated that >695 million persons in 51 countries had thus far participated. Not only has lymphatic filariasis been eliminated in some defined areas, but collateral benefits—avoidance of disability and treatment of intestinal helminths and other conditions (e.g., scabies and louse infestation)—have also been noted. The strategy of the global program is being refined, and attempts are being made to integrate this effort with other mass-treatment strategies (e.g., deworming programs, malaria control, and trachoma control).

TROPICAL PULMONARY EOSINOPHILIA

Tropical pulmonary eosinophilia (TPE) is a distinct syndrome that develops in some individuals infected with the lymphatic-dwelling filarial species. This syndrome affects males and females in a ratio of 4:1, often during the third decade of life. The majority of cases have been reported from India, Pakistan, Sri Lanka, Brazil, Guyana, and Southeast Asia.

CLINICAL FEATURES

The main features include a history of residence in filarial-endemic regions, paroxysmal cough and wheezing (usually nocturnal and probably related to the nocturnal periodicity of microfilariae), weight loss, low-grade fever, lymphadenopathy, and pronounced blood eosinophilia (>3000 eosinophils/μL). Chest x-rays or CT scans may be normal but generally show increased bronchovascular markings. Diffuse miliary lesions or mottled opacities may be present in the middle and lower lung fields. Tests of pulmonary function show restrictive abnormalities in most cases and obstructive defects in half. Characteristically, total serum IgE levels (10,000–100,000 ng/mL) and antifilarial antibody titers are markedly elevated.

PATHOLOGY

In TPE, microfilariae and parasite antigens are rapidly cleared from the bloodstream by the lungs. The clinical symptoms result from allergic and inflammatory reactions elicited by the cleared parasites. In some patients, trapping of microfilariae in other reticuloendothelial organs can cause hepatomegaly, splenomegaly, or lymphadenopathy. A prominent, eosinophil-enriched, intraalveolar infiltrate is often reported, and with it comes the release of cytotoxic proinflammatory eosinophil granule proteins that may mediate some of the pathology seen in TPE. In the absence of successful treatment, interstitial fibrosis can lead to progressive pulmonary damage.

DIFFERENTIAL DIAGNOSIS

TPE must be distinguished from asthma, Löffler's syndrome, allergic bronchopulmonary aspergillosis, allergic granulomatosis with angiitis (Churg-Strauss syndrome), the systemic vasculitides (most notably periarteritis nodosa and granulomatosis with polyangiitis [Wegener's]), chronic eosinophilic pneumonia, and the idiopathic hypereosinophilic syndrome.

TREATMENT Tropical Pulmonary Eosinophilia

DEC is used at a daily dosage of 4–6 mg/kg for 14 days. Symptoms usually resolve within 3–7 days after the initiation of therapy. Relapse, which occurs in ~12–25% of cases (sometimes after an interval of years), requires re-treatment.

ONCHOCERCIASIS

EPIDEMIOLOGY

Onchocerciasis ("river blindness") is caused by the filarial nematode *O. volvulus*, which infects an estimated 37 million individuals in 35 countries worldwide. The majority of individuals infected with *O. volvulus* live in the equatorial region of Africa extending from the Atlantic coast to the Red Sea. In the Americas, isolated foci have been identified in Mexico, Guatemala, Colombia, Ecuador, Venezuela, and Brazil. The infection is also found in Yemen.

ETIOLOGY

Infection in humans begins with the deposition of infective larvae on the skin by the bite of an infected blackfly. The larvae develop into adults, which are typically found in subcutaneous nodules. About 7 months to 3 years after infection, the gravid female releases microfilariae that migrate out of the nodule and throughout the tissues, concentrating in the dermis. Infection is transmitted to other persons when a female fly ingests microfilariae from the host's skin and these microfilariae then develop into infective larvae. Adult *O. volvulus* females and males are ~40–60 cm and ~3–6 cm in length, respectively. The life span of adults can be as long as 18 years, with an average of ~9 years. Because the blackfly vector breeds along free-flowing rivers and streams (particularly in rapids) and generally restricts its flight to an area within several kilometers of these breeding sites, both biting and disease transmission are most intense in these locations.

PATHOLOGY

Onchocerciasis primarily affects the skin, eyes, and lymph nodes. In contrast to the pathology in lymphatic filariasis, the damage in onchocerciasis is elicited by microfilariae and not by adult parasites. In the skin, there are mild but chronic inflammatory changes that can result in loss of elastic fibers, atrophy, and fibrosis. The subcutaneous nodules, or onchocercomata, consist primarily of fibrous tissues surrounding the adult worm, often with a peripheral ring of inflammatory cells (characterized as lymphatic in origin) surrounded by an endothelial layer. In the eye, neovascularization and corneal scarring lead to corneal opacities and blindness. Inflammation in the anterior and posterior chambers frequently results in anterior uveitis, chorioretinitis, and optic atrophy. Although punctate opacities are due to an inflammatory reaction surrounding dead or dying microfilariae, the pathogenesis of most manifestations of onchocerciasis is still unclear.

CLINICAL FEATURES

Skin

Pruritus and rash are the most common manifestations of onchocerciasis. The pruritus can be incapacitating; the rash is typically a papular eruption **(Fig. 128-3)** that is generalized rather than localized to a particular region of the body. Long-term infection results in exaggerated and premature wrinkling of the skin, loss of elastic fibers, and epidermal atrophy that can lead to loose, redundant skin and hypo- or hyperpigmentation. Localized eczematoid dermatitis can cause hyperkeratosis, scaling, and pigmentary changes. In an immunologically hyperreactive form of onchodermatitis (commonly termed *sowdah* or localized onchodermatitis), the affected skin darkens as a consequence of the profound inflammation that occurs as microfilariae in the skin are cleared.

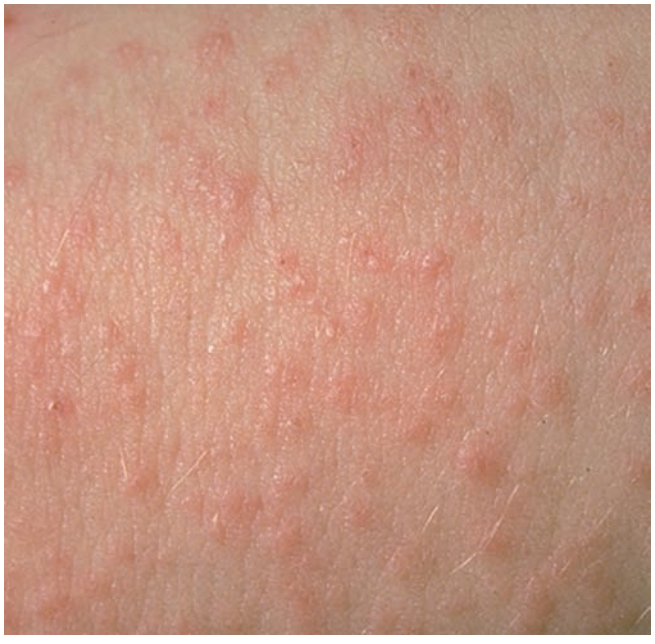


FIGURE 128-3
Papular eruption as a consequence of onchocerciasis.

Onchocercomata

These subcutaneous nodules, which can be palpable and/or visible, contain the adult worm. In African patients, they are common over the coccyx and sacrum, the trochanter of the femur, the lateral anterior crest, and other bony prominences; in patients from South and Central America, nodules tend to develop preferentially in the upper part of the body, particularly on the head, neck, and shoulders. Nodules vary in size and characteristically are firm and not tender. It has been estimated that, for every palpable nodule, there are four deeper nonpalpable ones.

Ocular tissue

Visual impairment is the most serious complication of onchocerciasis and usually affects only those persons with moderate or heavy infections. Lesions may develop in all parts of the eye. The most common early finding is conjunctivitis with photophobia. Punctate keratitis—acute

inflammatory reactions surrounding dying microfilariae and manifested as "snowflake" opacities—is common among younger patients and resolves without apparent complications.

Sclerosing keratitis occurs in 1–5% of infected persons and is the leading cause of onchocercal blindness in Africa. Anterior uveitis and iridocyclitis develop in ~5% of infected persons in Africa. In Latin America, complications of the anterior uveal tract (pupillary deformity) may cause secondary glaucoma. Characteristic chorioretinal lesions develop as a result of atrophy and hyperpigmentation of the retinal pigment epithelium. Constriction of the visual fields and overt optic atrophy may occur.

Lymph nodes

Mild to moderate lymphadenopathy is common, particularly in the inguinal and femoral areas, where the enlarged nodes may hang down in response to gravity ("hanging groin"), sometimes predisposing to inguinal and femoral hernias.

Systemic manifestations

Some heavily infected individuals develop cachexia with loss of adipose tissue and muscle mass. Among adults who become blind, there is a three- to fourfold increase in the mortality rate.

DIAGNOSIS

Definitive diagnosis depends on the detection of an adult worm in an excised nodule or, more commonly, of microfilariae in a skin snip. Skin snips are obtained with a corneal-scleral punch, which collects a blood-free skin biopsy sample extending to just below the epidermis, or by lifting of the skin with the tip of a needle and excision of a small (1- to 3-mm) piece with a sterile scalpel blade. The biopsy tissue is incubated in tissue culture medium or in saline on a glass slide or flat-bottomed microtiter plate. After incubation for 2–4 h (or occasionally overnight in light infections), microfilariae emergent from the skin can be seen by low-power microscopy.

Eosinophilia and elevated serum IgE levels are common but, because they occur in many parasitic infections, are not diagnostic in themselves. Assays to detect specific antibodies to *Onchocerca* and PCR to detect onchocercal DNA in skin snips are used in specialized laboratories and are highly sensitive and specific.

TREATMENT

The main goals of therapy are to prevent the development of irreversible lesions and to alleviate symptoms. Surgical excision is recommended when nodules are located on the head (because of the proximity of microfilaria-producing adult worms to the eye), but chemotherapy is the mainstay of management. Ivermectin, a semisynthetic macrocyclic lactone active against microfilariae, is the first-line agent for the treatment of onchocerciasis. It is given orally in a single dose of 150 μg/kg, either yearly or semiannually. Recently, more frequent ivermectin administration (every 3 months) has been suggested to ameliorate pruritus and skin disease. Moreover, quadrennial administration of ivermectin has some macrofilaricidal activity.

After treatment, most individuals have few or no reactions. Pruritus, cutaneous edema, and/or maculopapular rash occurs in ~1–10% of treated individuals. In areas of Africa coendemic for *O. volvulus* and *L. loa*, however, ivermectin is contraindicated (as it is for pregnant or breast-feeding women) because of severe posttreatment encephalopathy seen in patients, especially children, who are heavily microfilaremic for *L. loa* (>2000–5000 microfilariae/mL). Although ivermectin treatment results in a marked drop in microfilarial density, its effect can be short-lived (<3 months in some cases). Thus, it is occasionally necessary to give ivermectin more frequently for persistent symptoms.

A 6-week course of doxycycline is macrofilaristatic, rendering female adult worms sterile for long periods. Because this agent targets the *Wolbachia* endosymbiont of the filarial parasite, new approaches for definitive treatment (i.e., cure) may become available.

PREVENTION

Vector control has been beneficial in highly endemic areas in which breeding sites are vulnerable to insecticide spraying, but most areas endemic for onchocerciasis are not suited to this type of control. Community-based administration of ivermectin every 6–12 months is being used to interrupt transmission in endemic areas. This measure, in conjunction with vector control, has already helped reduce the prevalence of disease in endemic foci in Africa and Latin America. No drug has proved useful for prophylaxis of *O. volvulus* infection.

LOIASIS

ETIOLOGY AND EPIDEMIOLOGY

Loiasis is caused by *L. loa* (the African eye worm), which is present in the rain forests of West and Central Africa. Adult parasites (females, 50–70 mm long and 0.5 mm wide; males, 25–35 mm long and 0.25 mm wide) live in subcutaneous tissues. Microfilariae circulate in the blood with a diurnal periodicity that peaks between 12:00 noon and 2:00 p.m.

CLINICAL FEATURES

Manifestations of loiasis in natives of endemic areas may differ from those in temporary residents or visitors. Among the indigenous population, loiasis is often an asymptomatic infection with microfilaremia. Infection may be

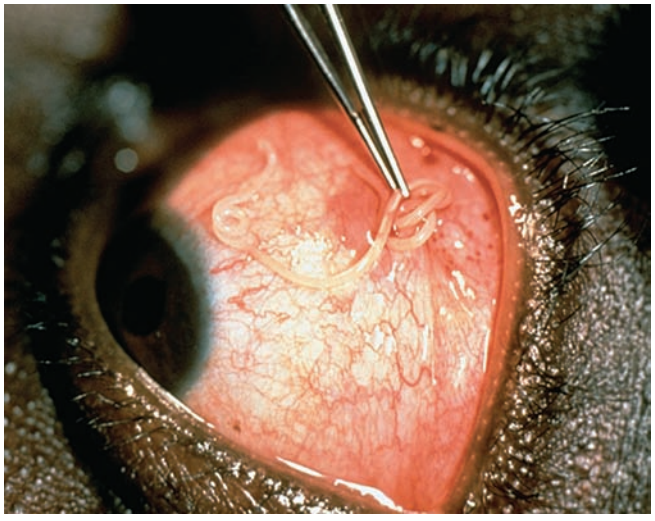


FIGURE 128-4
Adult *Loa loa* being surgically removed after its subconjunctival migration.

recognized only after subconjunctival migration of an adult worm (Fig. 128-4) or may be manifested by episodic Calabar swellings—evanescent localized areas of angioedema and erythema developing on the extremities and less frequently at other sites. Nephropathy, encephalopathy, and cardiomyopathy can occur but are rare. In patients who are not residents of endemic areas, allergic symptoms predominate, episodes of Calabar swelling tend to be more frequent and debilitating, microfilaremia is less common, and eosinophilia and increased levels of antifilarial antibodies are characteristic.

PATHOLOGY

The pathogenesis of the manifestations of loiasis is poorly understood. Calabar swellings are thought to result from a hypersensitivity reaction to adult worm antigens.

DIAGNOSIS

Definitive diagnosis of loiasis requires the detection of microfilariae in the peripheral blood or the isolation of the adult worm from the eye (Fig. 128-4) or from a subcutaneous biopsy specimen from a site of swelling developing after treatment. PCR-based assays for the detection of *L. loa* DNA in blood are available in specialized laboratories and are highly sensitive and specific, as are some newer recombinant antigen–based serologic techniques. In practice, the diagnosis must often be based on a characteristic history and clinical presentation, blood eosinophilia, and elevated levels of antifilarial antibodies, particularly in travelers to an endemic region, who are usually amicrofilaremic. Other clinical findings in the travelers include hypergammaglobulinemia, elevated levels of serum IgE, and elevated leukocyte and eosinophil counts.

TREATMENT **Loiasis**

DEC (8–10 mg/kg per day for 21 days) is effective against both the adult and the microfilarial forms of *L. loa*, but multiple courses are frequently necessary before loiasis resolves completely. In cases of heavy microfilaremia, allergic or other inflammatory reactions can take place during treatment, including central nervous system involvement with coma and encephalitis. Heavy infections can be treated initially with apheresis to remove the microfilariae and with glucocorticoids (40–60 mg of prednisone per day) followed by doses of DEC (0.5 mg/kg per day). If antifilarial treatment has no adverse effects, the prednisone dose can be rapidly tapered and the dose of DEC gradually increased to 8–10 mg/kg per day.

Albendazole or ivermectin is effective in reducing microfilarial loads, although neither is approved for this purpose by the U.S. Food and Drug Administration. Moreover, ivermectin is contraindicated in patients with >5000 microfilariae/mL because this drug has been associated with >1200 deaths in heavily infected patients with loiasis in West and Central Africa. DEC (300 mg weekly) is an effective prophylactic regimen for loiasis.

STREPTOCERCIASIS

Mansonella streptocerca, found mainly in the tropical forest belt of Africa from Ghana to the Democratic Republic of the Congo, is transmitted by biting midges. The major clinical manifestations involve the skin and include pruritus, papular rashes, and pigmentation changes. Many infected individuals have inguinal adenopathy, although most are asymptomatic. The diagnosis is made by detection of the characteristic microfilariae in skin snips. Ivermectin at a single dose of 150 μg/kg leads to sustained suppression of microfilariae in the skin and is probably the treatment of choice for streptocerciasis.

MANSONELLA PERSTANS INFECTION

M. perstans, distributed across the center of Africa and in northeastern South America, is transmitted by midges. Adult worms reside in serous cavities—pericardial, pleural, and peritoneal—as well as in the mesentery and the perirenal and retroperitoneal tissues. Microfilariae circulate in the blood without periodicity. The clinical and pathologic features of the infection are poorly defined. Most patients appear to be asymptomatic, but manifestations may include transient angioedema and pruritus of the arms, face, or other

parts of the body (analogous to the Calabar swellings of loiasis); fever; headache; arthralgias; and right-upper-quadrant pain. Occasionally, pericarditis and hepatitis occur. The diagnosis is based on the demonstration of microfilariae in blood or serosal effusions. Perstans filariasis is often associated with peripheral-blood eosinophilia and antifilarial antibody elevations.

With the identification of a *Wolbachia* endosymbiont in *M. perstans*, doxycycline (200 mg twice a day) for 6 weeks has been established as the first effective treatment for this infection.

MANSONELLA OZZARDI INFECTION

The distribution of *M. ozzardi* is restricted to Central and South America and certain Caribbean islands. Adult worms are rarely recovered from humans. Microfilariae circulate in the blood without periodicity. Although this organism has often been considered nonpathogenic, headache, articular pain, fever, pulmonary symptoms, adenopathy, hepatomegaly, pruritus, and eosinophilia have been ascribed to *M. ozzardi* infection. The diagnosis is made by detection of microfilariae in peripheral blood. Ivermectin (a single dose of 6 mg) is effective in treating this infection.

DRACUNCULIASIS (GUINEA WORM INFECTION)

ETIOLOGY AND EPIDEMIOLOGY

The incidence of dracunculiasis, caused by *Dracunculus medinensis*, has declined dramatically because of global eradication efforts. Current estimates suggest that there are slightly more than 3000 cases worldwide; the infection is endemic only in Ethiopia, Ghana, Mali, Niger, Nigeria, and Sudan. Asia has now been deemed dracunculiasis-free.

Humans acquire *D. medinensis* when they ingest water containing infective larvae derived from *Cyclops*, a crustacean that is the intermediate host. Larvae penetrate the stomach or intestinal wall, mate, and mature. The adult male probably dies; the female worm develops over a year and migrates to subcutaneous tissues, usually in the lower extremity. As the thin female worm, ranging in length from 30 cm to 1 m, approaches the skin, a blister forms that, over days, breaks down and forms an ulcer. When the blister opens, large numbers of motile, rhabditiform larvae can be released into stagnant water; ingestion by *Cyclops* completes the life cycle.

CLINICAL FEATURES

Few or no clinical manifestations of dracunculiasis are evident until just before the blister forms, when there is an onset of fever and generalized allergic symptoms, including periorbital edema, wheezing, and urticaria. The emergence of the worm is associated with local pain and swelling. When the blister ruptures (usually as a result of immersion in water) and the adult worm releases larva-rich fluid, symptoms are relieved. The shallow ulcer surrounding the emerging adult worm heals over weeks to months. Such ulcers, however, can become secondarily infected, the result being cellulitis, local inflammation, abscess formation, or (uncommonly) tetanus. Occasionally, the adult worm does not emerge but becomes encapsulated and calcified.

DIAGNOSIS

The diagnosis is based on the findings developing with the emergence of the adult worm, as described earlier.

TREATMENT

Gradual extraction of the worm by winding of a few centimeters on a stick each day remains the common and effective practice. Worms may be excised surgically. No drug is effective in treating dracunculiasis.

PREVENTION

Prevention, which remains the only real control measure, depends on the provision of safe drinking water.

ZOONOTIC FILARIAL INFECTIONS

Dirofilariae that affect primarily dogs, cats, and raccoons occasionally infect humans incidentally, as do *Brugia* and *Onchocerca* parasites that affect small mammals. Because humans are an abnormal host, the parasites never develop fully. Pulmonary dirofilarial infection caused by the canine heartworm *Dirofilaria immitis* generally presents in humans as a solitary pulmonary nodule. Chest pain, hemoptysis, and cough are uncommon. Infections with *D. repens* (from dogs) or *D. tenuis* (from raccoons) can cause local subcutaneous nodules in humans. Zoonotic *Brugia* infection can produce isolated lymph node enlargement, whereas zoonotic *Onchocerca* can cause subconjunctival masses. Eosinophilia levels and antifilarial antibody titers are not commonly elevated. Excisional biopsy is both diagnostic and curative. These infections usually do not respond to chemotherapy.

CHAPTER 129

SCHISTOSOMIASIS AND OTHER TREMATODE INFECTIONS

Adel A. F. Mahmoud

Trematodes, or flatworms, are a group of morphologically and biologically heterogeneous organisms that belong to the phylum Platyhelminthes. Human infection with trematodes occurs in many geographic areas and can cause considerable morbidity and mortality. The dependence on one drug—praziquantel—for treatment of most infections caused by helminths, including trematodes, raises the specter of developing resistance in these worms; several instances of reduced drug efficacy have already been reported.

ETIOLOGIC AGENTS AND THEIR LIFE CYCLES

For clinical purposes, significant trematode infections of humans may be divided according to tissues invaded by adult flukes: blood, biliary tree, intestines, and lungs (Table 129-1). Trematodes share some common morphologic features, including macroscopic size (from one to several centimeters); dorsoventral, flattened, bilaterally

TABLE 129-1

MAJOR HUMAN TREMATODE INFECTIONS

TREMATODE	TRANSMISSION	ENDEMIC AREA(S)
Blood Flukes		
Schistosoma mansoni	Skin penetration by cercariae released from snails	Africa, South America, Middle East
S. japonicum	Skin penetration by cercariae released from snails	China, Philippines, Indonesia
S. intercalatum	Skin penetration by cercariae released from snails	West Africa
S. mekongi	Skin penetration by cercariae released from snails	Southeast Asia
S. haematobium	Skin penetration by cercariae released from snails	Africa, Middle East
Biliary (Hepatic) Flukes		
Clonorchis sinensis	Ingestion of metacercariae in freshwater fish	Far East
Opisthorchis viverrini	Ingestion of metacercariae in freshwater fish	Far East, Thailand
O. felineus	Ingestion of metacercariae in freshwater fish	Far East, Europe
Fasciola hepatica	Ingestion of metacercariae on aquatic plants or in water	Worldwide
F. gigantica	Ingestion of metacercariae on aquatic plants or in water	Sporadic, Africa
Intestinal Flukes		
Fasciolopsis buski	Ingestion of metacercariae on aquatic plants	Southeast Asia
Heterophyes heterophyes	Ingestion of metacercariae in freshwater or brackish-water fish	Far East, North Africa
Lung Flukes		
Paragonimus westermani	Ingestion of metacercariae in crayfish or crabs	Global except North America and Europe

symmetric bodies (adult worms); and the prominence of two suckers. Except for schistosomes, all human parasitic trematodes are hermaphroditic. Their life cycles involve a definitive host (mammalian/human), in which adult worms initiate sexual reproduction, and an intermediate host (snails), in which asexual multiplication of larvae occurs. More than one intermediate host may be necessary for some species of trematodes. Human infection is initiated either by direct penetration of intact skin or by ingestion. Upon maturation within humans, adult flukes initiate sexual reproduction and egg production. Helminth ova leave the definitive host in excreta or sputum and, upon reaching suitable environmental conditions, they hatch, releasing free-living miracidia that seek specific snail intermediate hosts. After asexual reproduction, cercariae are released from infected snails. In certain species, these organisms infect humans; in others, they find a second intermediate host to allow encystment into metacercariae—the infective stage.

The host-parasite relationship in trematode infections is a product of certain biologic features of these organisms: they are multicellular, undergo several developmental changes within the host, and usually result in chronic infections. In general, the distribution of worm infections in human populations is *overdispersed*; i.e., it follows a negative binomial mathematical relationship in which most infected individuals harbor low worm burdens while a small percentage are heavily infected. It is the heavily infected minority who are particularly prone to disease sequelae and who constitute an epidemiologically significant reservoir of infection in endemic areas. Equally important is an appreciation that worms do not multiply within the definitive host and that they have a relatively long life span, ranging from a few months to a few years. Morbidity and death due to trematode infections reflect a multifactorial process that results from the tipping of a delicate balance between intensity of infection and host reactions, which initiate and modulate immunologic and pathologic outcome. Furthermore, the genetics of the parasite and of the human host contribute to the outcome of infection and disease. Infections with trematodes that migrate through or reside in host tissues are associated with a moderate to high degree of peripheral-blood eosinophilia; this association is of significance in protective and immunopathologic sequelae and is a useful clinical indicator of infection.

APPROACH TO THE PATIENT

Trematode Infection

The approach to individuals with suspected trematode infection begins with a question: Where have you been? Details of geographic history, exposure to freshwater bodies, and indulgence in local eating habits without ensuring safety of food and drink are all essential elements eliciting the history of present illness. The workup plan must include a detailed physical examination and tests appropriate for suspected infection. Diagnosis is based either on detection of the relevant stage of the parasite in excreta, sputum, or (rarely) tissue samples or on sensitive and specific serologic tests. Consultation with physicians familiar with these infections or with the U.S. Centers for Disease Control and Prevention (CDC) is helpful in guiding diagnosis and selecting therapy.

BLOOD FLUKES: SCHISTOSOMIASIS

Human schistosomiasis is caused by five species of the parasitic trematode genus *Schistosoma*: the intestinal species *S. mansoni*, *S. japonicum*, *S. mekongi*, and *S. intercalatum* and the urinary species *S. haematobium*. Infection may cause considerable morbidity in the intestines, liver, and urinary tract, and a proportion of affected individuals die. Other schistosomes (e.g., avian species) may invade human skin but then die in subcutaneous tissue, producing only self-limiting cutaneous manifestations.

ETIOLOGY

Human infection is initiated by penetration of intact skin with infective cercariae. These organisms, which are released from infected snails in freshwater bodies, measure ~2 mm in length and possess an anterior and a ventral sucker that attach to the skin and facilitate penetration. Once in subcutaneous tissue, cercariae transform into schistosomula, with morphologic, membrane, and immunologic changes. The cercarial outer membrane changes from a trilaminar to a heptalaminar structure that is then maintained throughout the organism's life span in humans. This transformation is thought to be the schistosome's main adaptive mechanism for survival in humans. Schistosomula begin their migration within 2–4 days via venous or lymphatic vessels, reaching the lungs and finally the liver parenchyma. Sexually mature worms descend into the venous system at specific anatomic locations: intestinal veins (*S. mansoni*, *S. japonicum*, *S. mekongi*, and *S. intercalatum*) and vesical veins (*S. haematobium*). After mating, adult gravid females travel against venous blood flow to small tributaries, where they deposit their ova intravascularly. Schistosome ova **(Fig. 129-1)** have specific morphologic features that vary with the species. Aided by enzymatic secretions through minipores in eggshells, ova move through the venous wall, traversing host tissues to reach the lumen of the intestinal or urinary tract, and are voided with stools or urine. Approximately 50% of ova are retained in host tissues locally (intestines or urinary tract) or are carried by venous blood flow to the liver and other organs. Schistosome ova that reach freshwater bodies hatch, releasing free-living miracidia that seek the snail intermediate host and undergo several cycles of asexual multiplication. Finally, infective cercariae are shed from snails.

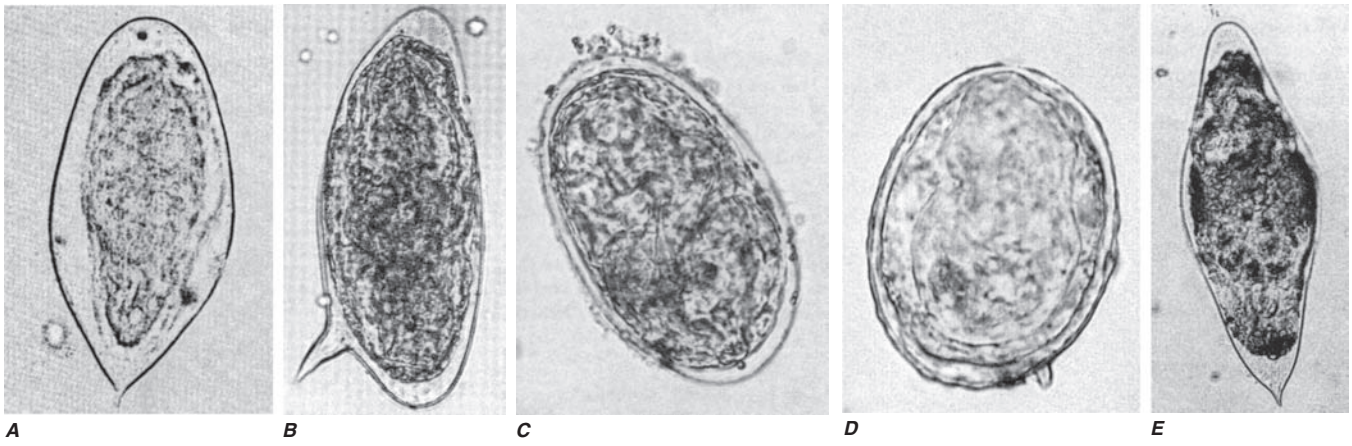


FIGURE 129-1

Morphology of schistosome eggs, the diagnostic stage of the parasite's life cycle. ***A.*** *S. haematobium* egg (in a urine sample) is large (~140 mm long), with a terminal spine. ***B.*** *S. mansoni* egg (in a fecal sample) is large (~150 mm long), with a thin shell and lateral spine. ***C.*** *S. japonicum* egg (fecal) is smaller than that of *S. mansoni* (~90 mm long), with a small spine or hooklike structure. ***D.*** *S. mekongi* egg (fecal) is similar to that of *S. japonicum* but smaller (~65 mm long). ***E.*** *S. intercalatum* egg (fecal) is larger than that of *S. haematobium* (~190 mm long), with a longer, sharply pointed spine. (*From LR Ash, TC Orihel: Atlas of Human Parasitology, 3rd ed. Chicago, ASCP Press, 1990; with permission.*)

Adult schistosomes are ~1–2 cm long. Males are slightly shorter than females, with flattened bodies and anteriorly curved edges forming the gynecophoral canal, in which mature adult females are usually held. Females are longer, slender, and rounded in cross-section. The precise nature of biochemical and reproductive exchanges between the two sexes is unknown, as are the regulatory mechanisms for pairing. Adult schistosomes parasitize specific sites in the host venous system. What guides adult intestinal schistosomes to branches of the superior or inferior mesenteric veins or adult *S. haematobium* worms to the vesical plexus is unknown. In addition, adult worms inhibit the coagulation cascade and evade the effector arms of the host immune responses by still-undetermined mechanisms. The genome of schistosomes is relatively large (~270 Mb) and is arrayed on seven pairs of autosomes and one pair of sex chromosomes. Sequencing of the *S. japonicum* and *S. mansoni* genomes has provided the first insight into the worms' genomic and proteomic features, offering an opportunity to discover new drug targets and to understand the molecular basis of pathogenesis.

EPIDEMIOLOGY

The global distribution of schistosome infection in human populations **(Fig. 129-2)** is dependent on both parasite and host factors. Information on prevalence and global distribution is inexact. The five *Schistosoma* species are estimated to infect 200–300 million individuals in South America, the Caribbean, Africa, the Middle East, and Southeast Asia. The total population living under conditions favoring transmission approximates double or triple that number—a fact reflecting the public health significance of schistosomiasis.

In endemic areas, the rate of yearly onset of new infection, or incidence, is generally low. Prevalence, on the other hand, starts to be appreciable by the age of 3–4 years and builds to a maximum that varies by endemic region (up to 100%) in the 15- to 20-year age group. Prevalence then stabilizes or decreases slightly in older age groups (>40 years). Intensity of infection (as measured by fecal or urinary egg counts, which correlate with adult worm burdens in most circumstances) follows the increase in prevalence up to the age of 15–20 years and then declines markedly in older age groups. This decline may reflect acquisition of resistance or may be due to changes in water contact patterns, since older people have less exposure. Infection with schistosomes in human populations has a peculiar pattern. Most infected individuals harbor low worm burdens, and only a small proportion suffer from high-intensity infection. This pattern may be due to differences in worm infectivity or to a spectrum of genetic susceptibilities in human populations.

Disease due to schistosome infection is the outcome of parasitologic, host, and associated viral infections or nutritional and environmental factors. Most disease syndromes relate to the presence of one or more of the parasite stages in humans. Disease manifestations in the populations of endemic areas correlate, in general, with intensity and duration of infection as well as with age and genetic susceptibility of the host. Overall, disease manifestations are clinically relevant in only a small proportion of persons infected with any of the intestinal schistosomes. In contrast, urinary schistosomiasis manifests clinically in most infected individuals. Estimates of total morbidity due to chronic schistosomiasis indicate a significantly greater burden than was previously appreciated.

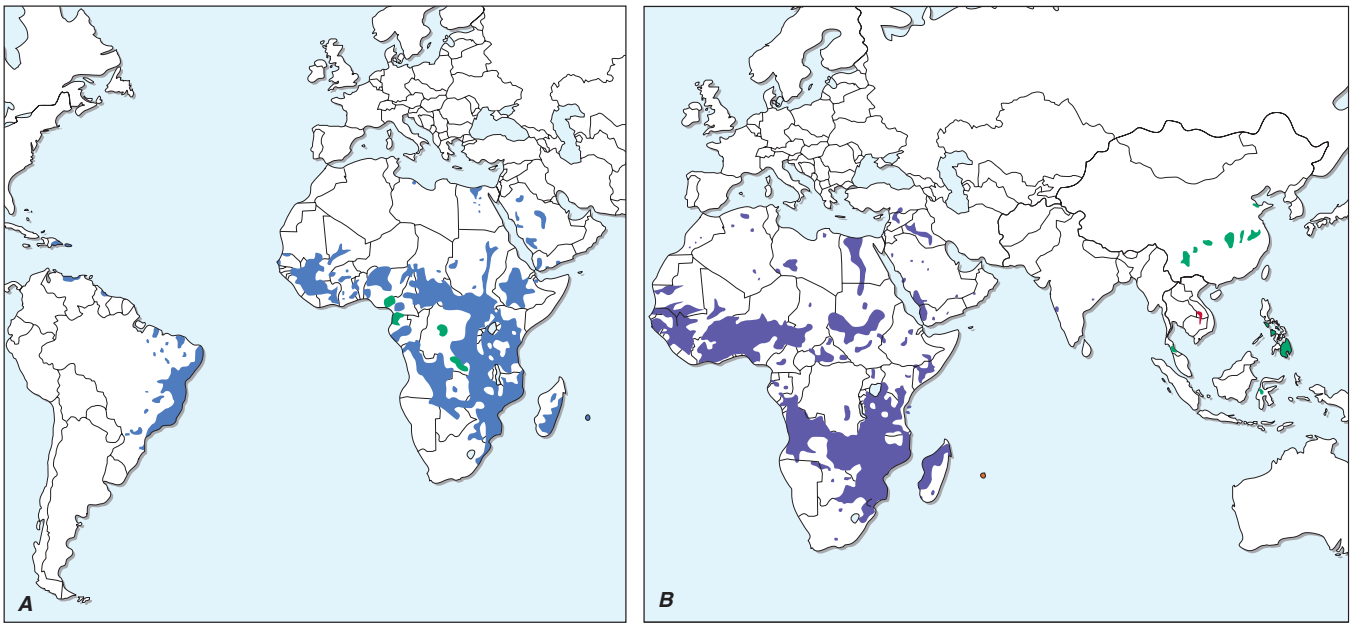


FIGURE 129-2
Global distribution of schistosomiasis. *A.* *S. mansoni* infection (*dark blue*) is endemic in Africa, the Middle East, South America, and a few Caribbean countries. *S. intercalatum* infection (*green*) is endemic in sporadic foci in West and Central Africa. ***B.*** *S. haematobium* infection (*purple*) is endemic in Africa and the Middle East. The major endemic countries for *S. japonicum* infection (*green*) are China, the Philippines, and Indonesia. *S. mekongi* infection (*red*) is endemic in sporadic foci in Southeast Asia.

Patients with both HIV infection and schistosomiasis excrete far fewer eggs in their stools than those infected with *S. mansoni* alone; the mechanism underlying this difference is unknown. Treatment with praziquantel may result in reduced HIV replication and increased CD4+ T lymphocyte counts.

PATHOGENESIS AND IMMUNITY

Cercarial invasion is associated with dermatitis arising from dermal and subdermal inflammatory responses, both humoral and cell-mediated. As the parasites approach sexual maturity in the liver of infected individuals and as oviposition commences, acute schistosomiasis or Katayama fever (a serum sickness–like illness; see "Clinical Features",) may occur. The associated antigen excess results in formation of soluble immune complexes, which may be deposited in several tissues, initiating multiple pathologic events. In chronic schistosomiasis, most disease manifestations are due to eggs retained in host tissues. The granulomatous response around these ova is cell-mediated and is regulated both positively and negatively by a cascade of cytokine, cellular, and humoral responses. Granuloma formation begins with recruitment of a host of inflammatory cells in response to antigens secreted by the living organism within the ova. Cells recruited initially include phagocytes, antigen-specific T cells, and eosinophils. Fibroblasts, giant cells, and B lymphocytes predominate later. These lesions reach a size many times that of parasite eggs, thus inducing organomegaly and obstruction. Immunomodulation or downregulation of host responses to schistosome eggs plays a significant role in limiting the extent of the granulomatous lesions—and consequently disease—in chronically infected experimental animals or humans. The underlying mechanisms involve another cascade of regulatory cytokines and idiotypic antibodies. Subsequent to the granulomatous response, fibrosis sets in, resulting in more permanent disease sequelae. Because schistosomiasis is also a chronic infection, the accumulation of antigen-antibody complexes results in deposits in renal glomeruli and may cause significant kidney disease.

The better-studied pathologic sequelae in schistosomiasis are those observed in liver disease. Ova that are carried by portal blood embolize to the liver. Because of their size (~150 × 60 μm in the case of *S. mansoni*), they lodge at presinusoidal sites, where granulomas are formed. These granulomas contribute to the hepatomegaly observed in infected individuals **(Fig. 129-3)**. Schistosomal liver enlargement is also associated with certain class I and class II human leukocyte antigen (HLA) haplotypes and markers; its genetic basis appears to be multigenic. Presinusoidal portal blockage causes several hemodynamic changes, including portal hypertension and associated development of portosystemic collaterals at the esophagogastric junction and other sites. Esophageal varices are most likely to break and cause repeated episodes of hematemesis. Because changes in hepatic portal blood flow occur slowly, compensatory arterialization of the blood flow through the liver is established. While this compensatory mechanism

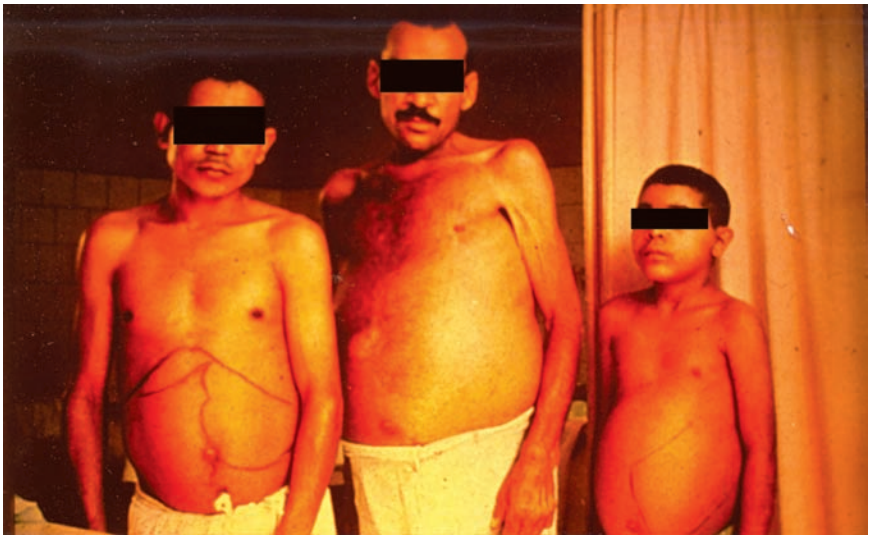


FIGURE 129-3
Chronic hepatosplenomegaly caused by schistosomiasis mansoni. Liver and spleen enlargement, ascites, and wasting are characteristically seen in patients with chronic *S. mansoni* infection.

may be associated with certain metabolic side effects, retention of hepatocyte perfusion permits maintenance of normal liver function for several years.

The second most significant pathologic change in the liver relates to fibrosis. It is characteristically periportal (Symmers' clay pipe–stem fibrosis) but may be diffuse. Fibrosis, when diffuse, may be seen in areas of egg deposition and granuloma formation but is also seen in distant locations such as portal tracts. Schistosomiasis results in pure fibrotic lesions in the liver; cirrhosis occurs when other nutritional factors or infectious agents (e.g., hepatitis B or C virus) are involved. Deposition of fibrotic tissue in the extracellular matrix results from the interaction of T lymphocytes with cells of the fibroblast series; several cytokines, such as interleukin (IL) 2, IL-4, IL-1, and transforming growth factor β (TGF-β), are known to stimulate fibrogenesis. The process may be dependent on the genetic constitution of the host. Furthermore, regulatory cytokines that can suppress fibrogenesis, such as interferon γ (IFN-γ) or IL-12, may play a role in modulating the response.

While the earlier description focuses on granuloma formation and fibrosis of the liver, similar processes occur in urinary schistosomiasis. Granuloma formation at the lower end of the ureters obstructs urinary flow, with subsequent development of hydroureter and hydronephrosis. Similar lesions in the urinary bladder cause the protrusion of papillomatous structures into its cavity; these may ulcerate and/or bleed. The chronic stage of infection is associated with scarring and deposition of calcium in the bladder wall.

Studies on immunity to schistosomiasis, whether innate or adaptive, have expanded our knowledge of the components of these responses and target antigens. The critical question, however, is whether humans acquire immunity to schistosomes. Epidemiologic data suggest the onset of acquired immunity during the course of infection in young adults. Curative treatment of infected populations in endemic areas is followed by differentiation in the pattern of reinfection. Some (susceptible) individuals acquire reinfection rapidly, whereas other (resistant) individuals are reinfected slowly. This difference may be explained by differences in transmission, immunologic response, or genetic susceptibility. The mechanism of acquired immunity involves antibodies, complement, and several effector cells, particularly eosinophils. Furthermore, the intensity of schistosome infection has been correlated with a region in chromosome 5. In several studies, a few protective schistosome antigens have been identified as vaccine candidates, but none has been evaluated in human populations to date.

CLINICAL FEATURES

In general, disease manifestations of schistosomiasis occur in three stages, which vary not only by species but also by intensity of infection and other host factors, such as age and genetics. During the phase of cercarial invasion, a form of dermatitis may be observed. This so-called swimmers' itch occurs most often with *S. mansoni* and *S. japonicum* infections, manifesting 2 or 3 days after invasion as an itchy maculopapular rash on the affected areas of the skin. The condition is particularly severe when humans are exposed to avian schistosomes. This form of cercarial dermatitis is also seen around freshwater lakes in the northern United States, particularly in the spring. Cercarial dermatitis is a self-limiting clinical entity. During worm maturation and at the beginning of oviposition (i.e., 8 weeks after skin invasion), acute schistosomiasis or Katayama fever—a serum sickness–like syndrome with fever, generalized lymphadenopathy, and hepatosplenomegaly—may develop. Individuals with

acute schistosomiasis show a high degree of peripheral-blood eosinophilia. Parasite-specific antibodies may be detected before schistosome eggs are identified in excreta.

Acute schistosomiasis has become an important clinical entity worldwide because of increased travel to endemic areas. Travelers are exposed to parasites while swimming or wading in freshwater bodies and upon their return present with acute manifestations. The course of acute schistosomiasis is generally benign, but deaths are occasionally reported in association with heavy exposure to schistosomes.

The main clinical manifestations of chronic schistosomiasis are species-dependent. Intestinal species (*S. mansoni*, *S. japonicum*, *S. mekongi*, and *S. intercalatum*) cause intestinal and hepatosplenic disease as well as several manifestations associated with portal hypertension. During the intestinal phase, which may begin a few months after infection and may last for years, symptomatic patients characteristically have colicky abdominal pain, bloody diarrhea, and anemia. Patients may also report fatigue and an inability to perform daily routine functions and may show evidence of growth retardation. Schistosomiasis morbidity is generally underappreciated. The severity of intestinal schistosomiasis is often related to the intensity of the worm burden. The disease runs a chronic course and may result in colonic polyposis, which has been reported from some endemic areas, such as Egypt.

The hepatosplenic phase of disease manifests early (during the first year of infection, particularly in children) with liver enlargement due to parasite-induced granulomatous lesions. Hepatomegaly is seen in ~15–20% of infected individuals; it correlates roughly with intensity of infection, occurs more often in children, and may be related to specific HLA haplotypes. In subsequent phases of infection, presinusoidal blockage of blood flow leads to portal hypertension and splenomegaly (Fig. 129-3). Moreover, portal hypertension may lead to varices at the lower end of the esophagus and at other sites. Patients with schistosomal liver disease may have right-upper-quadrant "dragging" pain during the hepatomegaly phase, and this pain may move to the left upper quadrant as splenomegaly progresses. Bleeding from esophageal varices may, however, be the first clinical manifestation of this phase. Patients may experience repeated bleeding but seem to tolerate its impact, since an adequate total hepatic blood flow permits normal liver function for a considerable duration. In late-stage disease, typical fibrotic changes occur along with liver function deterioration and the onset of ascites, hypoalbuminemia, and defects in coagulation. Intercurrent viral infections of the liver (especially hepatitis B and C) or nutritional deficiencies may well accelerate or exacerbate the deterioration of hepatic function.

The extent and severity of intestinal and hepatic disease in schistosomiasis mansoni and japonica have been well described. While it was originally thought that *S. japonicum* might induce more severe disease manifestations because the adult worms can produce 10 times more eggs than *S. mansoni*, subsequent field studies have not supported this claim. Clinical observations of individuals infected with *S. mekongi* or *S. intercalatum* have been less detailed, partly because of the limited geographic distribution of these organisms.

The clinical manifestations of *S. haematobium* infection occur relatively early and involve a high percentage of infected individuals. Up to 80% of children infected with *S. haematobium* have dysuria, frequency, and hematuria, which may be terminal. Urine examination reveals blood and albumin as well as an unusually high frequency of bacterial urinary tract infection and urinary sediment cellular metaplasia. These manifestations correlate with intensity of infection, the presence of urinary bladder granulomas, and subsequent ulceration. Along with local effects of granuloma formation in the urinary bladder, obstruction of the lower end of the ureters results in hydroureter and hydronephrosis, which may be seen in 25–50% of infected children. As infection progresses, bladder granulomas undergo fibrosis, which results in typical sandy patches visible on cystoscopy. In many endemic areas, an association between squamous cell carcinoma of the bladder and *S. haematobium* infection has been observed. Such malignancy is detected in a younger age group than is transitional cell carcinoma. In fact, *S. haematobium* has now been classified as a human carcinogen.

Significant disease may occur in other organs during chronic schistosomiasis. Lung and central nervous system (CNS) disease have been documented; other sites, such as the skin and the genital organs, are far less frequently affected. In pulmonary schistosomiasis, embolized eggs lodge in small arterioles, producing acute necrotizing arteriolitis and granuloma formation. During *S. mansoni* and *S. japonicum* infection, schistosome eggs reach the lungs after the development of portosystemic collateral circulation; in *S. haematobium* infection, ova may reach the lungs directly via connections between the vesical and systemic circulation. Subsequent fibrous tissue deposition leads to endarteritis obliterans, pulmonary hypertension, and cor pulmonale. The most common symptoms are cough, fever, and dyspnea. Cor pulmonale may be diagnosed radiologically on the basis of prominence of the right side of the heart and dilation of the pulmonary artery. Frank evidence of right-sided heart failure may be seen in late cases.

Although less common than pulmonary manifestations, CNS schistosomiasis is important, characteristically occurring in association with *S. japonicum* infection. Migratory worms deposit eggs in the brain and induce a granulomatous response. The frequency of this manifestation among infected individuals in some endemic areas (e.g., the Philippines) is calculated at 2–4%. Jacksonian epilepsy due to *S. japonicum* infection is the second most common cause of epilepsy in these areas. *S. mansoni* and *S. haematobium* infections have been associated with transverse myelitis. This syndrome is thought to be due to eggs traveling to the venous plexus around the spinal cord. In schistosomiasis mansoni, transverse myelitis is usually seen in the chronic stage after the development of portal hypertension and portosystemic shunts, which allow

ova to travel to the spinal cord veins. This proposed sequence of events has been challenged because of a few reports of transverse myelitis occurring early in the course of *S. mansoni* infection. More information is needed to confirm these observations. During schistosomiasis haematobia, ova may travel through communication between vesical and systemic veins, resulting in spinal cord disease that may be detected at any stage of infection. Pathologic study of lesions in schistosomal transverse myelitis may reveal eggs along with necrotic or granulomatous lesions. Patients usually present with acute or rapidly progressing lower-leg weakness accompanied by sphincter dysfunction.

DIAGNOSIS

Physicians in areas not endemic for schistosomiasis face considerable diagnostic challenges. In the most common clinical presentation, a traveler returns with symptoms and signs of acute syndromes of schistosomiasis—namely, cercarial dermatitis or Katayama fever. Central to a correct diagnosis is a thorough inquiry into the patient's history of travel and exposure to freshwater bodies—whether slow- or fast-running—in a nonendemic area. Differential diagnosis of fever in returned travelers includes a spectrum of infections whose etiologies are viral (e.g., Dengue fever), bacterial (e.g., enteric fever, leptospirosis), rickettsial, or protozoal (e.g., malaria). In cases of Katayama fever, prompt diagnosis is essential and is based on clinical presentation, high-level peripheral-blood eosinophilia, and a positive serologic assay for schistosomal antibodies. Two tests are available at the CDC: the Falcon assay screening test/enzyme-linked immunosorbent assay (FAST-ELISA) and the confirmatory enzyme-linked immunoelectrotransfer blot (EITB). Both tests are highly sensitive and ~96% specific. In some instances, examination of stool or urine for ova may yield positive results.

Individuals with established infection are diagnosed by a combination of geographic history, characteristic clinical presentation, and presence of schistosome ova in excreta. The diagnosis may also be established with the serologic assays mentioned earlier or with those that detect circulating schistosome antigens. These assays can be applied either to blood or to other body fluids (e.g., cerebrospinal fluid). For suspected schistosome infection, stool examination by the Kato thick smear or any other concentration method generally identifies all but the most lightly infected individuals. For *S. haematobium*, urine may be examined by microscopy of sediment or by filtration of a known volume through Nuclepore filters. Kato thick smear and Nuclepore filtration provide quantitative data on the intensity of infection, which is of value in assessing the degree of tissue damage and in monitoring the effect of chemotherapy. Schistosome infection may also be diagnosed by examination of tissue samples, typically rectal biopsies; other biopsy procedures (e.g., liver biopsy) are not needed, except in rare circumstances.

The differential diagnosis of schistosomal hepatomegaly must include viral hepatitis of all etiologies, miliary tuberculosis, malaria, visceral leishmaniasis, ethanol abuse, and causes of hepatic and portal vein obstruction. The differential diagnosis of hematuria in *S. haematobium* infection includes bacterial cystitis, tuberculosis, urinary stones, and malignancy.

TREATMENT Schistosomiasis

Treatment of schistosomiasis depends on the stage of infection and the clinical presentation. Other than topical dermatologic applications for relief of itching, no specific treatment is indicated for cercarial dermatitis caused by avian schistosomes. Therapy for acute schistosomiasis or Katayama fever needs to be adjusted appropriately for each case. While antischistosomal chemotherapy may be used, it does not have a significant impact on maturing worms. In severe acute schistosomiasis, management in an acute-care setting is necessary, with supportive measures and consideration of glucocorticoid treatment. Once the acute critical phase is over, specific chemotherapy is indicated for parasite elimination. For all individuals with established infection, treatment to eradicate the parasite should be administered. The drug of choice is praziquantel, which—depending on the infecting species (Table 129-2)—is administered PO as a total of 40 or 60 mg/kg in two or three doses over a single day.

TABLE 129-2

DRUG THERAPY FOR HUMAN TREMATODE INFECTIONS

INFECTION	DRUG OF CHOICE	ADULT DOSE AND DURATION
Blood Flukes		
S. mansoni, *S. intercalatum*, *S. haematobium*	Praziquantel	20 mg/kg, 2 doses in 1 day
S. japonicum, *S. mekongi*	Praziquantel	20 mg/kg, 3 doses in 1 day
Biliary (Hepatic) Flukes		
C. sinensis, *O. viverrini*, *O. felineus*	Praziquantel	25 mg/kg, 3 doses in 1 day
F. hepatica, *F. gigantica*	Triclabendazole	10 mg/kg once
Intestinal Flukes		
F. buski, *H. heterophyes*	Praziquantel	25 mg/kg, 3 doses in 1 day
Lung Flukes		
P. westermani	Praziquantel	25 mg/kg, 3 doses per day for 2 days

Praziquantel treatment results in parasitologic cure in ~85% of cases and reduces egg counts by >90%. Few side effects have been encountered, and those that do develop usually do not interfere with completion of treatment. Dependence on a single chemotherapeutic agent has raised the possibility of development of resistance in schistosomes; to date, such resistance does not seem to be clinically significant. The effect of antischistosomal treatment on disease manifestations varies by stage. Early hepatomegaly and bladder lesions are known to resolve after chemotherapy, but the late established manifestations, such as fibrosis, do not recede. Additional management modalities are needed for individuals with other manifestations, such as hepatocellular failure or recurrent hematemesis. The use of these interventions is guided by general medical and surgical principles.

PREVENTION AND CONTROL

Transmission of schistosomiasis is dependent on human behavior. Since the geographic distribution of infections in endemic regions of the world is not clearly demarcated, it is prudent for travelers to endemic areas to avoid contact with all freshwater bodies, irrespective of the speed of water flow or unsubstantiated claims of safety. Some topical agents, when applied to skin, may inhibit cercarial penetration, but none is currently available. If exposure occurs, a follow-up visit with a health care provider is strongly recommended. Prevention of infection in inhabitants of endemic areas is a significant challenge. Residents of these regions use freshwater bodies for sanitary, domestic, recreational, and agricultural purposes. Several control measures have been used, including application of molluscicides, provision of sanitary water and sewage disposal, chemotherapy, and health education. Current recommendations to countries endemic for schistosomiasis emphasize the use of multiple approaches. With the advent of an oral, safe, and effective antischistosomal agent, chemotherapy has been most successful in reducing the intensity of infection and reversing disease. The duration of this positive impact depends on the transmission dynamics of the parasite in any specific endemic region. The ultimate goal of research on prevention and control is the development of a vaccine. Although there are a few promising leads, this goal is probably not within reach during the next decade or so.

LIVER (BILIARY) FLUKES

Several species of biliary fluke infecting humans are particularly common in Southeast Asia and Russia. Other species are transmitted in Europe, Africa, and the Americas. On the basis of their migratory pathway in humans, these infections may be divided into the *Clonorchis* and *Fasciola* groups (Table 129-1).

CLONORCHIASIS AND OPISTHORCHIASIS

Infection with *Clonorchis sinensis*, the Chinese or oriental fluke, is endemic among fish-eating mammals in Southeast Asia. Humans are an incidental host; the prevalence of human infection is highest in China, Vietnam, and Korea. Infection with *Opisthorchis viverrini* and *O. felineus* is zoonotic in cats and dogs. Transmission to humans occurs occasionally, particularly in Thailand (*O. viverrini*) and in Southeast Asia and Eastern Europe (*O. felineus*). Data on the exact geographic distribution of these infectious agents in human populations are rudimentary.

Infection with any of these three species is established by ingestion of raw or inadequately cooked freshwater fish harboring metacercariae. These organisms excyst in the duodenum, releasing larvae that travel through the ampulla of Vater and mature into adult worms in bile canaliculi. Mature flukes are flat and elongated, measuring 1–2 cm in length. The hermaphroditic worms reproduce by releasing small operculated eggs, which pass with bile into the intestines and are voided with stools. The life cycle is completed in the environment in specific freshwater snails (the first intermediate host) and encystment of metacercariae in freshwater fish.

Except for late sequelae, the exact clinical syndromes caused by clonorchiasis and opisthorchiasis are not well defined. Since most infected individuals harbor a low worm burden, many are asymptomatic. Moderate to heavy infection may be associated with vague right-upper-quadrant pain. In contrast, chronic or repeated infection is associated with manifestations such as cholangitis, cholangiohepatitis, and biliary obstruction. Cholangiocarcinoma is epidemiologically related to *C. sinensis* infection in China and to *O. viverrini* infection in northeastern Thailand. This association has resulted in classification of these infectious agents as human carcinogens.

FASCIOLIASIS

Infections with *Fasciola hepatica* and *F. gigantica* are worldwide zoonoses that are particularly endemic in sheep-raising countries. Human cases have been reported in South America, Europe, Africa, Australia, and the Far East. Recent estimates indicate a worldwide prevalence of 17 million cases. High endemicity has been reported in certain areas of Peru and Bolivia. In most endemic areas the predominant species is *F. hepatica*, but in Asia and Africa a varying degree of overlap with *F. gigantica* has been observed.

Humans acquire fascioliasis by ingestion of metacercariae attached to certain aquatic plants, such as watercress. Infection may also be acquired by consumption of contaminated water or ingestion of food items washed with such water. Acquisition of human infection through consumption of freshly prepared raw liver containing immature flukes has been reported. Infection is initiated when metacercariae excyst, penetrate the gut wall, and travel through the peritoneal cavity to invade the liver capsule. Adult worms finally reach bile ducts, where they produce

large operculated eggs, which are voided in bile through the gastrointestinal tract to the outside environment. The flukes' life cycle is completed in specific snails (the first intermediate host) and encystment on aquatic plants.

Clinical features of fascioliasis relate to the stage and intensity of infection. Acute disease develops during parasite migration (1–2 weeks after infection) and includes fever, right-upper-quadrant pain, hepatomegaly, and eosinophilia. CT of the liver may show migratory tracks. Symptoms and signs usually subside as the parasites reach their final habitat. In individuals with chronic infection, bile duct obstruction and biliary cirrhosis are infrequently demonstrated. No relation to hepatic malignancy has been ascribed to fascioliasis.

DIAGNOSIS

Diagnosis of infection with any of the biliary flukes depends on a high degree of suspicion, elicitation of an appropriate geographic history, and stool examination for characteristically shaped parasite ova. Additional evidence may be obtained by documenting peripheral-blood eosinophilia or imaging the liver. Serologic testing is helpful, particularly in lightly infected individuals.

TREATMENT Biliary Flukes

Drug therapy (praziquantel or triclabendazole) is summarized in Table 129-2. Patients with anatomic lesions in the biliary tract or malignancy are managed according to general medical guidelines.

INTESTINAL FLUKES

Two species of intestinal flukes cause human infection in defined geographic areas worldwide (Table 129-1). The large *Fasciolopsis buski* (adults measure 2 × 7 cm) is endemic in Southeast Asia, while the smaller *Heterophyes heterophyes* is found in the Nile Delta of Egypt and in the Far East. Infection is initiated by ingestion of metacercariae attached to aquatic plants (*F. buski*) or encysted in freshwater or brackish-water fish (*H. heterophyes*). Flukes mature in human intestines, and eggs are passed with stools. Most individuals infected with intestinal flukes are asymptomatic. In heavy *F. buski* infection, diarrhea, abdominal pain, and malabsorption may be encountered. Heavy infection with *H. heterophyes* may be associated with abdominal pain and mucous diarrhea. The diagnosis is established by detection of characteristically shaped ova in stool samples. The drug of choice for treatment is praziquantel (Table 129-2).

LUNG FLUKES

Infection with the lung fluke *Paragonimus westermani* (Table 129-1) and related species (e.g., *P. africanus*) is endemic in many parts of the world, excluding North America and Europe. Endemicity is particularly noticeable in West Africa, Central and South America, and Asia. In nature, the reservoir hosts of *P. westermani* are wild and domestic felines. In Africa, *P. africanus* has been found in other species, such as dogs. Adult lung flukes, which are 7–12 mm in length, are found encapsulated in the lungs of infected persons. In rare circumstances, flukes are found encysted in the CNS (cerebral paragonimiasis) or the abdominal cavity. Humans acquire lung fluke infection by ingesting infective metacercariae encysted in the muscles and viscera of crayfish and freshwater crabs. In endemic areas, these crustaceans are consumed either raw or pickled. Once the organisms reach the duodenum, they excyst, penetrate the gut wall, and travel through the peritoneal cavity, diaphragm, and pleural space to reach the lungs. Mature flukes are found in the bronchioles surrounded by cystic lesions. Parasite eggs are either expectorated with sputum or swallowed and passed to the outside environment with feces. The life cycle is completed in snails and freshwater crustacea.

When maturing flukes lodge in lung tissues, they cause hemorrhage and necrosis, resulting in cyst formation. The adjacent lung parenchyma shows evidence of inflammatory infiltration, predominantly by eosinophils. Cysts usually measure 1–2 cm in diameter and may contain one or two worms each. With the onset of oviposition, cysts usually rupture in adjacent bronchioles—an event allowing ova to exit the human host. Older cysts develop thickened walls, which may undergo calcification. During the active phase of paragonimiasis, lung tissues surrounding parasite cysts may show evidence of pneumonia, bronchitis, bronchiectasis, and fibrosis.

Pulmonary paragonimiasis is particularly symptomatic in persons with moderate to heavy infection. Productive cough with brownish sputum or frank hemoptysis associated with peripheral-blood eosinophilia is usually the presenting feature. Chest examination may reveal signs of pleurisy. In chronic cases, bronchitis or bronchiectasis may predominate, but these conditions rarely proceed to lung abscess. Imaging of the lungs demonstrates characteristic features, including patchy densities, cavities, pleural effusion, and ring shadows. Cerebral paragonimiasis presents as either space-occupying lesions or epilepsy.

DIAGNOSIS

Pulmonary paragonimiasis is diagnosed by detection of parasite ova in sputum and/or stools. Serology is of considerable help in egg-negative cases and in cerebral paragonimiasis.

TREATMENT Lung Flukes

The drug of choice for treatment is praziquantel (Table 129-2). Other medical or surgical management may be needed for pulmonary or cerebral lesions.

CONTROL AND PREVENTION OF TISSUE FLUKES

For residents of nonendemic areas who are visiting an endemic region, the only effective preventive measure is to avoid ingestion of local plants, fish, or crustaceans; if their ingestion is necessary, these items should be washed or cooked thoroughly. Instruction on water and food preparation and consumption should be included in physicians' advice to travelers (Chap. 5). Interruption of transmission among residents of endemic areas depends on avoiding ingestion of infective stages and disposing of feces and sputum appropriately to prevent hatching of eggs in the environment. These two approaches rely greatly on socioeconomic development and health education. In countries where economic progress has resulted in financial and social improvements, transmission has decreased. The third approach to control in endemic communities entails selective use of chemotherapy for individuals posing the highest risk of transmission (i.e., those with heavy infections). The availability of praziquantel—a broad-spectrum, safe, and effective anthelmintic agent—provides a means for reducing the reservoirs of infection in human populations. However, the existence of most of these helminthic infections as zoonoses in several animal species complicates control efforts.

CHAPTER 130

CESTODE INFECTIONS

A. Clinton White, Jr. ■ Peter F. Weller

Cestodes, or tapeworms, are segmented worms. The adults reside in the gastrointestinal tract, but the larvae can be found in almost any organ. Human tapeworm infections can be divided into two major clinical groups. In one group, humans are the definitive hosts, with the adult tapeworms living in the gastrointestinal tract (*Taenia saginata*, *Diphyllobothrium*, *Hymenolepis*, and *Dipylidium caninum*). In the other, humans are intermediate hosts, with larval-stage parasites present in the tissues; diseases in this category include echinococcosis, sparganosis, and coenurosis. Humans may be either the definitive or the intermediate hosts for *Taenia solium*. Both stages of *Hymenolepis nana* are found simultaneously in the human intestines.

The ribbon-shaped tapeworm attaches to the intestinal mucosa by means of sucking cups or hooks located on the scolex. Behind the scolex is a short, narrow neck from which proglottids (segments) form. As each proglottid matures, it is displaced further back from the neck by the formation of new, less mature segments. The progressively elongating chain of attached proglottids, called the *strobila*, constitutes the bulk of the tapeworm. The length varies among species. In some, the tapeworm may consist of more than 1000 proglottids and may be several meters long. The mature proglottids are hermaphroditic and produce eggs, which are subsequently released. Since eggs of the different *Taenia* species are morphologically identical, differences in the morphology of the scolex or proglottids provide the basis for diagnostic identification to the species level.

Most human tapeworms require at least one intermediate host for complete larval development. After ingestion of the eggs or proglottids by an intermediate host, the larval oncospheres are activated, escape the egg, and penetrate the intestinal mucosa. The oncosphere migrates to tissues and develops into an encysted form known as a *cysticercus* (single scolex), a *coenurus* (multiple scolices), or a *hydatid* (cyst with daughter cysts, each containing several protoscolices). Ingestion by the definitive host of tissues containing a cyst enables a scolex to develop into a tapeworm.

TAENIASIS SAGINATA AND *TAENIASIS ASIATICA*

The beef tapeworm *T. saginata* occurs in all countries where raw or undercooked beef is eaten. It is most prevalent in sub-Saharan African and Middle Eastern countries. *T. asiatica* is closely related to *T. saginata* and is found in Asia with pigs as intermediate hosts.

The clinical manifestations and morphology of these two species are very similar and are therefore discussed together.

Etiology and pathogenesis

Humans are the only definitive host for the adult stage of *T. saginata* and *T. asiatica*. The tapeworms, which can reach 8 m in length with 1000–2000 proglottids, inhabit the upper jejunum. The scolex of *T. saginata* has four prominent suckers, whereas *T. asiatica* has an unarmed rostellum. Each gravid segment has 15–30 uterine branches (in contrast to 8–12 for *T. solium*). The eggs are indistinguishable from those of *T. solium*; they measure 30–40 μm, contain the oncosphere, and have a thick brown striated shell. Eggs deposited on vegetation can live for months or years until they are ingested by cattle or other herbivores (*T. saginata*) or pigs (*T. asiatica*). The embryo released after ingestion invades the intestinal wall and is carried to striated muscle or viscera, where it transforms into the cysticercus. When ingested in raw or undercooked meat, this form can infect humans. After the cysticercus is ingested, it takes ~2 months for the mature adult worm to develop.

Clinical manifestations

Patients become aware of the infection most commonly by noting passage of proglottids in their feces. The proglottids are often motile, and patients may experience perianal discomfort when proglottids are discharged. Mild abdominal pain or discomfort, nausea, change in appetite, weakness, and weight loss can occur.

Diagnosis

The diagnosis is made by the detection of eggs or proglottids in the stool. Eggs may also be present in the perianal area; thus, if proglottids or eggs are not found in the stool, the perianal region should be examined with use of a cellophane-tape swab (as in pinworm infection; Chap. 127). Distinguishing *T. saginata* or *T. asiatica* from *T. solium* requires examination of mature proglottids. All three species can be distinguished by examining the scolex. Available serologic tests are not helpful diagnostically. Eosinophilia and elevated levels of serum IgE may be detected.

TREATMENT **Taeniasis Saginata and Taeniasis Asiatica**

A single dose of praziquantel (10 mg/kg) is highly effective.

Prevention

The major method of preventing infection is the adequate cooking of beef or pork viscera; exposure to temperatures as low as 56°C for 5 min will destroy cysticerci. Refrigeration or salting for long periods or freezing at –10°C for 9 days also kills cysticerci in beef. General preventive measures include inspection of beef and proper disposal of human feces.

TAENIASIS SOLIUM AND CYSTICERCOSIS

The pork tapeworm *T. solium* can cause two distinct forms of infection in humans: adult tapeworms in the intestine or larval forms in the tissues (cysticercosis). Humans are the only definitive hosts for *T. solium*; pigs are the usual intermediate hosts, although other animals may harbor the larval forms.

T. solium exists worldwide but is most prevalent in Latin America, sub-Saharan Africa, China, India, and Southeast Asia. Cysticercosis occurs in industrialized nations largely as a result of the immigration of infected persons from endemic areas.

Etiology and pathogenesis

The adult tapeworm generally resides in the upper jejunum. The scolex attaches by both sucking disks and two rows of hooklets. Often only one adult worm is present, but that worm may live for years. The tapeworm, usually ~3 m in length, may have as many as 1000 proglottids, each of which produces up to 50,000 eggs. Groups of 3–5 proglottids are generally released and excreted into the feces, and the eggs in these proglottids are infective for both humans and animals. The eggs may survive in the environment for several months. After ingestion of eggs by the pig intermediate host, the larvae are activated, escape the egg, penetrate the intestinal wall, and are carried to many tissues; they are most frequently identified in striated muscle of the neck, tongue, and trunk. Within 60–90 days, the encysted larval stage develops. These cysticerci can survive for months to years. By ingesting undercooked pork containing cysticerci, humans acquire infections that lead to intestinal tapeworms. Infections that cause human cysticercosis follow the ingestion of *T. solium* eggs, usually from close contact with a tapeworm carrier. Autoinfection may occur if an individual with an egg-producing tapeworm ingests eggs derived from his or her own feces.

Clinical manifestations

Intestinal infections with *T. solium* may be asymptomatic. Fecal passage of proglottids may be noted by patients. Other symptoms are infrequent.

In cysticercosis, the clinical manifestations are variable. Cysticerci can be found anywhere in the body but are most commonly detected in the brain, cerebrospinal fluid (CSF), skeletal muscle, subcutaneous tissue, or eye. The clinical presentation of cysticercosis depends on the number and location of cysticerci as well as the extent of associated inflammatory responses or scarring. Neurologic manifestations are the most common **(Fig. 130-1)**. Seizures are associated with inflammation surrounding cysticerci in the brain parenchyma. These seizures may be generalized, focal, or Jacksonian. Hydrocephalus results from CSF flow obstruction by cysticerci and

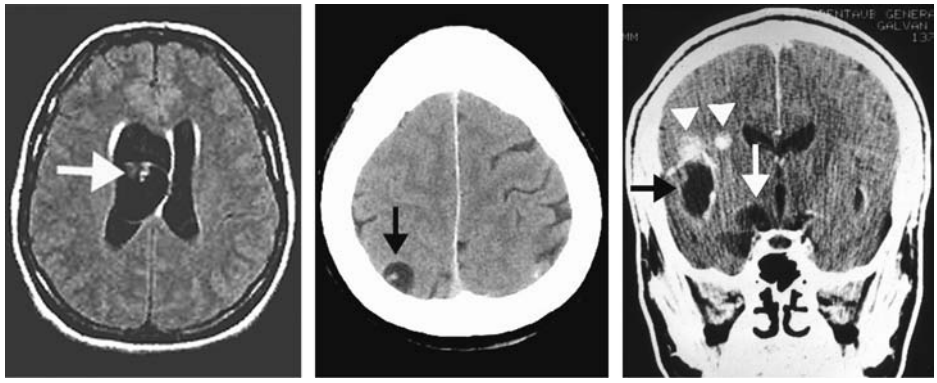


FIGURE 130-1

Neurocysticercosis is caused by *Taenia solium.* Neurologic infection can be classified on the basis of the location and viability of the parasites. When the parasites are in the ventricles, they often cause obstructive hydrocephalus. ***Left:*** MRI showing a cysticercus in the lateral ventricle, with resultant hydrocephalus. The arrow points to the scolex within the cystic parasite. ***Center:*** CT showing a parenchymal cysticercus, with enhancement of the cyst wall and an internal scolex (*arrow*). ***Right:*** Multiple cysticerci, including calcified lesions from prior infection (*arrowheads*), viable cysticerci in the basilar cisterns (*white arrow*), and a large degenerating cysticercus in the Sylvian fissure (*black arrow*). *(Modified with permission from JC Bandres et al: Clin Infect Dis 15:799, 1992. © The University of Chicago Press.)*

accompanying inflammation or by CSF outflow obstruction from arachnoiditis. Signs of increased intracranial pressure, including headache, nausea, vomiting, changes in vision, dizziness, ataxia, or confusion, are often evident. Patients with hydrocephalus may develop papilledema or display altered mental status. When cysticerci develop at the base of the brain or in the subarachnoid space, they may cause chronic meningitis or arachnoiditis, communicating hydrocephalus, or strokes.

Diagnosis

The diagnosis of intestinal *T. solium* infection is made by the detection of eggs or proglottids, as described for *T. saginata*. More sensitive methods, including antigen-capture ELISA, PCR, and serology for tapeworm stage-specific antigens, are currently available only as research techniques. In cysticercosis, diagnosis can be difficult. A consensus conference has delineated absolute, major, minor, and epidemiologic criteria for diagnosis **(Table 130-1)**. Diagnostic certainty is possible only with definite demonstration of the parasite (absolute criteria). This task can be accomplished by histologic observation of the parasite in excised tissue, by funduscopic visualization of the parasite in the eye (in the anterior chamber, vitreous, or subretinal spaces), or by neuroimaging studies demonstrating cystic lesions containing a characteristic scolex. With improving resolution of neuroimaging studies, the scolex can now be identified in many cases. In other instances, a clinical diagnosis is made on the basis of a combination of clinical presentation, radiographic studies, serologic tests, and exposure history.

Neuroimaging findings suggestive of neurocysticercosis constitute the primary major diagnostic criterion. These findings include cystic lesions with or without enhancement (e.g., ring enhancement), one or more nodular calcifications (which may also have associated enhancement), or focal enhancing lesions. Cysticerci in the brain parenchyma are usually 5–20 mm in diameter and rounded. Cystic lesions in the subarachnoid space or fissures may enlarge up to 6 cm in diameter and may be lobulated. For cysticerci within the subarachnoid space or ventricles, the walls may be very thin and the cyst fluid is often isodense with CSF. Thus, obstructive hydrocephalus or enhancement of the basilar meninges may be the only finding on CT in extraparenchymal neurocysticercosis. Cysticerci in the ventricles or subarachnoid space are usually visible to an experienced neuroradiologist on MRI or on CT with intraventricular contrast injection. CT is more sensitive than MRI in identifying calcified lesions, whereas MRI is better for identifying cystic lesions, scolices, and enhancement.

The second major diagnostic criterion is detection of specific antibodies to cysticerci. While most tests employing unfractionated antigen have high rates of false-positive and false-negative results, this problem can be overcome by using the more specific immunoblot assay. An immunoblot assay using lentil-lectin purified glycoproteins has >99% specificity and is highly sensitive. However, patients with single intracranial lesions or with calcifications may be seronegative. With this assay, serum samples provide greater diagnostic sensitivity than CSF. All of the diagnostic antigens have been cloned, and assays using recombinant antigens are being developed. Antigen detection assays using monoclonal antibodies to detect parasite antigen in the blood or CSF may also facilitate diagnosis and patient follow-up. However, these assays are not widely available at present.

Studies have demonstrated that clinical criteria can aid in diagnosis in selected cases. In patients from endemic areas who had single enhancing lesions presenting with seizures, a normal physical examination,

TABLE 130-1

DIAGNOSTIC CRITERIA FOR HUMAN CYSTICERCOSIS[a]

1. Absolute criteria
   a. Demonstration of cysticerci by histologic or microscopic examination of biopsy material
   b. Visualization of the parasite in the eye by funduscopy
   c. Neuroradiologic demonstration of cystic lesions containing a characteristic scolex
2. Major criteria
   a. Neuroradiologic lesions suggestive of neurocysticercosis
   b. Demonstration of antibodies to cysticerci in serum by enzyme-linked immunoelectrotransfer blot
   c. Resolution of intracranial cystic lesions spontaneously or after therapy with albendazole or praziquantel alone
3. Minor criteria
   a. Lesions compatible with neurocysticercosis detected by neuroimaging studies
   b. Clinical manifestations suggestive of neurocysticercosis
   c. Demonstration of antibodies to cysticerci or cysticercal antigen in cerebrospinal fluid by ELISA
   d. Evidence of cysticercosis outside the central nervous system (e.g., cigar-shaped soft-tissue calcifications)
4. Epidemiologic criteria
   a. Residence in a cysticercosis-endemic area
   b. Frequent travel to a cysticercosis-endemic area
   c. Household contact with an individual infected with *Taenia solium*

[a]Diagnosis is confirmed by either one absolute criterion or a combination of two major criteria, one minor criterion, and one epidemiologic criterion. A probable diagnosis is supported by the fulfillment of (1) one major criterion plus two minor criteria; (2) one major criterion plus one minor criterion and one epidemiologic criterion; or (3) three minor criteria plus one epidemiologic criterion.
Abbreviation: ELISA, enzyme-linked immunosorbent assay.
Source: Modified from OH Del Brutto et al: Neurology 57:177 2001.

and no evidence of systemic disease (e.g., no fever, adenopathy, or chest radiographic abnormalities), the constellation of rounded CT lesions 5–20 mm in diameter with no midline shift was almost always caused by neurocysticercosis. Finally, spontaneous resolution or resolution after therapy with albendazole alone is consistent with neurocysticercosis.

Minor diagnostic criteria include neuroimaging findings consistent with but less characteristic of cysticercosis, clinical manifestations suggestive of neurocysticercosis (e.g., seizures, hydrocephalus, or altered mental status), evidence of cysticercosis outside the central nervous system (CNS) (e.g., cigar-shaped soft-tissue calcifications), or detection of antibody in CSF by ELISA. Epidemiologic criteria include exposure to a tapeworm carrier or household member infected with *T. solium*, current or prior residence in an endemic area, and frequent travel to an endemic area.

The diagnosis is confirmed in patients with either one absolute criterion or a combination of two major criteria, one minor criterion, and one epidemiologic criterion (Table 130-1). A probable diagnosis is supported by the fulfillment of (1) one major criterion plus two minor criteria; (2) one major criterion plus one minor criterion and one epidemiologic criterion; or (3) three minor criteria plus one epidemiologic criterion. While the CSF is usually abnormal in neurocysticercosis, CSF abnormalities are not pathognomonic. Patients may have CSF pleocytosis with a predominance of lymphocytes, neutrophils, or eosinophils. The protein level in CSF may be elevated; the glucose concentration is usually normal but may be depressed.

TREATMENT Taeniasis Solium and Cysticercosis

Intestinal *T. solium* infection is treated with a single dose of praziquantel (10 mg/kg). However, praziquantel occasionally evokes an inflammatory response in the CNS if concomitant cryptic cysticercosis is present. Niclosamide (2 g) is also effective but is not widely available.

The initial management of neurocysticercosis should focus on symptom-based treatment of seizures or hydrocephalus. Seizures can usually be controlled with antiepileptic treatment. If parenchymal lesions resolve without development of calcifications and patients remain free of seizures, antiepileptic therapy can usually be discontinued after 1–2 years. Placebo-controlled trials are beginning to clarify the clinical advantage of antiparasitic drugs for parenchymal neurocysticercosis. Trends toward faster resolution of neuroradiologic abnormalities have been observed in most studies. The clinical benefits are less dramatic and consist mainly of shortening the period during which recurrent seizures occur and decreasing the number of patients who have many recurrent seizures. For the treatment of patients with brain parenchymal cysticerci, most authorities favor antiparasitic drugs, including albendazole (15 mg/kg per day for 8–28 days) or praziquantel (50–100 mg/kg daily in three divided doses for 15–30 days). Longer courses are often needed in patients with multiple subarachnoid cysticerci. Both agents may exacerbate the inflammatory response around the dying parasite, thereby exacerbating seizures or hydrocephalus as well. Thus, patients receiving these drugs should be carefully monitored, and high-dose glucocorticoids should be used during treatment. Since glucocorticoids induce first-pass metabolism of praziquantel and may decrease its antiparasitic effect, cimetidine should be co-administered to inhibit praziquantel metabolism. Pilot studies suggest that the two drugs in combination may be more effective than the individual agents.

For patients with hydrocephalus, the emergent reduction of intracranial pressure is the mainstay of therapy. In the case of obstructive hydrocephalus, the preferred approach is removal of the cysticercus via endoscopic surgery. However, this intervention is not always possible. An alternative approach is initially to

perform a diverting procedure, such as ventriculoperitoneal shunting. Historically, shunts have usually failed, but low failure rates have been attained with administration of antiparasitic drugs and glucocorticoids. Open craniotomy to remove cysticerci is now required only infrequently. For patients with subarachnoid cysts or giant cysticerci, glucocorticoids are needed to reduce arachnoiditis and accompanying vasculitis. Most authorities recommend prolonged courses of antiparasitic drugs and shunting when hydrocephalus is present. Methotrexate can be used as a steroid-sparing agent in patients requiring prolonged therapy. In patients with diffuse cerebral edema and elevated intracranial pressure due to multiple inflamed lesions, glucocorticoids are the mainstay of therapy, and antiparasitic drugs should be avoided. For ocular and spinal medullary lesions, drug-induced inflammation may cause irreversible damage. Most patients should be managed surgically, although case reports have described cures with medical therapy.

Prevention

Measures for the prevention of intestinal *T. solium* infection consist of the application to pork of precautions similar to those described earlier for beef with regard to *T. saginata* infection. The prevention of cysticercosis involves minimizing the opportunities for ingestion of fecally derived eggs by means of good personal hygiene, effective fecal disposal, and treatment and prevention of human intestinal infections. Mass chemotherapy has been administered to human and porcine populations in efforts at disease eradication. Finally, vaccines to prevent porcine cysticercosis have shown promise in studies and are under development.

ECHINOCOCCOSIS

Echinococcosis is an infection caused in humans by the larval stage of the *Echinococcus granulosus* complex, *E. multilocularis*, or *E. vogeli*. *E. granulosus* complex parasites, which produce unilocular cystic lesions and are prevalent in areas where livestock is raised in association with dogs, cause cystic hydatid disease. Molecular evidence suggests that *E. granulosus* strains may actually belong to more than one species; specifically, strains from sheep, cattle, pigs, horses, and camels probably represent separate species. These parasites are found on all continents, with areas of high prevalence in China, central Asia, the Middle East, the Mediterranean region, eastern Africa, and parts of South America. *E. multilocularis*, which causes multilocular alveolar lesions that are locally invasive, is found in Alpine, sub-Arctic, or Arctic regions, including Canada, the United States, and central and northern Europe; China; and central Asia. *E. vogeli* causes polycystic hydatid disease and is found only in Central and South America.

Like other cestodes, echinococcal species have both intermediate and definitive hosts. The definitive hosts are canines that pass eggs in their feces. After the ingestion of eggs, cysts develop in the intermediate hosts—sheep, cattle, humans, goats, camels, and horses for the *E. granulosus* complex and mice and other rodents for *E. multilocularis*. When a dog (*E. granulosus*) or fox (*E. multilocularis*) ingests infected meat containing cysts, the life cycle is completed.

Etiology

The small (5-mm-long) adult *E. granulosus* complex worms, which live for 5–20 months in the jejunum of dogs, have only three proglottids: one immature, one mature, and one gravid. The gravid segment splits to release eggs that are morphologically similar to *Taenia* eggs and are extremely hardy. After humans ingest the eggs, embryos escape from the eggs, penetrate the intestinal mucosa, enter the portal circulation, and are carried to various organs, most commonly the liver and lungs. Larvae develop into fluid-filled unilocular hydatid cysts that consist of an external membrane and an inner germinal layer. Daughter cysts develop from the inner aspect of the germinal layer, as do germinating cystic structures called *brood capsules*. New larvae, called *protoscolices*, develop in large numbers within the brood capsule. The cysts expand slowly over a period of years.

The life cycle of *E. multilocularis* is similar except that wild canines, such as foxes, serve as the definitive hosts and small rodents serve as the intermediate hosts. The larval form of *E. multilocularis*, however, is quite different in that it remains in the proliferative phase, the parasite is always multilocular, and vesicles without brood capsule or protoscolices progressively invade the host tissue by peripheral extension of processes from the germinal layer.

Clinical manifestations

Slowly enlarging echinococcal cysts generally remain asymptomatic until their expanding size or their space-occupying effect in an involved organ elicits symptoms. The liver and the lungs are the most common sites of these cysts. The liver is involved in about two-thirds of *E. granulosus* infections and in nearly all *E. multilocularis* infections. Since a period of years elapses before cysts enlarge sufficiently to cause symptoms, they may be discovered incidentally on a routine x-ray or ultrasound study.

Patients with hepatic echinococcosis who are symptomatic most often present with abdominal pain or a palpable mass in the right upper quadrant. Compression of a bile duct or leakage of cyst fluid into the biliary tree may mimic recurrent cholelithiasis, and biliary obstruction can result in jaundice. Rupture of or episodic leakage from a hydatid cyst may produce fever, pruritus, urticaria, eosinophilia, or anaphylaxis. Pulmonary hydatid cysts may rupture into the bronchial tree or peritoneal cavity and produce cough, salty phlegm, dyspnea, chest pain, or hemoptysis. Rupture of hydatid cysts, which can occur spontaneously or at surgery, may lead to multifocal dissemination of protoscolices, which can form additional cysts. Other presentations are due to the involvement

of bone (invasion of the medullary cavity with slow bone erosion producing pathologic fractures), the CNS (space-occupying lesions), the heart (conduction defects, pericarditis), and the pelvis (pelvic mass).

The larval forms of *E. multilocularis* characteristically present as a slowly growing hepatic tumor, with progressive destruction of the liver and extension into vital structures. Patients commonly report upper-quadrant and epigastric pain. Liver enlargement and obstructive jaundice may be apparent. The lesions may infiltrate adjoining organs (e.g., diaphragm, kidneys, or lungs) or may metastasize to the spleen, lungs, or brain.

Diagnosis

Radiographic and related imaging studies are important in detecting and evaluating echinococcal cysts. Plain x-rays will define pulmonary cysts of *E. granulosus*—usually as rounded masses of uniform density—but may miss cysts in other organs unless there is cyst wall calcification (as occurs in the liver). MRI, CT, and ultrasound reveal well-defined cysts with thick or thin walls. When older cysts contain a layer of hydatid sand that is rich in accumulated protoscolices, these imaging methods may detect this fluid layer of different density. However, the most pathognomonic finding, if demonstrable, is that of daughter cysts within the larger cyst. This finding, like eggshell or mural calcification on CT, is indicative of *E. granulosus* infection and helps to distinguish the cyst from carcinomas, bacterial or amebic liver abscesses, or hemangiomas. In contrast, ultrasound or CT of alveolar hydatid cysts reveals indistinct solid masses with central necrosis and plaquelike calcifications.

A specific diagnosis of *E. granulosus* infection can be made by the examination of aspirated fluids for protoscolices or hooklets, but diagnostic aspiration is not usually recommended because of the risk of fluid leakage resulting in either dissemination of infection or anaphylactic reactions. Serodiagnostic assays can be useful, although a negative test does not exclude the diagnosis of echinococcosis. Cysts in the liver elicit positive antibody responses in ~90% of cases, whereas up to 50% of individuals with cysts in the lungs are seronegative. Detection of antibody to specific echinococcal antigens by immunoblotting has the highest degree of specificity.

TREATMENT **Echinococcosis**

Therapy for cystic echinococcosis is based on considerations of the size, location, and manifestations of cysts and the overall health of the patient. Surgery has traditionally been the principal definitive method of treatment. Currently, ultrasound staging is recommended for *E. granulosus* infections (Fig. 130-2). Small C1, CE1, and CE3 lesions may respond to chemotherapy with albendazole. For CE1 lesions and uncomplicated CE3 lesions, PAIR (*p*ercutaneous *a*spiration, *i*nfusion of scolicidal agents, and *r*easpiration) is now recommended instead of surgery. PAIR is contraindicated for superficially

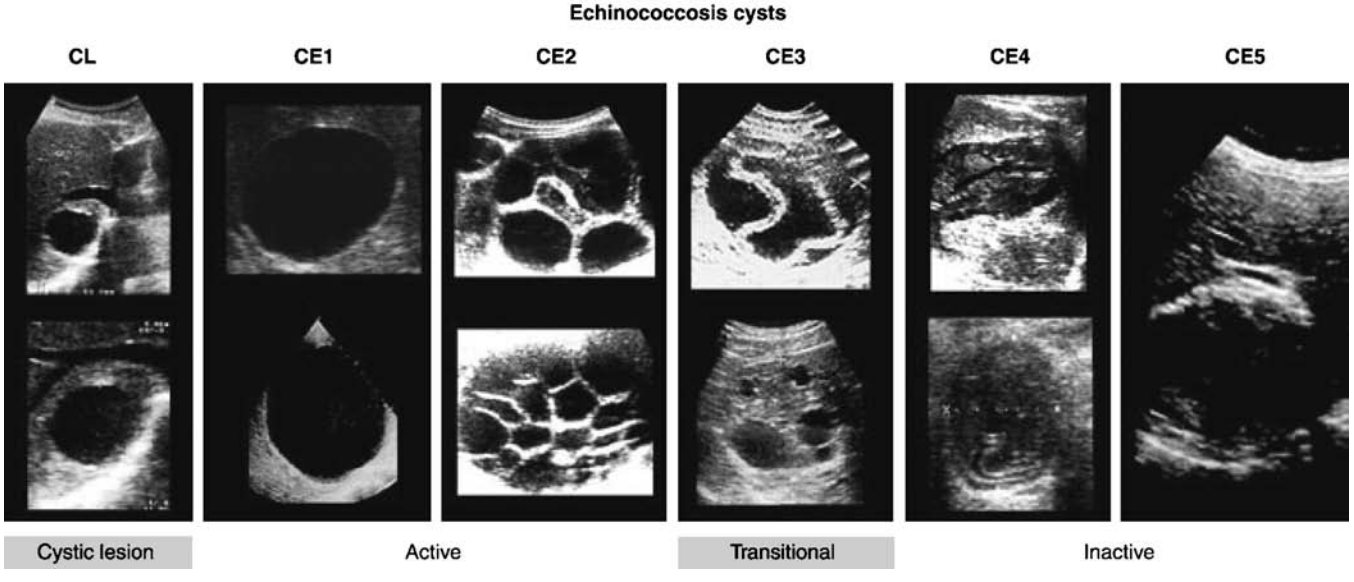


FIGURE 130-2

Management of cystic hydatid disease caused by *Echinococcus granulosus* should be based on viability of the parasite, which can be estimated from radiographic appearance. The ultrasound appearance includes lesions classified as active, transitional, and inactive. *Active* cysts include types CL (with a cystic lesion and no visible cyst wall), CE1 (with a visible cyst wall and internal echoes [snowflake sign]), and CE2 (with a visible cyst wall and internal septation). *Transitional cysts* (CE3) may have detached laminar membranes or may be partially collapsed. *Inactive cysts* include types CE4 (a nonhomogeneous mass) and CE5 (a cyst with a thick calcified wall). (*Adapted from RL Guerrant et al [eds]: Tropical Infectious Diseases: Principles, Pathogens and Practice, 2nd ed, p 1312. © 2005, with permission from Elsevier Science.*)

located cysts (because of the risk of rupture), for cysts with multiple thick internal septal divisions (honeycombing pattern), and for cysts communicating with the biliary tree. For prophylaxis of secondary peritoneal echinococcosis due to inadvertent spillage of fluid during PAIR, the administration of albendazole (15 mg/kg daily in two divided doses) should be initiated at least 4 days before the procedure and continued for at least 4 weeks afterward. Ultrasound- or CT-guided aspiration allows confirmation of the diagnosis by demonstration of protoscolices in the aspirate. After aspiration, contrast material should be injected to detect occult communications with the biliary tract. Alternatively, the fluid should be checked for bile staining by dipstick. If no bile is found and no communication visualized, the contrast material is reaspirated, with subsequent infusion of scolicidal agents (usually 95% ethanol; alternatively, hypertonic saline). This approach, when implemented by a skilled practitioner, yields rates of cure and relapse equivalent to those following surgery, with less perioperative morbidity and shorter hospitalization. In experienced hands, some CE2 lesions can be treated by aspiration with a trochar. Daughter cysts within the primary cyst may need to be punctured separately, and catheter drainage may be required.

Surgery remains the treatment of choice for complicated *E. granulosus* cysts (e.g., those communicating with the biliary tract) or for areas where PAIR is not possible. For *E. granulosus*, the preferred surgical approach is pericystectomy, in which the entire cyst and the surrounding fibrous tissue are removed. The risks posed by leakage of fluid during surgery or PAIR include anaphylaxis and dissemination of infectious protoscolices. The latter complication has been minimized by careful attention to the prevention of spillage of the cyst and by soaking of the drapes with hypertonic saline. Infusion of scolicidal agents is no longer recommended because of problems with hypernatremia, intoxication, or sclerosing cholangitis. Albendazole, which is active against *Echinococcus*, should be administered adjunctively, beginning several days before resection and continuing for several weeks for *E. granulosus*. Praziquantel (50 mg/kg daily for 2 weeks) may hasten the death of the protoscolices. Medical therapy with albendazole alone for 12 weeks to 6 months results in cure in ~30% of cases and in improvement in another 50%. In many instances of treatment failure, *E. granulosus* infections are subsequently treated successfully with PAIR or additional courses of medical therapy. Response to treatment is best assessed by serial imaging studies, with attention to cyst size and consistency. Some cysts may not demonstrate complete radiologic resolution even though no viable protoscolices are present. Some of these cysts with partial radiologic resolution (e.g., CE4 or CE5) can be managed with observation only.

Surgical resection remains the treatment of choice for *E. multilocularis* infection. Complete removal of the parasite continues to offer the best chance for cure. Ongoing therapy with albendazole for at least 2 years after presumptively curative surgery is recommended. Positron emission tomography (PET) scanning can be used to follow disease activity. Most cases are diagnosed at a stage at which complete resection is not possible; in these cases, albendazole treatment should be continued indefinitely, with careful monitoring. In some cases, liver transplantation has been used because of the size of the necessary liver resection. However, continuous immunosuppression favors the proliferation of *E. multilocularis* larvae and reinfection of the transplant. Thus, indefinite treatment with albendazole is required.

Prevention

In endemic areas, echinococcosis can be prevented by administering praziquantel to infected dogs, by denying dogs access to infected animals, or by vaccinating sheep. Limitation of the number of stray dogs is helpful in reducing the prevalence of infection among humans.

HYMENOLEPIASIS NANA

Infection with *H. nana*, the dwarf tapeworm, is the most common of all the cestode infections. *H. nana* is endemic in both temperate and tropical regions of the world. Infection is spread by fecal/oral contamination and is common among institutionalized children.

Etiology and pathogenesis

H. nana is the only cestode of humans that does not require an intermediate host. Both the larval and adult phases of the life cycle take place in the human. The adult—the smallest tapeworm parasitizing humans—is ~2 cm long and dwells in the proximal ileum. Proglottids, which are quite small and are rarely seen in the stool, release spherical eggs 30–44 μm in diameter, each of which contains an oncosphere with six hooklets. The eggs are immediately infective and are unable to survive for >10 days in the external environment. When the egg is ingested by a new host, the oncosphere is freed and penetrates the intestinal villi, becoming a cysticercoid larva. Larvae migrate back into the intestinal lumen, attach to the mucosa, and mature into adult worms over 10–12 days. Eggs may also hatch before passing into the stool, causing internal autoinfection with increasing numbers of intestinal worms. Although the life span of adult *H. nana* worms is only ~4–10 weeks, the autoinfection cycle perpetuates the infection.

Clinical manifestations

H. nana infection, even with many intestinal worms, is usually asymptomatic. When infection is intense, anorexia, abdominal pain, and diarrhea develop.

Diagnosis

Infection is diagnosed by the finding of eggs in the stool.

TREATMENT Hymenolepiasis Nana

Praziquantel (25 mg/kg once) is the treatment of choice, since it acts against both the adult worms and the cysticercoids in the intestinal villi. Nitazoxanide (500 mg bid for 3 days) may be used as an alternative.

Prevention

Good personal hygiene and improved sanitation can eradicate the disease. Epidemics have been controlled by mass chemotherapy coupled with improved hygiene.

HYMENOLEPIASIS DIMINUTA

Hymenolepis diminuta, a cestode of rodents, occasionally infects small children, who ingest the larvae in uncooked cereal foods contaminated by fleas and other insects in which larvae develop. Infection is usually asymptomatic and is diagnosed by the detection of eggs in the stool. Treatment with praziquantel results in cure in most cases.

DIPHYLLOBOTHRIASIS

Diphyllobothrium latum and other *Diphyllobothrium* species are found in the lakes, rivers, and deltas of the Northern Hemisphere, Central Africa, and South America.

Etiology and pathogenesis

The adult worm—the longest tapeworm (up to 25 m)—attaches to the ileal and occasionally to the jejunal mucosa by its suckers, which are located on its elongated scolex. The adult worm has 3000–4000 proglottids, which release ~1 million eggs daily into the feces. If an egg reaches water, it hatches and releases a free-swimming embryo that can be eaten by small freshwater crustaceans (*Cyclops* or *Diaptomus* species). After an infected crustacean containing a developed procercoid is swallowed by a fish, the larva migrates into the fish's flesh and grows into a plerocercoid, or sparganum larva. Humans acquire the infection by ingesting infected raw or smoked fish. Within 3–5 weeks, the tapeworm matures into an adult in the human intestine.

Clinical manifestations

Most *D. latum* infections are asymptomatic, although manifestations may include transient abdominal discomfort, diarrhea, vomiting, weakness, and weight loss. Occasionally, infection can cause acute abdominal pain and intestinal obstruction; in rare cases, cholangitis or cholecystitis may be produced by migrating proglottids. Because the tapeworm absorbs large quantities of vitamin B_{12} and interferes with ileal B_{12} absorption, vitamin B_{12} deficiency can develop, but this effect has been noted only in Scandinavia, where up to 2% of infected patients, especially the elderly, have megaloblastic anemia resembling pernicious anemia and may exhibit neurologic sequelae of B_{12} deficiency.

Diagnosis

The diagnosis is made readily by the detection of the characteristic eggs in the stool. The eggs possess a single shell with an operculum at one end and a knob at the other. Mild to moderate eosinophilia may be detected.

TREATMENT Diphyllobothriasis

Praziquantel (5–10 mg/kg once) is highly effective. Parenteral vitamin B_{12} should be given if B_{12} deficiency is manifest.

Prevention

Infection can be prevented by heating fish to 54°C for 5 min or by freezing it at –18°C for 24 h. Placing fish in brine with a high salt concentration for long periods kills the eggs.

DIPYLIDIASIS

Dipylidium caninum, a common tapeworm of dogs and cats, may accidentally infect humans. Dogs, cats, and occasionally humans become infected by ingesting fleas harboring cysticercoids. Children are more likely to become infected than adults. Most infections are asymptomatic, but abdominal pain, diarrhea, anal pruritus, urticaria, eosinophilia, or passage of segments in the stool may occur. The diagnosis is made by the detection of proglottids or ova in the stool. As in *D. latum* infection, therapy consists of praziquantel. Prevention requires anthelmintic treatment and flea control for pet dogs or cats.

SPARGANOSIS

Humans can be infected by the sparganum, or plerocercoid larva, of a diphyllobothrid tapeworm of the genus *Spirometra*. Infection can be acquired by the consumption of water containing infected *Cyclops*; by the ingestion of infected snakes, birds, or mammals; or by the application of infected flesh as poultices. The worm migrates slowly in tissues, and infection commonly presents as a subcutaneous swelling. Periorbital tissues can be involved, and ocular sparganosis may destroy the eye. Surgical excision is used to treat localized sparganosis.

COENUROSIS

This rare infection of humans by the larval stage (coenurus) of the dog tapeworm *Taenia multiceps* or *T. serialis* results in a space-occupying cystic lesion. As in cysticercosis, involvement of the CNS and subcutaneous tissue is most common. Both definitive diagnosis and treatment require surgical excision of the lesion. Chemotherapeutic agents generally are not effective.

This page intentionally left blank

SECTION IX

ENVENOMATIONS, INFESTATIONS, BITES, AND STINGS

CHAPTER 131

DISORDERS CAUSED BY VENOMOUS SNAKEBITES AND MARINE ANIMAL EXPOSURES

Paul S. Auerbach ■ Robert L. Norris

This chapter outlines general principles for the evaluation and management of victims of envenomation and poisoning by venomous snakes and marine creatures. Because the incidence of serious bites and stings is relatively low in developed nations, there is a paucity of relevant clinical research; as a result, therapeutic decision-making often is based on anecdotal information.

VENOMOUS SNAKEBITE

EPIDEMIOLOGY

Venomous snakes belong to the families Viperidae (subfamily Viperinae: Old World vipers; subfamily Crotalinae: New World and Asian pit vipers), Elapidae (including cobras, kraits, coral snakes, and all Australian venomous snakes), Hydrophiidae (sea snakes), Atractaspididae (burrowing asps), and Colubridae (a large family in which most species are nonvenomous and only a few are dangerously toxic to humans). Bite rates are highest in temperate and tropical regions where populations subsist by manual agriculture. Recent estimates indicate somewhere between 1.2 million and 5.5 million snakebites worldwide each year, with 421,000–1,841,000 envenomations and 20,000–94,000 deaths. Such wide-ranging estimates bear testimony to two facts: collection of data is problematic in the regions most affected by venomous snakes (the "developing world"), and what constitutes a "snakebite" varies among researchers. Some count all snakebites (a figure that may include bites by nonvenomous snakes), whereas others count only apparent envenomations.

SNAKE ANATOMY/IDENTIFICATION

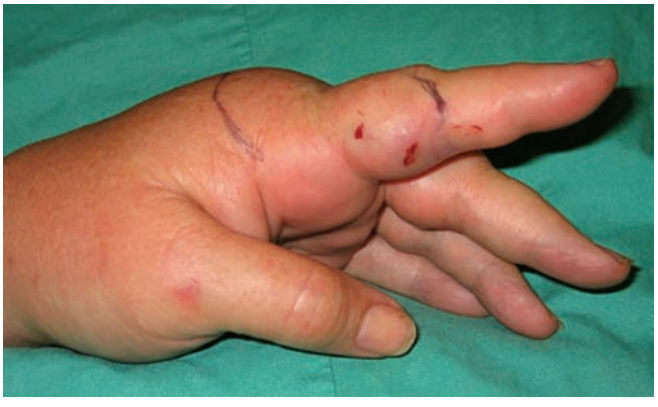
The typical snake-venom apparatus consists of bilateral venom glands situated below and behind the eye and connected by ducts to hollow anterior maxillary teeth. In viperids (vipers and pit vipers), those teeth are long mobile fangs that retract against the roof of the mouth when the animal is at rest. In elapids and sea snakes, the fangs are smaller and are relatively fixed in an erect position. In ~20% of pit viper bites and higher percentages of other snakebites (up to 75% for sea snakes), no venom is released ("dry" bites). Significant envenomation probably occurs in ~50% of all venomous snakebites.

Differentiation of venomous from nonvenomous snake species can be difficult. Viperids are characterized by somewhat triangular heads (a feature shared with many harmless snakes), elliptical pupils (also seen in some nonvenomous snakes, such as boas and pythons), enlarged maxillary fangs, and, in pit vipers, paired heat-sensing pits (foveal organs) on each side of the head. The New World rattlesnakes generally have a series of interlocking keratin plates (the rattle) on the tip of the tail; this rattle is used to dissuade potential threats. Color pattern is notoriously misleading in identifying most venomous snakes. Many harmless snakes have color patterns that closely mimic those of venomous snakes found in the same region.

VENOMS AND CLINICAL MANIFESTATIONS

Snake venoms are complex mixtures of enzymes, low-molecular-weight polypeptides, glycoproteins, metal ions, and other constituents. Among the deleterious components are hemorrhagins that promote vascular leakage and cause both local and systemic bleeding. Proteolytic enzymes cause local tissue necrosis, affect the coagulation pathway at various steps, and impair organ function. Myocardial depressant factors reduce cardiac output, and neurotoxins act either pre- or postsynaptically to inhibit peripheral nerve impulses. Most snake venoms have multisystem effects on their victims.

Envenomations by most viperids and some elapids with necrotizing venoms cause progressive local swelling, pain, ecchymosis **(Fig. 131-1)**, and (over a period of hours or days) hemorrhagic bullae and serum-filled vesicles. In serious bites, tissue loss can be significant **(Fig. 131-2)**. Systemic findings can include changes in taste, mouth numbness, muscle fasciculations, tachycardia or bradycardia, hypotension, pulmonary edema, hemorrhage (from essentially any anatomic site), and renal dysfunction. Envenomations by neurotoxic elapids such as kraits (*Bungarus* spp.), many Australian elapids (e.g., death adders [*Atractaspis* spp.] and tiger snakes [*Notechis* spp.]), some cobras (*Naja* spp.), and some viperids (e.g., the South American rattlesnake [*Crotalus durissus*] and some Indian Russell's vipers [*Daboia russelii*]) cause neurologic dysfunction. Early findings may consist of cranial nerve weakness (e.g., manifested by ptosis) and altered mental status. Severe envenomation may result in paralysis, including the muscles of respiration, and lead to death from respiratory failure and aspiration. After elapid bites, the time of onset of venom intoxication varies from minutes to hours, depending on the species involved, the anatomic location of the bite, and the amount of venom injected. Sea snake envenomation usually causes local pain (variable), myalgias, rhabdomyolysis, and neurotoxicity; these manifestations occasionally are delayed for hours.



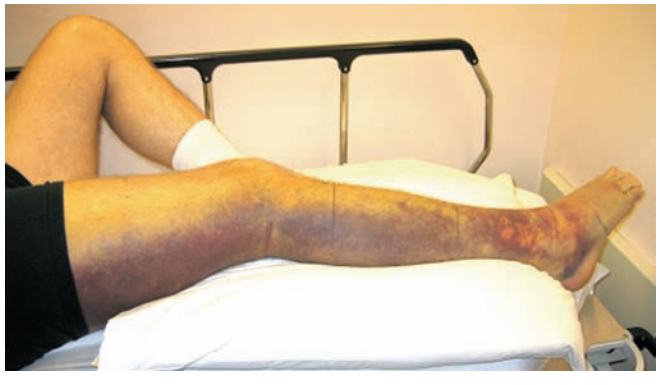


FIGURE 131-1
Northern Pacific rattlesnake (*Crotalus oreganus oreganus*) envenomations. ***Top:*** Moderately severe envenomation. Note edema and early ecchymosis 2 h after a bite to the finger. ***Bottom:*** Severe envenomation. Note extensive ecchymosis 5 days after a bite to the ankle.

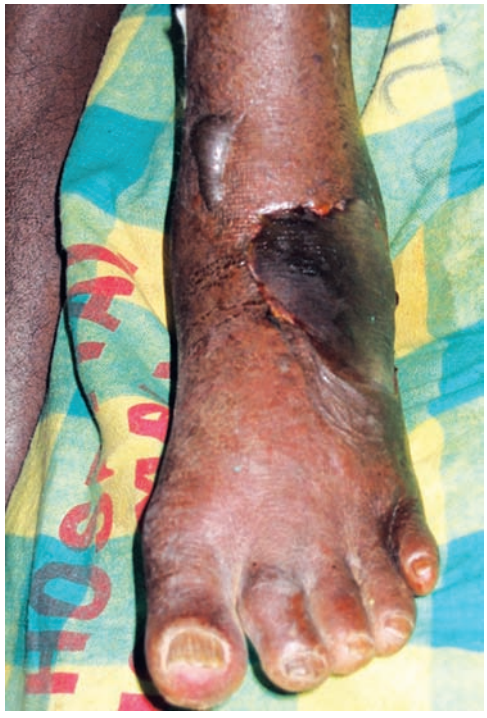


FIGURE 131-2
Early stages of severe, full-thickness necrosis 5 days after a **Russell's viper (*Daboia russelii*) bite** in southwestern India.

TREATMENT Venomous Snakebite

FIELD MANAGEMENT The most important aspect of prehospital care of a person bitten by a venomous snake is rapid delivery to a medical facility equipped to provide supportive care (airway, breathing, and circulation) and antivenom administration. Most of the first-aid recommendations made in the past are of little benefit, and some actually worsen outcome. It is reasonable to apply a splint to the bitten extremity to lessen bleeding and discomfort and, if possible, to keep the extremity at approximately heart level. In developing regions, indigenous people should be encouraged to seek care quickly at health care facilities equipped with antivenoms as opposed to consulting traditional healers and thus incurring significant delays in reaching appropriate care.

Incising wounds and/or applying suction to the bite should be avoided, as these measures are ineffective and exacerbate local tissue damage. Similarly ineffective and potentially damaging are the application of poultices, ice, and electric shock. Techniques or devices used in an effort to limit venom spread (e.g., lymphoocclusive bandages or tourniquets) are ineffective and may result in greater local-tissue damage, particularly that due to necrotic venoms. Tourniquet use can result in amputation and loss of function even in the absence of envenomation.

Elapid venoms that are primarily neurotoxic and have no significant effects on local tissue may be localized by

pressure-immobilization, a technique in which the entire limb is wrapped immediately with a bandage (e.g., crepe or elastic) and then immobilized. For this technique to be effective, the wrap pressure must be precise (40–70 mmHg in upper-extremity application and 55–70 mmHg in lower-extremity application), and the victim must be carried from the scene of the bite to avoid muscle-pump action that—regardless of the anatomic site of the bite—will disperse venom if the victim walks. Pressure-immobilization should be used only in cases in which the offending snake is reliably identified and known to be primarily neurotoxic, the rescuer is skilled in pressure-wrap application, the necessary supplies are readily available, and the victim can be carried to medical care—an uncommon combination of conditions, particularly in regions where such bites are most common.

HOSPITAL MANAGEMENT In the hospital, the victim should be closely monitored (vital signs, cardiac rhythm, oxygen saturation, urine output) while a history is obtained quickly and a rapid, thorough physical examination is performed. For objective evaluation of the progression of local envenomation, the level of swelling in the bitten extremity should be marked and limb circumferences measured every 15 min until swelling has stabilized. During this period of observation/monitoring, the extremity should be positioned at approximately heart level. Measures applied in the field (such as constriction bands or tourniquets) should be removed once IV access has been obtained, with cognizance that the release of such ligatures may result in hypotension or dysrhythmias when stagnant acidotic blood is released to the central circulation. Large-bore IV access in one or two unaffected extremities should be established. Early hypotension is due to pooling of blood in the pulmonary and splanchnic vascular beds. Later, systemic bleeding, hemolysis, and loss of intravascular volume into soft tissues may play important roles. Fluid resuscitation with isotonic saline (20–40 mL/kg IV) should be initiated if there is any evidence of hemodynamic instability, and a trial of 5% albumin (10–20 mL/kg) may be given when patients fail to respond to saline infusion. Only after aggressive volume resuscitation and antivenom administration (see next) should vasopressors (e.g., dopamine) be added. Invasive hemodynamic monitoring (central venous and/or pulmonary arterial pressures) can be helpful in such cases, although obtaining access is risky if coagulopathy has developed.

Blood should be drawn for typing and cross-matching and for laboratory evaluation as soon as possible. Important studies include a complete blood count to evaluate the degree of hemorrhage or hemolysis and to identify thrombocytopenia, studies of renal and hepatic function, coagulation studies to diagnose consumptive coagulopathy, and testing of urine for blood or myoglobin. In developing regions, the 20-min whole-blood clotting test can be used for reliable diagnosis of coagulopathy. A few milliliters of fresh blood are placed in a new, clean, plain glass receptacle (e.g., a test tube) and left undisturbed for 20 min. The tube then is tipped once to 45° to determine whether a clot has formed. If it has not, coagulopathy is diagnosed. Arterial blood gas studies, electrocardiography, and chest radiography may be helpful in severe envenomations or when there is significant comorbidity. Any arterial puncture in the setting of coagulopathy, however, requires great caution and must be performed at an anatomic site amenable to direct-pressure tamponade. After antivenom therapy (see next), laboratory values should be rechecked every 6 h until clinical stability is achieved. If initial laboratory values are normal, the complete blood count and coagulation studies should be repeated every hour until it is clear that no systemic envenomation has occurred. Victims of neurotoxic envenomation should be watched carefully for evidence of cranial nerve dysfunction (e.g., ptosis) that may precede the onset of difficulty swallowing or respiratory insufficiency and necessitate definitive securing of the airway by endotracheal intubation.

The key to management of venomous snakebite resulting in significant envenomation is the administration of specific antivenom. Antivenoms are produced by the injection of venoms from medically important snakes into animals, generally horses or sheep. Once the stock animals develop antibodies to the venoms, their serum is harvested and the antibodies are isolated for antivenom preparation, which may involve varying degrees of digestion and purification of the IgG molecules. The goal of antivenom administration is to allow antibodies (or antibody fragments) to bind up circulating venom components before they can attach to target tissues and cause deleterious effects. Antivenoms may be monospecific (for a particular snake species) or polyspecific (covering several medically important species in the region) but rarely offer cross-protection against snake species other than those used in their production unless the species are known to have homologous venoms. Thus, antivenom selection must be specific for the offending snake; if the antivenom chosen does not contain antibodies to that snake's venom components, it will be of no value and may lead to unnecessary complications (see next). In the United States, assistance in finding appropriate antivenom can be obtained from regional poison control centers.

Indications for antivenom administration to victims of bites by viperids or cytotoxic elapids include any evidence of systemic envenomation (systemic symptoms or signs, laboratory abnormalities) and significant progressive local findings (e.g., soft tissue swelling crossing a joint or involving more than half the bitten limb). Care must be used in determining the significance of isolated soft tissue swelling after the bite of an unidentified snake because the saliva of some relatively harmless species can cause mild edema at the bite site. In such bites, antivenoms are useless and potentially harmful. The efficacy of antivenoms in preventing tissue damage caused by necrotizing venoms is limited. It may be

impossible to prevent necrosis completely, as venom components bind to local tissues very quickly—before antivenom administration can be instituted. Nevertheless, antivenom administration should begin as soon as the need for it is identified to limit further tissue damage and systemic effects. Antivenom administration after the bites of neurotoxic elapids is indicated at the first sign of any evidence of neurotoxicity (cranial nerve dysfunction [e.g., ptosis] or peripheral neuropathy).

Specific comments related to the management of venomous snakebite in the United States and Canada appear in Table 131-1. The package insert for the selected antivenom can be consulted regarding species covered, method of administration, starting dose, and need (if any) for redosing. The information in antivenom package inserts, however, is not always accurate and reliable. Whenever possible, it is advisable for treating physicians to seek advice from experts in snakebite management regarding indications for and dosing of antivenom. For viperid bites, antivenom administration generally should be continued as needed until the victim shows definite improvement (e.g., stabilized vital signs, reduced pain, restored coagulation). Neurotoxicity from elapid bites may be harder to reverse with antivenom. Once neurotoxicity is established and endotracheal intubation is required, further doses of antivenom are unlikely to be beneficial. In such cases, the victim must be maintained on mechanical ventilation until recovery, which may take days or weeks.

Use of any heterologous serum product carries a risk of acute nonallergic (and, less commonly, allergic) anaphylaxis and delayed-type hypersensitivity reactions (serum sickness). Skin testing for potential allergy, although recommended by some antivenom manufacturers, is insensitive and nonspecific and should be omitted. Worldwide, the quality of antivenoms is highly variable. Rates of acute nonallergic anaphylactic reactions to some of these products exceed 50%. For this reason, some authorities have recommended pretreatment with IV antihistamines (e.g., diphenhydramine, 1 mg/kg to a maximum of 100 mg, and cimetidine, 5–10 mg/kg to a maximum of 300 mg) or even a prophylactic subcutaneous or intramuscular dose of epinephrine (0.01 mg/kg, up to 0.3 mg). Further research is necessary, however, to determine whether any pretreatment measures are truly beneficial. Modest expansion of the patient's intravascular volume with crystalloids may blunt acute adverse reactions. Epinephrine should always be immediately available, and the antivenom dose to be administered should be diluted in an appropriate volume of crystalloid according to the package insert. Antivenom should be given only by the IV route, and the infusion should be started slowly, with the physician at the bedside during the initial period to intervene immediately at the first signs of an acute reaction (which may be heralded by a single hive or mild itching or may present as bronchospasm or acute cardiovascular collapse). The rate of infusion can be increased gradually in the absence of a reaction until the full starting dose has been administered (over a total period of ~1 h). Further antivenom may be necessary if the patient's acute clinical condition worsens or fails to stabilize. There is some evidence that smaller-molecular-weight Fab-fragment antivenoms are cleared more quickly from the circulation than are whole-IgG or $F(ab)_2$ antivenoms and thus may require redosing if venom effects that were controlled initially begin to recur. The decision to administer further antivenom to a stabilized patient generally should be based on clinical evidence of persistent circulation of unbound venom components. Antivenom is effective only in reversing active venom toxicity; it is of no benefit in reversing effects that already have been established (e.g., renal failure, established paralysis, necrosis) and that will improve only with time and other therapies.

If the patient develops an acute reaction to antivenom, the infusion should be temporarily stopped and the reaction immediately treated with IM epinephrine and IV antihistamines and glucocorticoids. Once the reaction is controlled, if the severity of envenomation warrants additional antivenom, the dose should be diluted further in isotonic saline and restarted as soon as possible. Rarely, in recalcitrant cases, a concomitant IV infusion of epinephrine may be required to hold allergic sequelae at bay while further antivenom is administered. The patient must be monitored very closely, preferably in an intensive care setting, during such therapy.

Blood products are rarely necessary in the management of an envenomated patient. The venoms of many snake species can cause a drop in platelet count or hematocrit and depletion of coagulation factors. Nevertheless, these components usually rebound within hours after administration of adequate antivenom. If the need for blood products is thought to be great (e.g., for a dangerously low platelet count in a hemorrhaging patient), these products should be given only after adequate antivenom administration to avoid adding fuel to an ongoing consumptive coagulopathy.

Rhabdomyolysis and hemolysis should be managed in standard fashion. Victims who develop acute renal failure should be evaluated by a nephrologist and referred for peritoneal dialysis or hemodialysis as needed. Such renal failure, which usually is due to acute tubular necrosis, is frequently reversible. If bilateral cortical necrosis occurs, however, the prognosis for renal recovery is grimmer, and long-term dialysis with possible renal transplantation may be necessary.

Acetylcholinesterase inhibitors (e.g., edrophonium and neostigmine) may promote neurologic improvement in patients bitten by snakes with postsynaptic neurotoxins. Victims with objective evidence of neurologic dysfunction after snakebite should receive a trial of acetylcholinesterase inhibitors, as outlined in Table 131-2. If they respond, additional doses of long-acting neostigmine can be continued as needed. Special vigilance is required to prevent aspiration if repetitive dosing of neostigmine is used in an attempt to obviate endotracheal intubation.

TABLE 131-1

MANAGEMENT OF VENOMOUS SNAKEBITE IN THE UNITED STATES AND CANADA[a]

Pit viper bites (rattlesnakes [*Crotalus* and *Sistrurus* spp.], cottonmouth water moccasins [*Agkistrodon piscivorus*], and copperheads [*A. contortrix*])

- Stabilize airway, breathing, and circulation.
- Institute monitoring (cardiac and pulse oximetry).
- Establish two large-bore IV lines with normal saline infusion (administer a bolus of 20–40 mL/kg of body weight if the patient is hypotensive; if hypotension persists, consider albumin).
- Take rapid history and perform rapid physical examination (including vital signs).
- Measure/record circumferences of the bitten extremity every 15 min until swelling has stabilized.
- Identify the offending reptile if possible.
- Send laboratory studies (CBC, metabolic panel, PT/INR/PTT, fibrinogen level, FDP, blood type and screening, urinalysis).
  - If normal, repeat CBC, PT/INR/PTT, fibrinogen level, and FDP every hour until it is clear that no systemic envenomation has occurred.
  - If abnormal, repeat 6 h after antivenom administration (see below).
- Determine severity of envenomation.
  - None ("dry bite"): fang marks only
  - Mild: local findings only (e.g., pain, local ecchymosis, nonprogressive swelling)
  - Moderate: swelling that is clearly progressing, systemic signs or symptoms, and/or laboratory abnormalities
  - Severe: respiratory distress, neurologic dysfunction, and/or cardiovascular instability/shock
- Locate and administer antivenom as indicated: Crotalidae Polyvalent Immune Fab (CroFab) (Ovine) (Protherics US Inc., Brentwood, TN).
  - Starting dose
    - Based on severity of envenomation
      - None or mild: none
      - Moderate: 4–6 vials
      - Severe: 6 vials
    - Mix reconstituted vials in 250 mL of normal saline.
    - No pretesting for potential allergy; no premedication
    - Give IV over 1 h (with physician in close attendance).
  - If acute reaction to antivenom
    - Stop infusion.
    - Treat with standard doses of epinephrine (IM or IV; the latter route only in the setting of severe hypotension), antihistamines (IV), and glucocorticoids (IV).
    - When reaction is controlled, restart antivenom as soon as possible (may further dilute in a larger volume of normal saline).
  - Monitor clinical status over 1 h.
    - Stabilized, improved: hospital admission
    - Progressing or unimproved: repetition of starting dose (this pattern continued until patient's condition is stable or improved)
- Pain management: acetaminophen and/or narcotics as needed (avoid salicylates and nonsteroidal anti-inflammatory agents)
- Update tetanus immunization as needed.
- Prophylactic antibiotics are unnecessary unless prehospital care included incisions or mouth suction.
- Blood products and coagulation factors are rarely needed; if required, they should be given only after antivenom administration.
- Admit to hospital. (If no evidence of envenomation, monitor for 8 h before discharge.)
  - Give further CroFab (two vials q6h for three additional doses; close monitoring).
  - Monitor for evidence of rising intracompartmental pressures (see text).
  - Provide wound care (see text).
  - Begin physical therapy (see text).
- At discharge, warn patient of possible recurrent coagulopathy and signs/symptoms of delayed serum sickness.

Coral snakebites (*Micrurus* spp. and *Micruroides euryxanthus*)

- Stabilize airway, breathing, and circulation as needed.
- Institute monitoring (cardiac and pulse oximetry).
- Establish one large-bore IV line with normal saline infusion.
- Take rapid history and perform rapid physical examination (including vital signs).
- Identify the offending reptile if possible.
- Laboratory studies are unlikely to be helpful.
- If any evidence of neurologic dysfunction (e.g., any cranial nerve abnormalities such as ptosis):
  - Trial of anticholinesterase inhibitors (see Table 131-2)
  - With any evidence of difficulty swallowing or breathing, proceed with endotracheal intubation and ventilatory support (may be required for days or weeks).

(*continued*)

TABLE 131-1

MANAGEMENT OF VENOMOUS SNAKEBITE IN THE UNITED STATES AND CANADA[a] (*CONTINUED*)

- Update tetanus immunization as needed.
- Prophylactic antibiotics are unnecessary unless prehospital care included incisions or mouth suction.
- Admit to hospital (intensive care unit) even if there is no evidence of envenomation (monitor for at least 24 h).
- At the time of this publication, no coral snake antivenom is commercially available for routine use in the United States.

[a]These recommendations are specific to the care of victims of venomous snakebite in the United States and Canada and should not be applied to bites in other regions of the world.

Abbreviations: CBC, complete blood count; FDP, fibrin degradation products; PT/INR/PTT, prothrombin time/international normalized ratio/activated partial thromboplastin time.

Care of the bite wound includes application of a dry, sterile dressing and splinting of the extremity with padding between the digits. Once the administration of antivenom has been initiated, the extremity should be elevated above heart level to relieve edema. Tetanus immunization should be updated as appropriate. Prophylactic antibiotics are generally unnecessary after bites by North American snakes, as the incidence of secondary infection is low. Antibiotics can be considered, however, if misguided first aid efforts have included incisions or mouth suction. In some regions, secondary bacterial infection is more common and the consequences are dire. In these regions, prophylactic antibiotics (e.g., cephalosporins) are used commonly. Pain control should be achieved with acetaminophen or narcotic analgesics. Salicylates and nonsteroidal anti-inflammatory agents should be avoided because of their effects on blood clotting.

Most snake envenomations involve subcutaneous deposition of venom. On occasion, however, venom can be injected more deeply into muscle compartments, particularly if the offending snake was large and the bite occurred to the lower leg or the forearm or hand. If swelling in the bitten extremity raises concern that subfascial muscle edema may be impeding tissue perfusion (muscle-compartment syndrome), intracompartmental pressures (ICPs) should be checked by any minimally invasive technique—e.g., wick catheter or ICP monitor (Stryker Instruments, Kalamazoo, MI). If any ICP is high (>30–40 mmHg), the extremity should be kept elevated while further antivenom is given. A dose of IV mannitol (1 g/kg) can be given in an effort to reduce muscle edema if the patient's hemodynamic status is stable. If, after 1 h of such therapy, the ICP remains elevated, a surgical consultation for possible fasciotomy should be obtained. Although preliminary evidence from studies in animals suggests that fasciotomy actually may worsen myonecrosis, compartmental decompression is still required to preserve nerve function. Fortunately, the incidence of muscle-compartment syndrome is very low after snakebite, with fasciotomies required in <1% of cases. Nevertheless, vigilance is required; if a fasciotomy is deemed necessary, it should be undertaken with the patient's informed consent whenever possible.

Wound care in the days after the bite may require careful aseptic debridement of clearly necrotic tissue once coagulation has been restored. Intact serum-filled vesicles or hemorrhagic blebs should be left undisturbed. If ruptured, they should be debrided with sterile technique. Any debridement of damaged muscle should be conservative, as there is evidence that such muscle may recover to a significant degree.

Physical therapy should be started when pain allows so that the victim can return to a functional state. The incidence of long-term loss of function (e.g., reduced range of motion, impaired sensory function) is unclear but is probably quite high (>30%), particularly after viperid bites.

Any patient with signs of envenomation should be observed in the hospital for at least 24 h. In North America, a patient with an apparently "dry" viperid bite should be watched for at least 8 h before discharge, as significant toxicity occasionally develops after a delay of several hours. The onset of systemic symptoms commonly is delayed for a number of hours after bites by several of the elapids (including coral snakes, *Micrurus* spp.), some non–North American viperids (e.g., the

TABLE 131-2

USE OF ACETYLCHOLINESTERASE INHIBITORS IN NEUROTOXIC SNAKE ENVENOMATION

1. Patients with clear, objective evidence of neurotoxicity after snakebite (e.g., ptosis or inability to maintain upward gaze) should receive a trial of edrophonium (if available) or neostigmine.
   a. Pretreat with atropine: 0.6 mg IV (children, 0.02 mg/kg; minimum of 0.1 mg)
   b. Follow with:
      Edrophonium: 10 mg IV (children, 0.25 mg/kg)
      or
      Neostigmine: 1.5–2.0 mg IM (children, 0.025–0.08 mg/kg)
2. If objective improvement is evident at 5 min, continue neostigmine at a dose of 0.5 mg (children, 0.01 mg/kg) IV or SC every 30 min as needed, with continued administration of atropine by continuous infusion of 0.6 mg over 8 h (children, 0.02 mg/kg over 8 h).
3. Maintain vigilance regarding aspiration risk and secure the airway with endotracheal intubation as needed.

hump-nosed pit viper [*Hypnale hypnale*]), and sea snakes. Patients bitten by these reptiles should be observed in the hospital for at least 24 h. Patients whose condition is not stable should be admitted to an intensive care setting.

At discharge, victims of venomous snakebite should be warned about signs and symptoms of wound infection, antivenom-related serum sickness, and potential long-term sequelae, such as pituitary insufficiency in Russell's viper (*D. russelii*) bites. If coagulopathy developed in the acute stages of envenomation, it can recur during the first 2–3 weeks after the bite. In such cases, victims should be warned to avoid elective surgery or activities posing a high risk of trauma during this period. Outpatient analgesic treatment and physical therapy should be continued.

In the event of serum sickness (fever, chills, urticaria, myalgias, arthralgias, and possibly renal or neurologic dysfunction developing 1–2 weeks after antivenom administration), the victim should be treated with systemic glucocorticoids (e.g., oral prednisone, 1–2 mg/kg daily) until all findings resolve; the dose is then tapered over 1–2 weeks. Oral antihistamines and analgesics provide additional relief of symptoms.

MORBIDITY AND MORTALITY

The overall mortality rates for venomous snakebite are low in areas with rapid access to medical care and appropriate antivenoms. In the United States, for example, the mortality rate is <1% for victims who receive antivenom. Eastern and western diamondback rattlesnakes (*Crotalus adamanteus* and *C. atrox*, respectively) are responsible for the majority of snakebite deaths in the United States. Snakes responsible for large numbers of deaths in other countries include cobras (*Naja* spp.), carpet and saw-scaled vipers (*Echis* spp.), Russell's vipers (*D. russelii*), large African vipers (*Bitis* spp.), lancehead pit vipers (*Bothrops* spp.), and tropical rattlesnakes (*C. durissus*).

The incidence of morbidity—defined as permanent functional loss in a bitten extremity—is difficult to estimate but is substantial. Morbidity may be due to muscle, nerve, or vascular injury or to scar contracture. Such morbidity can have devastating consequences for victims in the developing world when their ability to work and provide for their families is lost. In the United States, functional loss tends to be more common and severe after rattlesnake bites than after bites by copperheads (*Agkistrodon contortrix*) or water moccasins (*A. piscivorus*).

THE GLOBAL CRISIS

In many developing countries where snakebite is common, scarce access to medical care and antivenom resources contributes to high rates of morbidity and death. In many countries, the available antivenoms are inappropriate and ineffective against the venoms of medically important indigenous snakes. In those regions, further research is necessary to determine the actual impact of venomous snakebite and the specific antivenom needs in terms of both quantity and spectrum of coverage. Without accurate statistics, it is difficult to persuade antivenom manufacturers to begin and sustain production of appropriate antisera in developing nations. There is evidence that antivenoms can be produced in much more cost-effective ways than those currently being used. Just as important as getting the correct antivenoms into underserved regions is the need to educate populations about the prevention of snakebite and train medical care providers in proper management approaches. Local protocols written with significant input from experienced providers in the region of concern should be developed and distributed. Appropriate antivenoms must be available at the likely first point of medical contact for patients (e.g., primary health centers) to minimize the common practice of referring victims to more distant, higher levels of care for the initiation of antivenom therapy. Those who care for snakebite victims in these often remote clinics must have the skills and confidence required to begin antivenom treatment (and to treat possible reactions) as soon as possible when needed.

MARINE ENVENOMATIONS

Much of the management of envenomation by marine creatures is supportive in nature. A specific marine antivenom can be used when appropriate.

INVERTEBRATES

Cnidarians

The Golgi apparatus of the cnidoblast cells within cnidarians such as hydroids, fire coral, jellyfish, Portuguese men-of-war, and sea anemones secretes specialized living stinging organelles called *cnidae* (also referred to as *cnidocysts*, a term that encompasses nematocysts, ptychocysts, and spirocysts). Within each organelle resides a stinging mechanism ("thread tube") and venom. In the stinging process, cnidocysts are released and discharged upon mechanosensory stimulation. The venoms from these organisms are mixtures of proteins, carbohydrates, and other components. Victims usually report immediate prickling or burning, pruritus, paresthesias, and painful throbbing with radiation. The skin becomes reddened, darkened, edematous, and/or blistered. A legion of neurologic, cardiovascular, respiratory, rheumatologic, gastrointestinal, renal, and ocular symptoms have been described. Anaphylaxis is possible. *Irukandji syndrome*, associated with the Australian jellyfish *Carukia barnesi* and other species, is a potentially fatal condition that most commonly is characterized by severe back, chest, and abdominal pain; nausea and vomiting; headache; sweating; and, in the most serious cases, myocardial

troponin leak and pulmonary edema. This syndrome is thought to be mediated, at least in part, by the release of endogenous catecholamines.

Rescuers should note that envenomations by different cnidarians (typified by jellyfish) may respond differently to similar therapies; thus, the recommendations in this chapter must be tailored to local species and clinical practices. During stabilization, the skin should be decontaminated immediately with a generous application of vinegar (5% acetic acid), which is the all-purpose agent useful for inactivating the nematocysts in the greatest number of species. Rubbing alcohol (40–70% isopropyl alcohol), baking soda (sodium bicarbonate), papain (unseasoned meat tenderizer), fresh lemon or lime juice, household ammonia, olive oil, or sugar may be effective, depending on the species of stinging creature. For the sting of the venomous box-jellyfish (*Chironex fleckeri*), vinegar should be used. Local application of heat (up to 45°C/113°F), commonly by immersion in hot water, may be as effective. Commercial (chemical) cold packs or real ice packs applied over a thin dry cloth or plastic membrane have been shown to be effective in alleviating mild or moderate *Physalia utriculus* (bluebottle jellyfish) stings but may be less effective than application of heat. Perfume, aftershave lotion, and high-proof ethanol are not efficacious and may be detrimental; formalin, ether, gasoline, and other organic solvents should not be used. Shaving the skin helps remove remaining nematocysts. Freshwater irrigation and rubbing lead to further stinging by adherent nematocysts and should be avoided. After decontamination, topical application of an anesthetic ointment (lidocaine, benzocaine), an antihistamine (diphenhydramine), or a glucocorticoid (hydrocortisone) may be helpful. Persistent severe pain after decontamination may be treated with morphine, meperidine, fentanyl, or another narcotic analgesic. Muscle spasms may respond to diazepam (2–5 mg, titrated upward as necessary) or 10% calcium gluconate (5–10 mL) given IV. An ovine-derived antivenom is available from Commonwealth Serum Laboratories (see the section on antivenom sources, later in the chapter) for stings from the box-jellyfish found in Australian and Indo-Pacific waters. Ongoing discussion about its efficacy centers on the notion that *C. fleckeri* venom acts more rapidly than the antivenom can bind to the venom. As of this writing, this antivenom has not been used to treat envenomation by the box-shaped jellyfish (possibly of the genus *Chiropsalmus*) that has been found in Florida waters. Treatment for Irukandji syndrome may require the administration of $MgSO_4$ and aggressive antihypertensive treatment.

The pressure-immobilization technique is no longer recommended for venom containment in the setting of a jellyfish sting. Safe Sea, a "jellyfish-safe" sunblock (*www.nidaria.com*) applied to the skin before an individual enters the water, inactivates the recognition and discharge mechanisms of nematocysts, has been tested successfully against a number of marine stingers, and may prevent or diminish the effects of coelenterate stings. Whenever possible, a dive skin or wet suit should be worn when entering ocean waters.

Sea sponges

Touching a sea sponge may result in dermatitis. The afflicted skin should be gently dried and adhesive tape used to remove embedded spicules. Vinegar should be applied immediately and then for 10–30 min three or four times a day. Rubbing alcohol may be used if vinegar is unavailable. After spicule removal and skin decontamination, steroid or antihistamine cream may be applied to the skin. Severe vesiculation should be treated with a 2-week course of systemic glucocorticoids.

Annelid worms

Annelid worms (bristleworms) possess rows of soft, cactus-like spines capable of inflicting painful stings. Contact results in symptoms similar to those of nematocyst envenomation. Without treatment, pain usually subsides over several hours, but inflammation may persist for up to a week. Victims should resist the urge to scratch, since scratching may fracture retrievable spines. Visible bristles should be removed with forceps and adhesive tape or a commercial facial peel; alternatively, a thin layer of rubber cement can be used to entrap the spines. Use of vinegar, rubbing alcohol, or dilute ammonia or a brief application of unseasoned meat tenderizer (papain) may provide additional relief. Local inflammation should be treated with topical or systemic glucocorticoids.

Sea urchins

Sea urchins possess either hollow, venom-filled calcified spines or triple-jawed, globiferous pedicellariae with venom glands. The venom contains toxic components, including steroid glycosides, hemolysins, proteases, serotonin, and cholinergic substances. Contact with either venom apparatus produces immediate and intensely painful stings. The affected part should be immersed immediately in hot water (see next). Accessible embedded spines should be removed but may break off and remain lodged in the victim. Residual dye from the surface of a spine remaining after the spine's removal may mimic a retained spine but is otherwise of no consequence. Soft tissue radiography or MRI can confirm the presence of retained spines, which may warrant referral for attempted surgical removal if the spines are near vital structures (e.g., joints, neurovascular bundles). Retained spines may cause the formation of granulomas that are amenable to excision or to intralesional injection with triamcinolone hexacetonide (5 mg/mL). Chronic granulomatous arthritis of the proximal interphalangeal joints has been treated with synovectomy and removal of granulation tissue. Erbium-YAG laser ablation has been deployed to destroy multiple sea urchin spines embedded in the foot and identified visually at surface level without causing thermal necrosis of the adjacent tissues. Eosinophilic pneumonia and local and diffuse neuropathies have been observed separately after penetration by multiple spines of the black sea urchin (presumed *Diadema* spp.). The pathophysiology of this phenomenon has not been determined.

Octopuses

Serious envenomations and deaths have followed bites of Australian blue-ringed octopuses (*Octopus maculosus* and *O. lunulata*). Although these animals rarely exceed 20 cm in length, their venom contains a potent neurotoxin (maculotoxin) that inhibits peripheral-nerve transmission by blocking sodium conductance. Oral numbness and facial numbness develop within several minutes of a serious envenomation and rapidly progress to total flaccid paralysis, including failure of respiratory muscles. Immediately after envenomation, a circumferential pressure-immobilization dressing 15 cm wide should be applied over a gauze pad (~7 × 7 × 2 cm) that has been placed directly over the sting. The dressing should be applied at venous-lymphatic pressure, with the preservation of distal arterial pulses. The limb should then be splinted. Once the victim has been transported to the nearest medical facility, the bandage can be released. Since there is no antidote, treatment is supportive. If respirations are assisted, the victim may remain awake although completely paralyzed. Even with serious envenomations, significant recovery often takes place within 4–10 h. Sequelae are uncommon unless related to hypoxia.

VERTEBRATES

Stingrays

A stingray injury is both an envenomation and a traumatic wound. Thoracic and cardiac penetration, major vessel laceration, and compartment syndrome have all been observed. The venom, which contains serotonin, 5'-nucleotidase, and phosphodiesterase, causes immediate, intense pain that may last up to 48 h. The wound often becomes ischemic in appearance and heals poorly, with adjacent soft tissue swelling and prolonged disability. Systemic effects include weakness, diaphoresis, nausea, vomiting, diarrhea, dysrhythmias, syncope, hypotension, muscle cramps, fasciculations, paralysis, and (in rare cases) death. Because of the differences in toxins present on the tissues covering the stingers, freshwater stingrays may cause more severe injuries than do marine stingrays.

Scorpionfish

The designation *scorpionfish* encompasses members of the family Scorpaenidae and includes not only scorpionfish but also lionfish and stonefish. A complex venom with neuromuscular toxicity is delivered through 12 or 13 dorsal, 2 pelvic, and 3 anal spines. In general, the sting of a stonefish is regarded as the most serious (severe to life-threatening); that of the scorpionfish is of intermediate seriousness; and that of the lionfish is the least serious. Like that of a stingray, the sting of a scorpionfish is immediately and intensely painful. Pain from a stonefish envenomation may last for days. Systemic manifestations of scorpionfish stings are similar to those of stingray envenomations but may be more pronounced, particularly in the case of a stonefish sting. The rare deaths that follow stonefish envenomation usually occur within 6–8 h.

Other fish

Two species of marine catfish—*Plotosus lineatus* (the oriental catfish) and *Galeichthys felis* (the common sea catfish)—as well as several species of freshwater catfish are capable of stinging humans. Venom is delivered through a single dorsal spine and two pectoral spines. Clinically, a catfish sting is comparable to that of a stingray, although marine catfish envenomations are generally more severe than those of their freshwater counterparts. Surgeonfish (doctorfish, tang), weeverfish, ratfish, and horned venomous sharks have also envenomated humans.

TREATMENT **Marine Vertebrate Stings**

The stings of all marine vertebrates are treated in a similar fashion. Except for stonefish and serious scorpionfish envenomations (see next), no antivenom is available. The affected part should be immersed immediately in nonscalding hot water (45°C/113°F) for 30–90 min or until there is significant relief of pain. Recurrent pain may respond to repeated hot-water treatment. Cryotherapy is contraindicated. Opiates will help alleviate the pain, as will local wound infiltration or regional nerve block with 1% lidocaine, 0.5% bupivacaine, and sodium bicarbonate mixed in a 5:5:1 ratio. After soaking and anesthetic administration, the wound must be explored and debrided. Radiography (in particular, MRI) may be helpful in identification of foreign bodies. After exploration and debridement, the wound should be irrigated vigorously with warm sterile water, saline, or 1% povidone-iodine in solution. Bleeding usually can be controlled by sustained local pressure for 10–15 min. In general, wounds should be left open to heal by secondary intention or treated by delayed primary closure. Tetanus immunization should be updated. Antibiotic treatment should be considered for serious wounds and for envenomation in immunocompromised hosts. The initial antibiotics should cover *Staphylococcus* and *Streptococcus* spp. If the victim is immunocompromised, if a wound is primarily repaired and is more than minor, or if an infection develops, antibiotic coverage should be broadened to include *Vibrio* spp. Infection with *Aeromonas* spp. is of similar concern for wounds associated with natural freshwater.

APPROACH TO THE PATIENT **Marine Envenomations**

It is useful to be familiar with the local marine fauna and to recognize patterns of injury.

A large puncture wound or jagged laceration (particularly on the lower extremity) that is more painful than one would expect from the size and configuration of the wound is likely to be a stingray envenomation. Smaller punctures, as described earlier, represent the activity of a sea urchin or starfish. Stony corals cause rough abrasions and, in rare instances, lacerations or puncture wounds.

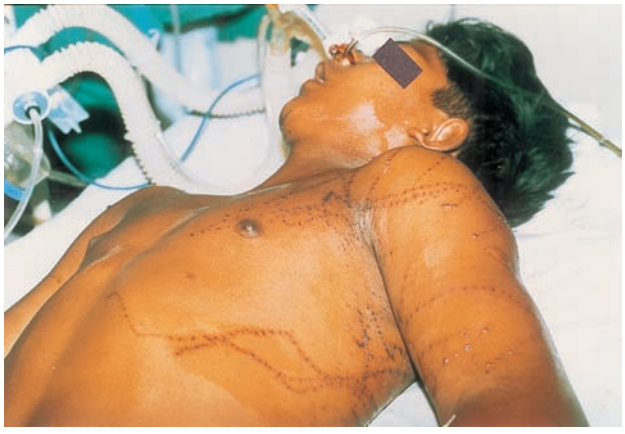


FIGURE 131-3
Skin lesions caused by *Chironex fleckeri (box-jellyfish)* sting. (*Courtesy of Dr. V. Pranava Murthy; with permission.*)

Coelenterate (marine invertebrate) stings sometimes create diagnostic skin patterns. A diffuse urticarial rash on exposed skin is often indicative of exposure to fragmented hydroids or larval anemones. A linear, whiplike print pattern appears where a jellyfish tentacle has contacted the skin. In the case of the dreaded box-jellyfish (Fig. 131-3), a cross-hatched appearance, followed by development of dark purple coloration within a few hours of the sting, heralds skin necrosis. A frosted appearance may be created by aluminum salt–based remedies applied to the wound. An encounter with fire coral causes immediate pain and swollen red skin irritation in the pattern of contact, similar to but more severe than the imprint left by exposure to an intact feather hydroid. Seabather's eruption, caused by thimble jellyfishes and larval anemones, may produce a diffuse rash that consists of clusters of erythematous macules or raised papules and is accompanied by intense itching (Fig. 131-4). Toxic sponges create a burning and painful red rash on exposed skin, which may blister and later desquamate. Virtually all marine stingers invoke the sequelae of inflammation, so that local erythema, swelling, and adenopathy are fairly nonspecific.

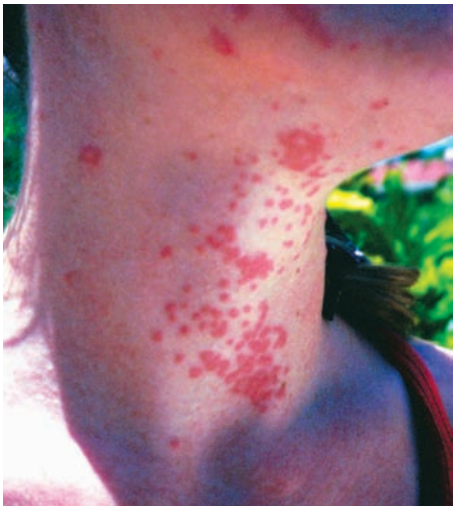


FIGURE 131-4
Erythematous, papular rash typical of seabather's eruption caused by thimble jellyfish and larval anemones.

SOURCES OF ANTIVENOMS AND OTHER ASSISTANCE

The best way to locate a specific antivenom in the United States is to call a regional poison control center and ask for assistance. Divers Alert Network, a nonprofit organization designed to assist in the care of injured divers, also may help with the treatment of marine injuries. The network can be reached on the Internet at *www.diversalertnetwork.org* or by telephone 24 h a day at (919) 684-9111. An antivenom for stonefish (and severe scorpionfish) envenomation is made in Australia by the Commonwealth Serum Laboratories (CSL; 45 Poplar Road, Parkville, Victoria, Australia 3052; *www.csl.com.au*; 61-3-9389-1911). Polyvalent sea snake antivenom is also available from CSL. It is no longer recommended that tiger snake antivenom be used if sea snake antivenom is unavailable.

MARINE POISONINGS

CIGUATERA

Epidemiology and pathogenesis

Ciguatera poisoning is the most common nonbacterial food poisoning associated with fish in the United States; most U.S. cases occur in Florida and Hawaii. The poisoning almost exclusively involves tropical and semitropical marine coral reef fish common in the Indian Ocean, the South Pacific, and the Caribbean Sea. Among reported cases, 75% (except in Hawaii) involve the barracuda, snapper, jack, or grouper. The ciguatera syndrome is associated with at least five polyether sodium channel activator toxins that originate in photosynthetic dinoflagellates (such as *Gambierdiscus toxicus*) and accumulate in the food chain. Three major ciguatoxins are found in the flesh and viscera of ciguateric fishes: CTX-1, -2, and -3. TRPV1, a nonselective cation channel expressed in nociceptive neurons, may play a role in the unique neurologic disturbances in ciguatera poisoning. Most, if not all, ciguatoxins are unaffected by freeze-drying, heat, cold, and gastric acid. None of the toxins affects the odor, color, or taste of fish. Cooking methods may alter the relative concentrations of the various toxins.

Clinical manifestations

The onset of symptoms may come within 15–30 min of ingestion and typically takes place within 2–6 h. Symptoms increase in severity over the ensuing 4–6 h. Most victims develop symptoms within 12 h of ingestion, and virtually all are afflicted within 24 h. The >150 symptoms

reported include abdominal pain, nausea, vomiting, diarrhea, chills, paresthesias, pruritus, tongue and throat numbness or burning, sensation of "carbonation" during swallowing, odontalgia or dental dysesthesias, dysphagia, dysuria, dyspnea, weakness, fatigue, tremor, fasciculations, athetosis, meningismus, aphonia, ataxia, vertigo, pain and weakness in the lower extremities, visual blurring, transient blindness, hyporeflexia, seizures, nasal congestion and dryness, conjunctivitis, maculopapular rash, skin vesiculations, dermatographism, sialorrhea, diaphoresis, headache, arthralgias, myalgias, insomnia, bradycardia, hypotension, central respiratory failure, and coma. Death is rare.

Diarrhea, vomiting, and abdominal pain usually develop 3–6 h after ingestion of a ciguatoxic fish. Symptoms may persist for 48 h and then generally resolve (even without treatment). A pathognomonic symptom is the reversal of hot and cold tactile perception, which develops in some persons after 3–5 days and may last for months. Tachycardia and hypertension have been described, in some cases after potentially severe transient bradycardia and hypotension. More severe reactions tend to occur in persons previously stricken with the disease. Persons who have ingested parrotfish (scaritoxin) may develop classic ciguatera poisoning as well as a "second-phase" syndrome (after 5–10 days' delay) of disequilibrium with locomotor ataxia, dysmetria, and resting or kinetic tremor. This syndrome may persist for 2–6 weeks.

Diagnosis

The differential diagnosis of ciguatera includes paralytic shellfish poisoning, eosinophilic meningitis, type E botulism, organophosphate insecticide poisoning, tetrodotoxin poisoning, and psychogenic hyperventilation. At present, the diagnosis of ciguatera poisoning is made on clinical grounds because no routinely used laboratory test detects ciguatoxin in human blood. High-performance liquid chromatography (HPLC) is available for ciguatoxins and okadaic acid but is of limited clinical value because most health care institutions do not have the equipment needed to perform the test. A ciguatoxin enzyme immunoassay or radioimmunoassay may be used to test small portions of the suspected fish, but even these tests may not detect the very small amount of toxin (0.1 ppb) necessary to render fish flesh toxic.

TREATMENT **Ciguatera Poisoning**

Therapy is supportive and is based on symptoms. Nausea and vomiting may be controlled with an antiemetic such as ondansetron (4–8 mg IV). Hypotension may require the administration of IV crystalloid and, in rare cases, a pressor drug. Bradyarrhythmias that lead to cardiac insufficiency and hypotension generally respond well to atropine (0.5 mg IV, up to 2 mg). Cool showers or the administration of hydroxyzine (25 mg PO every 6–8 h) may relieve pruritus. Amitriptyline (25 mg PO twice a day) reportedly alleviates pruritus and dysesthesias. In three cases unresponsive to amitriptyline, tocainide appeared to be efficacious. Nifedipine has been used to treat headache. IV infusion of mannitol may be beneficial in moderate or severe cases, particularly for the relief of distressing neurologic or cardiovascular symptoms, although the efficacy of this therapy has been challenged and has not been definitively proved. The infusion is rendered initially as 1 g/kg per day over 45–60 min during the acute phase (days 1–5). If symptoms improve, a second dose may be given within 3–4 h and repeated on the next day. Care must be taken to avoid dehydration in a treated patient. The mechanism of the benefit against ciguatera intoxication is perhaps hyperosmotic water-drawing action, which reverses ciguatoxin-induced Schwann cell edema. Mannitol may also act in some fashion as a "hydroxyl scavenger" or may competitively inhibit ciguatoxin at the cell membrane.

During recovery from ciguatera poisoning, the victim should exclude the following from the diet: fish (fresh or preserved), fish sauces, shellfish, shellfish sauces, alcoholic beverages, nuts, and nut oils. Consumption of fish in ciguatera-endemic regions should be avoided. All oversized fish of any predacious reef species should be suspected of harboring ciguatoxin. Neither moray eels nor the viscera of tropical marine fish should ever be eaten.

PARALYTIC SHELLFISH POISONING

Paralytic shellfish poisoning is induced by ingestion of any of a variety of feral or aquacultured filter-feeding organisms, including clams, oysters, scallops, mussels, chitons, limpets, starfish, and sand crabs. The origin of their toxicity is the chemical toxin they accumulate and concentrate by feeding on various planktonic dinoflagellates (e.g., *Protogonyaulax*, *Ptychodiscus,* and *Gymnodinium*) and protozoan organisms. The unicellular phytoplanktonic organisms form the foundation of the food chain, and in warm summer months these organisms "bloom" in nutrient-rich coastal temperate and semitropical waters. These planktonic species can release massive amounts of toxic metabolites into the water and cause mortality in bird and marine populations. The paralytic shellfish toxins are water-soluble as well as heat- and acid-stable; they cannot be destroyed by ordinary cooking. The best-characterized and most frequently identified paralytic shellfish toxin is saxitoxin, which takes its name from the Alaska butter clam *Saxidomus giganteus*. A toxin concentration of >75 μg/100 g of foodstuff is considered hazardous to humans. In the 1972 New England "red tide," the concentration of saxitoxin in blue mussels exceeded 9000 μg/100 g of foodstuff. Saxitoxin appears to block sodium conductance, inhibiting neuromuscular transmission at the axonal and muscle membrane levels.

The onset of intraoral and perioral paresthesias (notably of the lips, tongue, and gums) comes within minutes to a few hours after ingestion of contaminated shellfish,

and these paresthesias progress rapidly to involve the neck and distal extremities. The tingling or burning sensation later changes to numbness. Other symptoms rapidly develop and include light-headedness, disequilibrium, incoordination, weakness, hyperreflexia, incoherence, dysarthria, sialorrhea, dysphagia, thirst, diarrhea, abdominal pain, nausea, vomiting, nystagmus, dysmetria, headache, diaphoresis, loss of vision, chest pain, and tachycardia. Flaccid paralysis and respiratory insufficiency may follow 2–12 h after ingestion. In the absence of hypoxia, the victim often remains alert but paralyzed.

TREATMENT **Paralytic Shellfish Poisoning**

Treatment is supportive and is based on symptoms. If the victim comes to medical attention within the first few hours after poison ingestion, the stomach should be emptied by gastric lavage and then irrigated with 2 L (in 200-mL aliquots) of a solution of 2% sodium bicarbonate; this intervention has not been proved to be of benefit but is based on the notion that gastric acidity may enhance the potency of saxitoxin. Because breathing difficulty can be rapid in onset, induction of emesis is not advised. The administration of activated charcoal (50–100 g) and a cathartic (sorbitol, 20–50 g) makes empirical sense since these shellfish toxins are believed to bind well to charcoal. Some authors advise against administration of magnesium-based solutions (e.g., certain cathartics), cautioning that hypermagnesemia may contribute to suppression of nerve conduction.

The most serious problem is respiratory paralysis. The victim should be closely observed in a hospital for at least 24 h for respiratory distress. With prompt recognition of ventilatory failure, endotracheal intubation and assisted ventilation prevent anoxic myocardial and brain injury.

A direct human serum assay to identify the toxin responsible for paralytic shellfish poisoning is not yet clinically available; the mouse bioassay in widespread use may be replaced by an automated tissue culture bioassay. A polyclonal enzyme-linked immunosorbent assay (ELISA) to measure specific toxins is under development, as is fluorimetric HPLC.

DOMOIC ACID INTOXICATION (AMNESTIC SHELLFISH POISONING)

In late 1987 in eastern Canada, an outbreak of gastrointestinal and neurologic symptoms (amnestic shellfish poisoning) was documented in persons who had consumed mussels found to be contaminated with domoic acid. In this outbreak, the source of the toxin was *Nitzschia pungens*, a diatom ingested by the mussels. In 1991, an epidemic of domoic acid poisoning in the state of Washington was attributed to the consumption of razor clams. A heat-stable neuroexcitatory amino acid whose biochemical analogues are kainic acid and glutamic acid, domoic acid binds to the kainate type of glutamate receptor with three times the affinity of kainic acid and is 20 times as powerful a toxin. Shellfish can be tested for domoic acid by mouse bioassay and HPLC. The regulatory limit for domoic acid in shellfish is 20 parts per million.

The abnormalities noted within 24 h of ingesting contaminated mussels (*Mytilus edulis*) include arousal, confusion, disorientation, and memory loss. The median time of onset is 5.5 h. Other prominent symptoms include severe headache, nausea, vomiting, diarrhea, abdominal cramps, hiccups, arrhythmias, hypotension, seizures, ophthalmoplegia, pupillary dilation, piloerection, hemiparesis, mutism, grimacing, agitation, emotional lability, coma, copious bronchial secretions, and pulmonary edema. Histologic study of brain tissue taken at autopsy has shown neuronal necrosis or cell loss and astrocytosis, most prominently in the hippocampus and the amygdaloid nucleus—findings similar to those in animals poisoned with kainic acid. Several months after the primary intoxication, victims still display chronic residual memory deficits and motor neuronopathy or axonopathy. Nonneurologic illness does not persist.

TREATMENT **Domoic Acid Intoxication**

Therapy is supportive and is based on symptoms. Since kainic acid neuropathology seems to be nearly entirely seizure-mediated, the emphasis should be on anticonvulsive therapy, for which diazepam appears to be as effective as any other drug.

SCOMBROID POISONING

Scombroid (mackerel-like) fish include the albacore, bluefin, and yellowfin tuna; mackerel; saury; needlefish; wahoo; skipjack; and bonito. Nonscombroid fish that produce scombroid poisoning include the dolphinfish (Hawaiian mahimahi, *Coryphaena hippurus*), kahawai, sardine, black marlin, pilchard, anchovy, herring, amberjack, and Australian ocean salmon. In the northeastern and mid-Atlantic United States, bluefish (*Pomatomus saltatrix*) has been linked to scombroid poisoning. Because greater numbers of nonscombroid fish are being recognized as scombrotoxic, the syndrome may more appropriately be called pseudoallergic fish poisoning.

Under conditions of inadequate preservation or refrigeration, the musculature of these dark- or red-fleshed fish undergoes bacterial decomposition, which includes decarboxylation of the amino acid l-histidine to histamine, histamine phosphate, and histamine hydrochloride. Histamine levels of 20–50 mg/100 g are noted in toxic fish, with levels >400 mg/100 g on occasion. However, it is possible that some other compound may be responsible for this intoxication, since large doses of oral histamine do not reproduce the affliction. Whatever toxin or toxins are involved are heat-stable and are not destroyed by domestic or commercial cooking. Affected fish typically have a

sharply metallic or peppery taste; however, they may be normal in appearance, color, and flavor. Not all persons who eat a contaminated fish necessarily become ill, perhaps because of uneven distribution of decay within the fish.

Symptoms develop within 15–90 min of ingestion and include flushing (sharply demarcated; exacerbated by ultraviolet exposure; particularly pronounced on the face, neck, and upper trunk), a sensation of warmth without elevated core temperature, conjunctival hyperemia, pruritus, urticaria, angioneurotic edema, bronchospasm, nausea, vomiting, diarrhea, epigastric pain, abdominal cramps, dysphagia, headache, thirst, pharyngitis, gingival burning, palpitations, tachycardia, dizziness, and hypotension. Without treatment, the symptoms generally resolve within 8–12 h. Because of blockade of gastrointestinal tract histaminase, the reaction may be more severe in a person who is concurrently ingesting isoniazid.

TREATMENT **Scombroid Poisoning**

Therapy is directed at reversing the histamine effect with antihistamines, either H-1 or H-2. If bronchospasm is severe, an inhaled bronchodilator—or in rare, extremely severe circumstances, injected epinephrine—may be used. Glucocorticoids are of no proven benefit. Protracted nausea and vomiting, which may empty the stomach of toxin, may be controlled with a specific antiemetic, such as prochlorperazine. The persistent headache of scombroid poisoning may respond to cimetidine or a similar antihistamine if standard analgesics are not effective.

CHAPTER 132

ECTOPARASITE INFESTATIONS AND ARTHROPOD BITES AND STINGS

Richard J. Pollack

Ectoparasites are arthropods or helminths that infest the skin or hair of other animals, from which they derive sustenance and shelter. They may penetrate beneath the surface of the host or attach superficially by their mouthparts and specialized claws. These organisms damage their hosts by inflicting direct injury, eliciting a hypersensitivity reaction, inoculating toxins or pathogens, and inciting fear. The main medically important ectoparasites are arachnids (including mites and ticks), insects (including lice, fleas, bedbugs, and flies), pentastomes (tongue worms), and leeches. Arthropods also may harm humans through brief encounters during which they take a blood meal or attempt to defend themselves by biting, stinging, or exuding venoms. Various arachnids (spiders, scorpions), insects (bees, hornets, wasps, ants, flies, bugs, caterpillars, and beetles), millipedes, and centipedes produce ill effects in these manners, as do certain ectoparasites of animals, including ticks, biting mites, and fleas. In the United States, more people die each year from arthropod stings than from the bites of poisonous snakes. Lesions resulting from the bites and stings of arthropods are so diverse and variable that it is rarely possible to identify precisely what kind of insect or tick is involved without a bona fide specimen and entomologic expertise.

SCABIES

The human itch mite, *Sarcoptes scabiei*, is a common cause of itching dermatosis, infesting ~300 million persons worldwide. Gravid female mites that measure ~0.3 mm in length burrow superficially beneath the stratum corneum, depositing three or fewer eggs per day. Nymphs mature in ~2 weeks and then emerge as adults to the surface of the skin, where they mate and (re)invade the skin of the same or another host. Transfer of newly fertilized female mites from person to person occurs mainly by intimate contact and is facilitated by crowding, poor hygiene, and multiple sexual partners. Generally, these mites die within a day or so in the absence of host contact. Transmission via

sharing of contaminated bedding or clothing therefore occurs infrequently. In the United States, scabies may account for up to 5% of visits to dermatologists. Outbreaks occur in nursing homes, mental institutions, and hospitals.

The itching and rash associated with scabies derive from a sensitization reaction directed against the excreta that the mite deposits in its burrow. An initial infestation remains asymptomatic for up to 6 weeks, and a reinfestation produces a hypersensitivity reaction without delay. Burrows become surrounded by infiltrates of eosinophils, lymphocytes, and histiocytes, and a generalized hypersensitivity rash later develops in remote sites. Immunity and associated scratching limit most infestations to <15 mites per person. Hyperinfestation with thousands of mites, a condition known as *crusted scabies* or *Norwegian scabies*, may result from glucocorticoid use, immunodeficiency, and neurologic and psychiatric illnesses that limit itching and scratching.

Intense itching worsens at night and after a hot shower. Typical burrows may be difficult to find because they are few in number and may be obscured by excoriations. Burrows appear as dark wavy lines in the epidermis and measure up to 15 mm. Lesions occur most frequently on the volar wrists, between the fingers, on the elbows, and on the penis. Small papules and vesicles, often accompanied by eczematous plaques, pustules, or nodules, are distributed symmetrically in those sites and in skinfolds under the breasts and around the navel, axillae, belt line, buttocks, upper thighs, and scrotum. Except in infants, the face, scalp, neck, palms, and soles are spared. Crusted scabies resembles psoriasis in its typical widespread erythema, thick keratotic crusts, scaling, and dystrophic nails. Characteristic burrows are not seen in crusted scabies, and patients usually do not itch, although their infestations are highly contagious and have been responsible for outbreaks of classic scabies in hospitals.

Scabies should be considered in patients with pruritus and symmetric polymorphic skin lesions in characteristic locations, particularly if there is a history of household contact with an affected person. Burrows should be sought and unroofed with a sterile needle or scalpel blade, and the scrapings should be examined microscopically for the mite, its eggs, and its fecal pellets. Biopsies (including superficial cyanoacrylate biopsy), scrapings, and dermascopic imaging of papulovesicular lesions as well as microscopic inspection of clear adhesive tape lifted from lesions also may be diagnostic. In the absence of identifiable mites or mite products, the diagnosis is based on clinical presentation and history. Diverse kinds of dermatitis due to other causes frequently are misdiagnosed as scabies.

TREATMENT **Scabies**

Permethrin cream (5%) is less toxic than 1% lindane preparations and is effective against lindane-tolerant infestations. Scabicides are applied thinly but thoroughly behind the ears and from the neck down after bathing and are removed 8 h later with soap and water. Successful treatment of crusted scabies requires preapplication of a keratolytic agent such as 6% salicylic acid and then of scabicides to the scalp, face, and ears. Repeated treatments or the sequential use of several agents may be necessary. Ivermectin has not been approved by the U.S. Food and Drug Administration (FDA) for use against any form of scabies, but a single oral dose (200 µg/kg) effectively treats scabies in otherwise healthy persons; patients with crusted scabies may require two doses separated by an interval of 1–2 weeks.

Although effectively treated scabies infestations become noninfectious within a day, itching and rash due to hypersensitivity to the dead mites and their excreted and secreted products frequently persist for weeks or months. Unnecessary re-treatment with topical agents may provoke contact dermatitis. Antihistamines, salicylates, and calamine lotion relieve itching during treatment, and topical glucocorticoids are useful for pruritus that lingers after effective treatment. To prevent reinfestations, bedding and clothing should be washed and/or dried on high heat or heat-pressed, and close contacts, even if asymptomatic, should be treated simultaneously.

CHIGGERS AND OTHER BITING MITES

Chiggers are the larvae of trombiculid (harvest) mites that normally feed on mice in grassy or brush-covered sites in the tropics and subtropics and less frequently in temperate areas during warm months. They wait for hosts on low vegetation and attach themselves to passing animals or humans. The larva pierces the skin of its host and produces a secreted tubelike structure (*stylostome*) in the dermis through which it imbibes tissue fluids. The stylostome is highly antigenic and causes an exceptionally pruritic papular, papulovesicular, or papulourticarial lesion (≤2 cm in diameter) that develops within hours of attachment in persons previously sensitized to mite antigen. Feeding mites appear as tiny red vesicles adjacent to hair follicles. Scratching invariably destroys the body of a mite. Generally, lesions vesiculate and develop a hemorrhagic base. Itching and burning persist for weeks. The rash is common on the ankles and areas where clothing obstructs the further wanderings of the mites. Repellents are useful for preventing chigger bites.

Diverse mites associated with birds and rodents can be particularly bothersome when they invade homes and bite human inhabitants. In North America, the northern fowl mite, the chicken mite, the tropical rat mite, and the house mouse mite normally feed on poultry, various songbirds, and small mammals and are abundant in and near their hosts' nests. These mites invade homes after their natural hosts die or leave their nests. Although the mites often are not seen because of their small size, their bites can be painful and pruritic. Painful bitelike sensations associated only with certain rooms of a home may be due to biting mites. Rodent- and bird-associated mites are best eliminated

by excluding hosts, removing nests, and cleaning and treating the nesting area with appropriate acaricides. *Pyemotes* and other mites that infest grain, straw, cheese, hay, or other products occasionally produce similar episodes of rash and discomfort.

Diagnosis of mite-induced dermatitides (including those caused by chiggers) relies on confirmation of the mite's identity or elicitation of a history of exposure to the mite's source. Antihistamines or topical steroids effectively reduce mite-induced pruritus.

TICK BITES AND TICK PARALYSIS

Ticks attach and feed painlessly; blood is their only food. Their secretions produce local reactions, a febrile illness, or paralysis and transmit diverse pathogens. Generally, soft ticks attach for <1 h and may produce erythematous macular lesions ≤3 cm in diameter. Some species in Africa, the western United States, and Mexico produce painful hemorrhagic lesions. In contrast, hard ticks attach and feed for several days or sometimes for >1 week. At the site of hard-tick bites, small areas of induration with surrounding erythema and occasionally necrotic ulcers develop. Chronic nodules (tick granulomas) reach several centimeters in diameter and may require surgical excision. Tick-induced fever, associated with headache, nausea, and malaise, usually resolves ≤36 h after the tick is removed.

Tick paralysis, an acute ascending flaccid paralysis, is believed to be caused by one or more toxins in tick saliva that produce neuromuscular block, decreased nerve conduction, and sometimes hypertension. Throughout the world, this rare complication has followed the bites of >60 kinds of ticks; in the United States, dog and wood ticks are most commonly involved. Weakness begins in the lower extremities ≤6 days after the tick's attachment and ascends symmetrically over several days to result in complete paralysis of the extremities and cranial nerves. Deep tendon reflexes are diminished or lacking altogether, but sensory examination and findings on lumbar puncture are typically normal. Removal of the tick generally results in improvement within a few hours and complete recovery after several days, although the patient's condition may continue to deteriorate for up to 1 day. Failure to remove the tick may lead to dysarthria, dysphagia, and ultimately death from aspiration or respiratory paralysis. Diagnosis depends on finding the tick, which is often hidden beneath hair. An antiserum to the saliva of *Ixodes holocyclus*, the usual cause of tick paralysis in Australia, effectively reverses paralysis caused by these ticks.

Ticks should be removed by firm traction with fine-tipped forceps placed near the point of attachment. Use of occlusive dressings, heat, or other substances merely delays tick removal. The site of attachment should be disinfected. Tick mouthparts remaining in the skin generally are shed within days without excision. Removal of ticks during the first 36 h of attachment nearly always prevents transmission of the agents of Lyme disease, babesiosis, anaplasmosis, and ehrlichiosis. Gentle handling (to avoid rupture of ticks) and use of gloves may avert accidental contamination with tick fluids containing pathogens. Rather than awaiting results of tick testing or seroconversion to Lyme disease, adult patients with bites thought to be associated with deer ticks **(Fig. 132-1)** in Lyme disease–endemic areas from Maryland to Maine and in Wisconsin and Minnesota may be treated presumptively with a single oral dose of doxycycline (200 mg) within 72 h of tick removal.

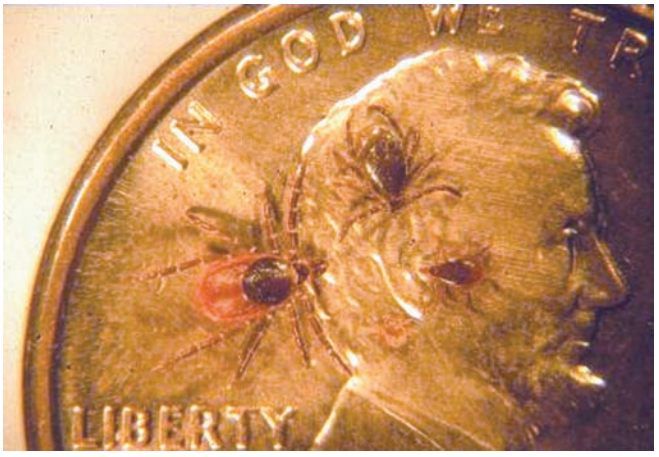


FIGURE 132-1
Deer ticks (*Ixodes scapularis*, black-legged ticks) on a U.S. penny: larva (*below ear*), nymph (*right*), adult male (*above*), and adult female (*left*).

LOUSE INFESTATION (PEDICULIASIS AND PTHIRIASIS)

Nymphs and adults of all three kinds of human lice feed at least once a day, ingesting human blood exclusively. Head lice (*Pediculus capitis*) infest mainly the hair of the scalp, body lice (*Pediculus humanus*) the clothing, and crab or pubic lice (*Pthirus pubis*) mainly the hair of the pubis. The saliva of lice produces an irritating maculopapular or urticarial rash in certain sensitized persons. Female head and pubic lice cement their eggs firmly to hair, and female body lice cement their eggs to clothing. A nymph hatches after ~10 days of development. The empty egg (nit) may remain affixed for months thereafter.

In North America, head lice infest ~1% of elementary school–age children. Head lice are transmitted mainly by direct head-to-head contact rather than by fomites (shared headgear, grooming implements, bedding). Infestations by head lice tend to be asymptomatic. Pruritus, due mainly to hypersensitivity to the louse's saliva, generally is transient and mild. Head lice removed from a person succumb to desiccation and starvation within ~1 day. Head lice are unimportant as vectors of pathogenic agents.

Body lice remain on clothing except when feeding and generally succumb in ≤2 days if separated from their host. These lice mainly infest disaster victims or indigent people who are in close contact with other infested individuals. Body lice are acquired by direct contact or by sharing of clothing and bedding. These lice are vectors for the agents of louse-borne typhus (Chap. 79),

louse-borne relapsing fever (Chap. 77), and trench fever (Chap. 65). Pruritic lesions from their bites are particularly common around the neckline. Chronic infestations result in a postinflammatory hyperpigmentation and thickening of skin known as *vagabonds' disease*.

The crab or pubic louse is transmitted mainly by sexual contact. These lice occur mainly on pubic hair and less frequently on hair of the axillae and the face, including the eyelashes. Children and adults may acquire pubic lice by sexual or close nonsexual contact. Intensely pruritic lesions and blue macules ~3 mm in diameter (*maculae ceruleae*) develop at the site of bites. Blepharitis commonly accompanies infestations of the eyelashes.

Pediculiasis may be suspected upon the detection of nits on hairs or in clothing, but confirmation should be based on discovery of a live louse.

TREATMENT **Louse Infestation**

Generally, treatment is warranted only if live lice are discovered. The presence of nits alone is evidence of former—not current—infestation. Mechanical removal of lice and their eggs by means of a fine-toothed louse or nit comb (Fig. 132-2) often fails to eliminate infestations. Treatment of newly identified active infestations generally relies on a 10-min application of ~1% permethrin or pyrethrins, with a second application 10 days later. Lice persisting after this treatment may be resistant to pyrethroids (see below). Chronic infestations may be treated for ≤12 h with 0.5% malathion. Lindane is applied for just 4 min but seems less effective and may pose a greater risk of adverse reactions, particularly when misused. Resistance of head lice to permethrin, malathion, and lindane has been reported. Newer pediculicides contain benzyl alcohol, dimethicone, or spinosad. Although children infested by head lice are frequently isolated or excluded from school, this practice increasingly is seen as unjustified.

Body lice usually are eliminated by bathing and by changing to laundered clothes. Application of topical pediculicides from head to foot may be necessary for hirsute patients. Clothes and bedding are effectively deloused by heating in a clothes dryer at ≤55°C (131°F) for 30 min or by heat-pressing. Emergency mass delousing of persons and clothing may be warranted during periods of civil strife and after natural disasters to reduce the risk of pathogen transmission by body lice.

Pubic louse infestations are treated with topical pediculicides except for eyelid infestations (*pthiriasis palpebrum*), which generally respond to a coating of petrolatum applied for 3–4 days.

FIGURE 132-2
Adult female human head louse (*Pediculus capitis*) on a nit (louse-egg) comb.

MYIASIS (FLY INFESTATION)

Myiasis refers to infestations by diverse kinds of fly larvae (maggots) that invade living or necrotic tissue or body cavities and produce different clinical syndromes, depending on the species of fly.

In forested parts of Central and South America, larvae of the human botfly *Dermatobia hominis* produce boil-like subcutaneous nodules ≤3 cm in diameter. The adult female captures a mosquito or another bloodsucking insect and deposits her eggs on its abdomen. When the carrier insect attacks a human or bovine host several days later, the warmth and moisture of the host's surface stimulate the larvae to hatch. The larvae promptly penetrate intact skin. After 6–12 weeks of development, mature larvae emerge from the skin and drop to the ground. The African tumbu fly *Cordylobia anthropophaga* deposits its eggs on sand or drying laundry contaminated with urine or sweat. Larvae hatch on contact with the body, penetrate the skin, and produce boils from which they emerge ~9 days later. Furuncular myiasis is suggested by uncomfortable lesions with a central breathing pore that emits bubbles when submerged in water. A sensation of movement under the patient's skin may lead to severe emotional distress. Botfly larvae may be induced to emerge if the air pore is coated with petrolatum or another occlusive substance. Removal may be facilitated by injection of a local anesthetic into the surrounding tissue, but surgical excision is often necessary because upward-pointing spines of some species hold the larva firmly in place.

Larvae of the horse botfly *Gasterophilus intestinalis* do not mature after penetrating human skin but migrate for weeks in the epidermis. The resulting pruritic and serpiginous eruption resembles cutaneous larva migrans caused by hookworms (Chap. 126). Horseback riders become infested when eggs deposited on the flank of the horse hatch against their bare legs. The larvae of the cattle botfly invade more deeply and produce boil-like swellings, and larvae of rabbit and rodent *Cuterebra* occasionally cause dermal or tracheopulmonary myiasis.

Certain flies are attracted to blood and pus, and their newly hatched larvae enter wounds or diseased skin. Larvae of the green bottle fly usually remain superficial and confined to necrotic tissue, but specially prepared "surgical maggots" sometimes are used intentionally for wound debridement. Larvae of screwworm flies and the flesh fly invade viable tissue more deeply and produce large suppurating lesions. Larvae that infest wounds also may

infest body cavities such as the mouth, nose, ears, sinuses, anus, vagina, and lower urinary tract, particularly in unconscious or otherwise debilitated patients. The consequences range from harmless colonization to destruction of the nose, meningitis, and deafness. Treatment involves removal of maggots and debridement of tissue.

The maggots responsible for furuncular and wound myiasis also may cause ophthalmomyiasis. Sequelae include nodules in the eyelid, retinal detachment, and destruction of the globe. Most instances in which maggots are found in human feces result from larviposition by flesh flies on recently passed stools.

PENTASTOMIASIS

Pentastomids (tongue worms) inhabit the respiratory passages of reptiles and carnivorous mammals. Human infestation by *Linguatula serrata* is common in the Middle East and results from the ingestion of encysted larval stages in raw liver or lymph nodes of sheep and goats—the intermediate hosts. Larvae migrate to the nasopharynx and produce an acute self-limiting syndrome known as *Halzoun* or *Marrara*, which is characterized by pain and itching of the throat and ears, coughing, hoarseness, dysphagia, and dyspnea. Severe edema may cause obstruction that necessitates tracheostomy; ocular invasion has been described. Diagnostic larvae measuring ≤10 mm in length appear in copious nasal discharge or vomitus. Individuals become infected with *Armillifer armillatus* by ingesting eggs in contaminated food or drink or after handling the definitive host, the African python. Larvae encyst in various organs but rarely cause symptoms. Cysts occasionally require surgical removal as they enlarge during molting, but they usually are encountered as an incidental finding at autopsy. Parasite-induced lesions may be misinterpreted as a malignancy, with the correct diagnosis confirmed by histopathologic findings. Cutaneous larva migrans syndromes due to other pentastomes have been reported from Southeast Asia and Central America.

LEECH INFESTATIONS

Medically important leeches are annelid worms that attach to their hosts with chitinous cutting jaws and draw blood through muscular suckers. The medicinal leech *Hirudo medicinalis* is still used occasionally to reduce venous congestion in surgical flaps or replanted body parts. This practice has been complicated by intractable bleeding, wound infections, myonecrosis, and sepsis due to *Aeromonas hydrophila*, which colonizes the gullets of commercially available leeches.

Ubiquitous aquatic leeches that parasitize fish, frogs, and turtles readily attach to the skin of humans and avidly suck blood. More notorious are the land leeches that live among moist vegetation of tropical rain forests. Attachment is usually painless. Hirudinin, a powerful anticoagulant secreted by the leech, causes continued bleeding after the leech has detached. Healing of the wound is slow, and bacterial infections are not uncommon. Several kinds of aquatic leeches in Africa, Asia, and southern Europe can enter through the mouth, nose, and genitourinary tract and attach to mucosal surfaces at sites as deep as the esophagus and trachea. Externally attached leeches generally drop off after they have engorged, but removal is hastened by gentle scraping aside of the anterior and posterior suckers and traction or by application of alcohol, salt, vinegar, insect repellent, or a flame or heated instrument to the leech. Internally attached leeches may detach on exposure to gargled saline or may be removed by forceps.

SPIDER BITES

Of the >30,000 recognized species of spiders, only ~100 defend themselves aggressively and have fangs sufficiently long to penetrate human skin. The venom that spiders use to immobilize and digest their prey can cause necrosis of skin and systemic toxicity. Whereas the bites of most spiders are painful but not harmful, envenomations by recluse or fiddle spiders (*Loxosceles* species) and widow spiders (*Latrodectus* species) may be life-threatening. Identification of the offending spider should be attempted both because specific treatments exist for bites of widow and brown recluse spiders and because injuries attributed to spiders are frequently due to other causes. Except in cases where the patient actually observes a spider immediately associated with the bite or fleeing from the site, lesions reported to be due to spider bites are most often due to other injuries or to infections with bacteria such as methicillin-resistant *Staphylococcus aureus*.

Recluse spider bites and necrotic arachnidism

Brown recluse spiders occur mainly in the southern and midwestern United States, and their close relatives are found in the Americas, Africa, and the Middle East. Most bites by the brown recluse spider result in only minor injury with edema and erythema. Envenomation, however, may cause severe necrosis of skin and subcutaneous tissue and systemic hemolysis. These spiders are not aggressive toward human beings and bite only if threatened or pressed against the skin. They hide under rocks and logs or in caves and animal burrows. They invade homes and seek dark and undisturbed hiding spots in closets, in folds of clothing, or under furniture and rubbish in storage rooms, garages, and attics. Despite their impressive abundance in some homes, these spiders only infrequently bite humans. Bites tend to occur while the victim is dressing and are sustained primarily on the arms, neck, and lower abdomen.

The venoms of these spiders contain an esterase, alkaline phosphatase, proteases, and other enzymes that produce tissue necrosis and hemolysis. Sphingomyelinase D, the most important dermonecrotic factor, binds cell membranes and promotes chemotaxis of neutrophils, leading to vascular thrombosis and an Arthus-like reaction. Initially, the bite is painless or produces a stinging sensation. Within the next few hours, the

site becomes painful and pruritic, with central induration surrounded by a pale zone of ischemia and a zone of erythema. In most cases, the lesion resolves without treatment in just a few days. In severe cases, the erythema spreads, and the center of the lesion becomes hemorrhagic and necrotic with an overlying bulla. A black eschar forms and sloughs several weeks later, leaving an ulcer that eventually may result in a depressed scar. Healing usually takes place in ≤6 months but may take as long as 3 years if adipose tissue is involved. Local complications include injury to nerves and secondary infection. Fever, chills, weakness, headache, nausea, vomiting, myalgia, arthralgia, maculopapular rash, and leukocytosis may develop ≤72 h after the bite. In rare instances, acute complications such as hemolytic anemia, hemoglobinuria, and renal failure are fatal.

TREATMENT **Recluse Spider Bites**

Initial management includes RICE (rest, ice, compression, elevation). Analgesics, antihistamines, antibiotics, and tetanus prophylaxis should be administered if indicated. Debridement and later skin grafting may be necessary after signs of acute inflammation have subsided, but immediate surgical excision of the wound is detrimental. Patients should be monitored closely for signs of hemolysis, renal failure, and other systemic complications.

Widow spider bites

The black widow, which is best known and most abundant in the southeastern United States, measures ≤1 cm in body length and 5 cm in leg span and is shiny black with a red hourglass marking on the ventral abdomen. Other dangerous *Latrodectus* species occur elsewhere in temperate and subtropical parts of the world. The bites of the female widow spiders are notorious for their potent neurotoxins.

Widow spiders spin their webs under stones, logs, plants, or rock piles and in dark spaces in barns, garages, and outhouses. Bites are most common in the summer and early autumn and occur when the web is disturbed or when the spider is trapped or provoked. The initial bite goes unnoticed or is perceived as a sharp pinprick. Fang puncture marks are uncommon. The venom that is injected does not produce local necrosis, and some persons experience no other symptoms. α-Latrotoxin, the most active component of the venom, binds irreversibly to nerves and causes release and eventual depletion of acetylcholine, norepinephrine, and other neurotransmitters from presynaptic terminals. Painful cramps may spread within 60 min from the bite site to large muscles of the extremities and trunk. Extreme rigidity of the abdominal muscles and excruciating pain may suggest peritonitis, but the abdomen is not tender on palpation. The pain begins to subside during the first 12 h but may recur during several days or weeks before resolving spontaneously. Other features include salivation, diaphoresis, vomiting, hypertension, tachycardia, labored breathing, anxiety, headache, weakness, fasciculations, paresthesia, hyperreflexia, urinary retention, uterine contractions, and premature labor. Rhabdomyolysis and renal failure have been reported, and respiratory arrest, cerebral hemorrhage, or cardiac failure may end fatally, especially in very young, elderly, or debilitated persons.

TREATMENT **Widow Spider Bites**

Treatment consists of RICE and tetanus prophylaxis. Hypertension that does not respond to analgesics and antispasmodics (e.g., benzodiazepines or methocarbamol) requires specific antihypertensive medication. The efficacy of antivenom is controversial. Because of the risk of anaphylaxis and serum sickness, antivenom should be reserved for severe cases involving respiratory arrest, uncontrollable hypertension, seizures, or pregnancy.

Tarantulas and other spiders

Tarantulas are hairy spiders of which 30 species are found in the United States, mainly in the Southwest. The tarantulas that have become popular household pets are usually imported species. Tarantulas bite only when threatened and cause no more harm than a bee sting, but the venom occasionally provokes deep pain and swelling. Tarantulas of several species are covered with urticating hairs that are brushed off in the thousands when a threatened spider rubs its hind legs across its dorsal abdomen. These hairs penetrate human skin and produce pruritic papules that may persist for weeks. Failure to wear gloves or to wash the hands after handling the Chilean Rose tarantula, a popular pet spider, has resulted in transfer of hairs to the eye and devastating ocular inflammation. Treatment of bites includes local washing and elevation of the bitten area, tetanus prophylaxis, and analgesic administration. Antihistamines and topical or systemic glucocorticoids are given for exposure to urticating hairs.

Atrax robustus, a funnel-web spider of Australia, and *Phoneutria* species, the South American banana spiders, are among the most dangerous spiders in the world because of their aggressive behavior and potent neurotoxins. Envenomation by *A. robustus* causes a rapidly progressive neuromotor syndrome that can be fatal within 2 h. The bite of a banana spider causes severe local pain followed by profound systemic symptoms and respiratory paralysis that can lead to death within 2–6 h. Specific antivenoms for envenomation by each of these spiders are available. Yellow sac spiders (*Cheiracanthium)* are common in homes worldwide. Their bites, though painful, generally lead to only minor erythema, edema, and pruritus.

SCORPION STINGS

Scorpions are arachnids that feed on ground-dwelling arthropods and small lizards, which they paralyze by

injecting venom from a stinger on the tip of the tail. Painful but relatively harmless scorpion stings need to be distinguished from the potentially lethal envenomations that are produced by ~30 of the ~1000 known species and that cause >5000 deaths worldwide each year. Scorpions feed at night and remain hidden during the day in crevices or burrows or under wood, loose bark, or rocks on the ground. They seek cool spots under buildings and often enter houses, where they hide in shoes, clothing, or bedding or enter bathtubs and sinks in search of water. Scorpions sting human beings only when disturbed.

Of the 40 or so scorpion species in the United States, only the bark scorpion (*Centruroides sculpturatus* or *C. exilicauda*) produces venom that can be lethal. This venom contains neurotoxins that cause sodium channels to remain open and neurons to fire repetitively. Such envenomations usually are associated with little swelling, but prominent pain, paresthesia, and hyperesthesia can be accentuated by tapping on the affected area (the tap test). These symptoms soon spread to other locations; dysfunction of cranial nerves and hyperexcitability of skeletal muscles develop within hours. Patients present with restlessness, blurred vision, abnormal eye movements, profuse salivation, lacrimation, rhinorrhea, slurred speech, difficulty in handling secretions, diaphoresis, nausea, and vomiting. Muscle twitching, jerking, and shaking may be mistaken for a seizure. Complications include tachycardia, arrhythmias, hypertension, hyperthermia, rhabdomyolysis, and acidosis. Symptoms progress to maximal severity in ~5 h and subside within a day or two, although pain and paresthesia can last for weeks. Fatal respiratory arrest is most common among young children and the elderly.

Envenomations by *Leiurus quinquestriatus* in the Middle East and North Africa, by *Mesobuthus tamulus* in India, by *Androctonus* species along the Mediterranean littoral and in North Africa and the Middle East, and by *Tityus serrulatus* in Brazil cause massive release of endogenous catecholamines with hypertensive crises, arrhythmias, pulmonary edema, and myocardial damage. Acute pancreatitis occurs with stings of *Tityus trinitatis* in Trinidad, and central nervous toxicity complicates stings of *Parabuthus* and *Buthotus* scorpions of South Africa. Tissue necrosis and hemolysis may follow stings of the Iranian *Hemiscorpius lepturus*.

Stings of most other species cause immediate sharp local pain followed by edema, ecchymosis, and a burning sensation. Symptoms typically resolve within a few hours, and skin does not slough. Allergic reactions to the venom sometimes develop.

TREATMENT **Scorpion Stings**

Identification of the offending scorpion aids in planning therapy. Stings of nonlethal species require at most ice packs, analgesics, or antihistamines. Because most victims experience only local discomfort, they can be managed at home with instructions to return to the emergency department if signs of cranial-nerve or neuromuscular dysfunction develop. Aggressive supportive care and judicious use of antivenom can reduce or eliminate deaths from more severe envenomations. Keeping the patient calm and applying pressure dressings and cold packs to the sting site are measures that decrease the absorption of venom. A continuous IV infusion of midazolam controls the agitation, flailing, and involuntary muscle movements produced by scorpion stings. Close monitoring during treatment with this drug and other sedatives or narcotics is necessary for persons with neuromuscular symptoms because of the risk of respiratory arrest. Hypertension and pulmonary edema respond to nifedipine, nitroprusside, hydralazine, or prazosin, and bradyarrhythmias can be controlled with atropine.

Commercially prepared antivenoms are available in several countries for some of the most dangerous species. A *C. sculpturatus* antivenom (not yet approved by the FDA) is available as an investigational drug only in Arizona. IV administration of antivenom rapidly reverses cranial-nerve dysfunction and muscular symptoms but does not affect pain and paresthesia. The benefit of scorpion antivenom has not been established in controlled trials.

HYMENOPTERA STINGS

Insects that sting to defend their colonies or subdue their prey belong to the order Hymenoptera, which includes bees, wasps, hornets, yellow jackets, and ants. Their venoms contain a wide array of amines, peptides, and enzymes that cause local and systemic reactions. Although the toxic effect of multiple stings can be fatal, nearly all of the ≤100 deaths due to hymenopteran stings in the United States each year result from allergic reactions.

Bee and wasp stings

Honeybees often lose their stinging apparatus and the attached venom sac in the act of stinging and subsequently die, whereas other bees, ants, and vespids can sting numerous times in succession. The familiar honeybees (*Apis mellifera*) and bumblebees (*Bombus* and other genera) generally attack only when a colony is disturbed. Africanized honeybees, however, respond to minimal intrusions more aggressively. Since their introduction into Brazil in 1957, these "killer bees" have spread through South and Central America to the southern and western United States.

In bees and wasps, venom is produced in glands at the posterior end of the abdomen and is expelled rapidly by contraction of muscles of the venom sac, which has a capacity of up to 0.1 mL. The venoms of different species of hymenopterans are biochemically and immunologically distinct. Direct toxic effects are mediated by mixtures of low-molecular-weight compounds such as serotonin, histamine, and acetylcholine and

several kinins. Polypeptide toxins in honeybee venom include mellitin, which damages cell membranes; mast cell–degranulating protein, which causes histamine release; apamin, a neurotoxin; and adolapin, which has anti-inflammatory activity. Enzymes in venom include hyaluronidase, which allows the spread of other venom components, and phospholipases, which may be among the major venom allergens. There appears to be little cross-sensitization between honeybee and wasp venoms.

Uncomplicated stings cause immediate pain, a wheal-and-flare reaction, and local edema and swelling that subside in a few hours. Stings from accidentally swallowed insects may induce life-threatening edema of the upper airways. Multiple stings can lead to vomiting, diarrhea, generalized edema, dyspnea, hypotension, and collapse. Rhabdomyolysis and intravascular hemolysis may cause renal failure. Death from the direct effects of venom has followed 300–500 honeybee stings.

Large local reactions that spread ≤10 cm around the sting site over 24–48 h are not uncommon. These reactions may resemble cellulitis but are caused by hypersensitivity rather than secondary infection. Such reactions tend to recur on subsequent exposure but are seldom accompanied by anaphylaxis and are not prevented by venom immunotherapy.

An estimated 0.4–4.0% of the U.S. population exhibits clinical immediate-type hypersensitivity to insect stings, and 15% may have asymptomatic sensitization manifested by positive skin tests. Persons who experience severe allergic reactions are likely to have similar reactions after subsequent stings; occasionally, adults who have had mild reactions later experience serious reactions. Mild anaphylactic reactions from insect stings, as from other causes, consist of nausea, abdominal cramping, generalized urticaria, flushing, and angioedema. Serious reactions, including upper airway edema, bronchospasm, hypotension, and shock, may be rapidly fatal. Severe reactions usually begin within 10 min of the sting and only rarely develop after 5 h.

TREATMENT **Bee and Wasp Stings**

Honeybee stingers embedded in the skin should be removed as promptly as possible to limit the quantity of venom delivered. The stinger and venom sac may be scraped off with a blade or a fingernail or grasped with forceps. The site should be cleansed and disinfected and ice packs applied to slow the spread of venom. Elevation of the affected site and administration of analgesics, oral antihistamines, and topical calamine lotion relieve symptoms. Large local reactions may require a short course of oral therapy with glucocorticoids. Patients with numerous stings should be monitored for 24 h for evidence of renal failure or coagulopathy.

Anaphylaxis is treated with subcutaneous (SC) injection of 0.3–0.5 mL of epinephrine hydrochloride in a 1:1000 dilution; treatment is repeated every 20–30 min as necessary. IV epinephrine (2–5 mL of a 1:10,000 solution administered by slow push) is indicated for profound shock. A tourniquet may slow the spread of venom. Parenteral antihistamines, fluid resuscitation, bronchodilators, oxygen, intubation, and vasopressors may be required. Patients should be observed for 24 h for recurrent anaphylaxis.

Persons with a history of allergy to insect stings should carry a sting kit with a preloaded syringe containing epinephrine for self-administration. These patients should seek medical attention immediately after using the kit.

Repeated injections of purified venom produce a blocking IgG antibody response to venom and reduce the incidence of recurrent anaphylaxis. Honeybee, wasp, yellow jacket, and mixed vespid venoms are commercially available for desensitization and for skin testing. Results of skin tests and venom-specific radioallergosorbent tests aid in the selection of patients for immunotherapy and guide the design of such treatment.

Stinging ants

Stinging fire ants are an important medical problem in the United States. Imported fire ants infest southern states from Texas to North Carolina, with colonies in California, New Mexico, Arizona, and Virginia. Slight disturbances of their mound nests have provoked massive outpourings of ants and as many as 10,000 stings on a single person. Elderly and immobile persons are at high risk for attacks when fire ants invade dwellings.

Fire ants attach to skin with powerful mandibles and rotate their bodies while repeatedly injecting venom with posteriorly situated stingers. The alkaloid venom consists of cytotoxic and hemolytic piperidines and several proteins with enzymatic activity. The initial wheal-and-flare reaction, burning, and itching resolve in ~30 min, and a sterile pustule develops within 24 h. The pustule ulcerates over the next 48 h and then heals in ≤1 week. Large areas of erythema and edema lasting several days are not uncommon and in extreme cases may compress nerves and blood vessels. Anaphylaxis occurs in ≤2% of persons, and seizures and mononeuritis have been reported. Stings are treated with ice packs, topical glucocorticoids, and oral antihistamines. Covering pustules with bandages and antibiotic ointment may prevent bacterial infection. Epinephrine and supportive measures are indicated for anaphylactic reactions. Whole-body extracts are available for skin testing and immunotherapy, which appears to lower the rate of anaphylactic reactions.

The western United States is home to harvester ants. The painful local reaction that follows harvester ant stings often extends to lymph nodes and may be accompanied by anaphylaxis.

DIPTERAN (FLY AND MOSQUITO) BITES

In the process of feeding on vertebrate blood, adults of certain fly species inflict painful bites, produce local allergic reactions, or transmit pathogenic agents. Bites of mosquitoes, tiny "no-see-um" midges, and phlebotomine sand flies typically produce a wheal and a pruritic papule.

Nodular lesions at the site of midge bites may last for months. Bites of small humpbacked black flies (simuliids) leave a bleeding laceration and a painful and pruritic sore that are slow to heal; regional lymphadenopathy, fever, or anaphylaxis occasionally ensues. The widely distributed deer and horse flies as well as the tsetse flies of Africa are stout flies measuring ≤25 mm in length that attack during the day and produce large and painful bleeding punctures.

TREATMENT **Fly and Mosquito Bites**

Treatment of fly bites is symptom-based. Topical application of antipruritic agents, glucocorticoids, or antiseptic lotions may relieve itching and pain. Allergic reactions may require oral antihistamines. Antibiotics may be necessary for the treatment of large bite wounds that become secondarily infected.

FLEA BITES

Common human-biting fleas include the dog and cat fleas (*Ctenocephalides* species) and the rat flea (*Xenopsylla cheopis*), which inhabit the nests and resting sites of their hosts. Sensitized persons develop erythematous pruritic papules, urticaria, and occasionally vesicles and bacterial superinfection at the site of the bite. Treatment consists of antihistamines and antipruritics.

Flea infestations are eliminated by frequent cleaning of nesting sites and of the host's bedding and by application of contact insecticides. Flea infestations in the home may abate if pets are treated with veterinary antiparasitic agents and insect growth regulators.

Tunga penetrans, like other fleas, is a wingless, laterally flattened insect that feeds on blood. Also known as the chigoe flea, sand flea, or jigger, it occurs in tropical regions of Africa and the Americas. Adults live in sandy soil and burrow under the skin between toes, under nails, or on the soles of bare feet. Chigoes engorge on blood and grow from pinpoint to pea size during a 2-week period. The lesions they produce resemble a white pustule with a central black depression and may be pruritic or painful. Occasional complications include tetanus, bacterial infections, and autoamputation of toes. Tungiasis is treated by removal of the intact flea with a sterile needle or scalpel, tetanus vaccination, and topical application of antibiotics.

HEMIPTERAN (TRUE BUG) BITES

Several true bugs of the family Reduviidae inflict bites that produce allergic reactions and are sometimes painful. The cone-nose bugs, so called because of their elongated heads, include the assassin and wheel bugs, which feed on other insects and bite vertebrates only in self-defense, and the kissing bugs, which routinely feed on vertebrate blood. The bites of the nocturnally feeding kissing bugs are painless. Reactions to such bites depend on prior sensitization and include tender and pruritic papules, vesicular or bullous lesions, giant urticaria, fever, lymphadenopathy, and anaphylaxis. Bug bites are treated with topical antipruritics or oral antihistamines. Persons with anaphylactic reactions to reduviid bites should keep an epinephrine kit available. The cosmopolitan bedbugs (*Cimex* species) hide in crevices of mattresses, bed frames and other furniture, walls, and picture frames and under loose wallpaper. Bedbugs have become resurgent, recently attaining populations and spreading to an extent not encountered since the mid-twentieth century. These bugs are now a fairly common nuisance in homes, dormitories, and hotels and on cruise ships. The bugs hide during the day and take their blood meal at night. Their bite is painless, but sensitized persons develop erythema, itching, and wheals around a central hemorrhagic punctum. Bedbugs are not known to transmit pathogens.

CENTIPEDE BITES AND MILLIPEDE DERMATITIS

The fangs of centipedes of the genus *Scolopendra* can penetrate human skin and deliver a venom that produces intense burning pain, swelling, erythema, and lymphangitis. Dizziness, nausea, and anxiety occasionally are described, and rhabdomyolysis and renal failure have been reported. Treatment includes washing of the site, application of cold dressings, oral analgesic administration or local lidocaine infiltration, and tetanus prophylaxis.

Millipedes, unlike centipedes, do not bite, but some secrete defensive fluids that burn and discolor human skin. Affected skin turns brown overnight and may blister and exfoliate. Secretions in the eye cause intense pain and inflammation that may lead to corneal ulceration and blindness. Management includes irrigation with copious amounts of water or saline, use of analgesics, and local care of denuded skin.

CATERPILLAR STINGS AND DERMATITIS

The surface of caterpillars of several moth species is covered with hairs or spines that produce mechanical irritation and may contain or be coated with venom. Contact with these caterpillars causes an immediate burning sensation followed by local swelling and erythema and occasionally by regional lymphadenopathy, nausea, vomiting, and headache; shock, seizures, and coagulopathy are rare complications. In the United States, dermatitis most often is associated with io, puss, saddleback, and brown-tail moths. Contact with even detached hairs of other caterpillars, such as gypsy moth larvae, can later produce a pruritic urticarial or papular rash. Spines may be deposited on tree trunks and drying laundry or may be airborne and cause irritation of the eyes and upper airways. Treatment of caterpillar stings consists of repeated application of adhesive or cellophane tape to remove the hairs, which can then be identified microscopically. Local ice packs, topical steroids, and oral antihistamines relieve symptoms.

BEETLE VESICATION

When disturbed, blister beetles extrude cantharidin, a low-molecular-weight toxin that produces thin-walled blisters measuring ≤5 cm in diameter 2–5 h after contact. The blisters are not painful or pruritic unless broken and resolve without treatment in ≤10 days. Nephritis may follow unusually heavy cantharidin exposure. Contact occurs when individuals sit on the ground, work in the garden, or deliberately handle the beetles. The hemolymph of certain rove beetles contains paederin, a potent vesicant. When these beetles are crushed or brushed against the skin, the released fluid may provoke erythematous and bullous lesions. These beetles occur worldwide but are most numerous and problematic in parts of Africa and Asia. Ocular lesions are common from impacts with the flying beetles at night or transfer of the vesicant on the fingers. Treatment is rarely necessary, although ruptured blisters should be kept clean and bandaged.

DELUSIONAL INFESTATIONS

The groundless conviction that one is infested with arthropods or other parasites is an extremely difficult disorder to treat and unfortunately is not rare. Patients report infestations of their skin, clothing, or homes and describe sensations of something moving in or on their skin. Excoriations often accompany reports of pruritus or insect bites. Frequently, patients submit as evidence of infestation specimens that consist of plant-feeding and nonbiting peridomestic arthropods, pieces of skin, vegetable matter, or inanimate objects. It is imperative to rule out true infestations and bites by arthropods, endocrinopathies, neuropathies, drug use, environmental irritants (e.g., fragments or threads of glass insulation), and other causes of tingling or prickling sensations. Frequently, such patients repeatedly seek medical consultations, resist alternative explanations for their symptoms, and exacerbate their discomfort by self-treatment. Pharmacotherapy with pimozide or other psychotropic agents has been more helpful than psychotherapy in treating this disorder.

ACKNOWLEDGMENT

The substantial contributions of James H. Maguire to this chapter in previous editions of Harrison's Principles of Internal Medicine are gratefully acknowledged.

This page intentionally left blank

APPENDIX

LABORATORY VALUES OF CLINICAL IMPORTANCE

Alexander Kratz ■ Michael A. Pesce ■ Robert C. Basner ■ Andrew J. Einstein

This Appendix contains tables of reference values for laboratory tests, special analytes, and special function tests. A variety of factors can influence reference values. Such variables include the population studied, the duration and means of specimen transport, laboratory methods and instrumentation, and even the type of container used for the collection of the specimen. The reference or "normal" ranges given in this appendix may therefore not be appropriate for all laboratories, and these values should only be used as general guidelines. Whenever possible, reference values provided by the laboratory performing the testing should be utilized in the interpretation of laboratory data. Values supplied in this Appendix reflect typical reference ranges in adults. Pediatric reference ranges may vary significantly from adult values.

In preparing the Appendix, the authors have taken into account the fact that the system of international units (SI, système international d'unités) is used in most countries and in some medical journals. However, clinical laboratories may continue to report values in "traditional" or conventional units. Therefore, both systems are provided in the Appendix. The dual system is also used in the text except for (1) those instances in which the numbers remain the same but only the terminology is changed (mmol/L for meq/L or IU/L for mIU/mL), when only the SI units are given; and (2) most pressure measurements (e.g., blood and cerebrospinal fluid pressures), when the traditional units (mmHg, mmH_2O) are used. In all other instances in the text the SI unit is followed by the traditional unit in parentheses.

REFERENCE VALUES FOR LABORATORY TESTS

TABLE 1

HEMATOLOGY AND COAGULATION

ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Activated clotting time	WB	70–180 s	70–180 s
Activated protein C resistance (factor V Leiden)	P	Not applicable	Ratio >2.1
ADAMTS13 activity	P	≥0.67	≥67%
ADAMTS13 inhibitor activity	P	Not applicable	≤0.4 U
ADAMTS13 antibody	P	Not applicable	≤18 U
$Alpha_2$ antiplasmin	P	0.87–1.55	87–155%
Antiphospholipid antibody panel			
PTT-LA (lupus anticoagulant screen)	P	Negative	Negative
Platelet neutralization procedure	P	Negative	Negative
Dilute viper venom screen	P	Negative	Negative
Anticardiolipin antibody	S		
IgG		0–15 arbitrary units	0–15 GPL
IgM		0–15 arbitrary units	0–15 MPL

(*continued*)

TABLE 1

HEMATOLOGY AND COAGULATION (*CONTINUED*)

ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Antithrombin III	P		
Antigenic		220–390 mg/L	22–39 mg/dL
Functional		0.7–1.30 U/L	70–130%
Anti-Xa assay (heparin assay)	P		
Unfractionated heparin		0.3–0.7 kIU/L	0.3–0.7 IU/mL
Low-molecular-weight heparin		0.5–1.0 kIU/L	0.5–1.0 IU/mL
Danaparoid (Orgaran)		0.5–0.8 kIU/L	0.5–0.8 IU/mL
Autohemolysis test	WB	0.004–0.045	0.4–4.50%
Autohemolysis test with glucose	WB	0.003–0.007	0.3–0.7%
Bleeding time (adult)		<7.1 min	<7.1 min
Bone marrow: See Table 7			
Clot retraction	WB	0.50–1.00/2 h	50–100%/2 h
Cryofibrinogen	P	Negative	Negative
D-dimer	P	220–740 ng/mL FEU	220–740 ng/mL FEU
Differential blood count	WB		
Relative counts:			
Neutrophils		0.40–0.70	40–70%
Bands		0.0–0.05	0–5%
Lymphocytes		0.20–0.50	20–50%
Monocytes		0.04–0.08	4–8%
Eosinophils		0.0–0.6	0–6%
Basophils		0.0–0.02	0–2%
Absolute counts:			
Neutrophils		$1.42–6.34 \times 10^9$/L	1420–6340/mm^3
Bands		$0–0.45 \times 10^9$/L	0–450/mm^3
Lymphocytes		$0.71–4.53 \times 10^9$/L	710–4530/mm^3
Monocytes		$0.14–0.72 \times 10^9$/L	140–720/mm^3
Eosinophils		$0–0.54 \times 10^9$/L	0–540/mm^3
Basophils		$0–0.18 \times 10^9$/L	0–180/mm^3
Erythrocyte count	WB		
Adult males		$4.30–5.60 \times 10^{12}$/L	$4.30–5.60 \times 10^6$/mm^3
Adult females		$4.00–5.20 \times 10^{12}$/L	$4.00–5.20 \times 10^6$/mm^3
Erythrocyte life span	WB		
Normal survival		120 days	120 days
Chromium labeled, half-life ($t_{1/2}$)		25–35 days	25–35 days
Erythrocyte sedimentation rate	WB		
Females		0–20 mm/h	0–20 mm/h
Males		0–15 mm/h	0–15 mm/h
Euglobulin lysis time	P	7200–14400 s	120–240 min
Factor II, prothrombin	P	0.50–1.50	50–150%
Factor V	P	0.50–1.50	50–150%
Factor VII	P	0.50–1.50	50–150%
Factor VIII	P	0.50–1.50	50–150%
Factor IX	P	0.50–1.50	50–150%
Factor X	P	0.50–1.50	50–150%
Factor XI	P	0.50–1.50	50–150%
Factor XII	P	0.50–1.50	50–150 %
Factor XIII screen	P	Not applicable	Present
Factor inhibitor assay	P	<0.5 Bethesda Units	<0.5 Bethesda Units
Fibrin(ogen) degradation products	P	0–1 mg/L	0–1 µg/mL
Fibrinogen	P	2.33–4.96 g/L	233–496 mg/dL
Glucose-6-phosphate dehydrogenase (erythrocyte)	WB	<2400 s	<40 min
Ham's test (acid serum)	WB	Negative	Negative

(*continued*)

TABLE 1

HEMATOLOGY AND COAGULATION (*CONTINUED*)

ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Hematocrit	WB		
Adult males		0.388–0.464	38.8–46.4
Adult females		0.354–0.444	35.4–44.4
Hemoglobin			
Plasma	P	6–50 mg/L	0.6–5.0 mg/dL
Whole blood:	WB		
Adult males		133–162 g/L	13.3–16.2 g/dL
Adult females		120–158 g/L	12.0–15.8 g/dL
Hemoglobin electrophoresis	WB		
Hemoglobin A		0.95–0.98	95–98%
Hemoglobin A_2		0.015–0.031	1.5–3.1%
Hemoglobin F		0–0.02	0–2.0%
Hemoglobins other than A, A_2, or F		Absent	Absent
Heparin-induced thrombocytopenia antibody	P	Negative	Negative
Immature platelet fraction (IPF)	WB	0.011–0.061	1.1–6.1%
Joint fluid crystal	JF	Not applicable	No crystals seen
Joint fluid mucin	JF	Not applicable	Only type I mucin present
Leukocytes			
Alkaline phosphatase (LAP)	WB	0.2–1.6 μkat/L	13–100 μ/L
Count (WBC)	WB	$3.54–9.06\times10^9$/L	$3.54–9.06\times10^3$/mm^3
Mean corpuscular hemoglobin (MCH)	WB	26.7–31.9 pg/cell	26.7–31.9 pg/cell
Mean corpuscular hemoglobin concentration (MCHC)	WB	323–359 g/L	32.3–35.9 g/dL
Mean corpuscular hemoglobin of reticulocytes (CH)	WB	24–36 pg	24–36 pg
Mean corpuscular volume (MCV)	WB	79–93.3 fL	79–93.3 μm^3
Mean platelet volume (MPV)	WB	9.00–12.95 fL	9.00–12.95
Osmotic fragility of erythrocytes	WB		
Direct		0.0035–0.0045	0.35–0.45%
Indirect		0.0030–0.0065	0.30–0.65%
Partial thromboplastin time, activated	P	26.3–39.4 s	26.3–39.4 s
Plasminogen	P		
Antigen		84–140 mg/L	8.4–14.0 mg/dL
Functional		0.70–1.30	70–130%
Plasminogen activator inhibitor 1	P	4–43 μg/L	4–43 ng/mL
Platelet aggregation	PRP	Not applicable	>65% aggregation in response to adenosine diphosphate, epinephrine, collagen, ristocetin, and arachidonic acid
Platelet count	WB	$165–415\times10^9$/L	$165–415\times10^3$/mm^3
Platelet, mean volume	WB	6.4–11 fL	6.4–11.0 μm^3
Prekallikrein assay	P	0.50–1.5	50–150%
Prekallikrein screen	P		No deficiency detected
Protein C	P		
Total antigen		0.70–1.40	70–140%
Functional		0.70–1.30	70–130%
Protein S	P		
Total antigen		0.70–1.40	70–140%
Functional		0.65–1.40	65–140%
Free antigen		0.70–1.40	70–140%
Prothrombin gene mutation G20210A	WB	Not applicable	Not present
Prothrombin time	P	12.7–15.4 s	12.7–15.4 s

(*continued*)

TABLE 1

HEMATOLOGY AND COAGULATION (*CONTINUED*)

ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Protoporphyrin, free erythrocyte	WB	0.28–0.64 μmol/L of red blood cells	16–36 μg/dL of red blood cells
Red cell distribution width	WB	<0.145	<14.5%
Reptilase time	P	16–23.6 s	16–23.6 s
Reticulocyte count	WB		
Adult males		0.008–0.023 red cells	0.8–2.3% red cells
Adult females		0.008–0.020 red cells	0.8–2.0% red cells
Reticulocyte hemoglobin content	WB	>26 pg/cell	>26 pg/cell
Ristocetin cofactor (functional von Willebrand factor)	P		
Blood group O		0.75 mean of normal	75% mean of normal
Blood group A		1.05 mean of normal	105% mean of normal
Blood group B		1.15 mean of normal	115% mean of normal
Blood group AB		1.25 mean of normal	125% mean of normal
Serotonin release assay	S	<0.2 release	<20% release
Sickle cell test	WB	Negative	Negative
Sucrose hemolysis	WB	<0.1	<10% hemolysis
Thrombin time	P	15.3–18.5 s	15.3–18.5 s
Total eosinophils	WB	150–300×10^6/L	150–300/mm^3
Transferrin receptor	S, P	9.6–29.6 nmol/L	9.6–29.6 nmol/L
Viscosity			
Plasma	P	1.7–2.1	1.7–2.1
Serum	S	1.4–1.8	1.4–1.8
von Willebrand factor (vWF) antigen (factor VIII:R antigen)	P		
Blood group O		0.75 mean of normal	75% mean of normal
Blood group A		1.05 mean of normal	105% mean of normal
Blood group B		1.15 mean of normal	115% mean of normal
Blood group AB		1.25 mean of normal	125% mean of normal
von Willebrand factor multimers	P	Normal distribution	Normal distribution
White blood cells: see “Leukocytes”			

Abbreviations: JF, joint fluid; P, plasma; PRP, platelet-rich plasma; S, serum; WB, whole blood.

TABLE 2

CLINICAL CHEMISTRY AND IMMUNOLOGY

ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Acetoacetate	P	49–294 μmol/L	0.5–3.0 mg/dL
Adrenocorticotropin (ACTH)	P	1.3–16.7 pmol/L	6.0–76.0 pg/mL
Alanine aminotransferase (ALT, SGPT)	S	0.12–0.70 μkat/L	7–41 U/L
Albumin	S	40–50 g/L	4.0–5.0 mg/dL
Aldolase	S	26–138 nkat/L	1.5–8.1 U/L
Aldosterone (adult)			
Supine, normal sodium diet	S, P	<443 pmol/L	<16 ng/dL
Upright, normal	S, P	111–858 pmol/L	4–31 ng/dL
Alpha fetoprotein (adult)	S	0–8.5 μg/L	0–8.5 ng/mL
$Alpha_1$ antitrypsin	S	1.0–2.0 g/L	100–200 mg/dL
Ammonia, as NH_3	P	11–35 μmol/L	19–60 μg/dL
Amylase (method dependent)	S	0.34–1.6 μkat/L	20–96 U/L

(*continued*)

TABLE 2

CLINICAL CHEMISTRY AND IMMUNOLOGY (*CONTINUED*)

ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Androstendione (adult)	S		
Males		0.81–3.1 nmol/L	23–89 ng/dL
Females			
Premenopausal		0.91–7.5 nmol/L	26–214 ng/dL
Postmenopausal		0.46–2.9 nmol/L	13–82 ng/dL
Angiotensin-converting enzyme (ACE)	S	0.15–1.1 µkat/L	9–67 U/L
Anion gap	S	7–16 mmol/L	7–16 mmol/L
Apolipoprotein A-1	S		
Male		0.94–1.78 g/L	94–178 mg/dL
Female		1.01–1.99 g/L	101–199 mg/dL
Apolipoprotein B	S		
Male		0.55–1.40 g/L	55–140 mg/dL
Female		0.55–1.25 g/L	55–125 mg/dL
Arterial blood gases	WB		
$[HCO_3^-]$		22–30 mmol/L	22–30 meq/L
P_{CO_2}		4.3–6.0 kPa	32–45 mmHg
pH		7.35–7.45	7.35–7.45
P_{O_2}		9.6–13.8 kPa	72–104 mmHg
Aspartate aminotransferase (AST, SGOT)	S	0.20–0.65 µkat/L	12–38 U/L
Autoantibodies	S		
Anti-centromere antibody IgG		≤29 AU/mL	≤29 AU/mL
Anti-double-strand (native) DNA		<25 IU/L	<25 IU/L
Anti-glomerular basement membrane antibodies			
Qualitative IgG, IgA		Negative	Negative
Quantitative IgG antibody		≤19 AU/mL	≤19 AU/mL
Anti-histone antibodies		<1.0 U	<1.0 U
Anti-Jo-1 antibody		≤29 AU/mL	≤29 AU/mL
Anti-mitochondrial antibody		Not applicable	<20 Units
Anti-neutrophil cytoplasmic autoantibodies		Not applicable	<1:20
Serine proteinase 3 antibodies		≤19 AU/mL	≤19 AU/mL
Myeloperoxidase antibodies		≤19 AU/mL	≤19 AU/mL
Antinuclear antibody		Not applicable	Negative at 1:40
Anti-parietal cell antibody		Not applicable	None detected
Anti-RNP antibody		Not applicable	<1.0 U
Anti-Scl 70 antibody		Not applicable	<1.0 U
Anti-Smith antibody		Not applicable	<1.0 U
Anti–smooth muscle antibody		Not applicable	<1.0 U
Anti-SSA antibody		Not applicable	<1.0 U
Anti-SSB antibody		Not applicable	Negative
Anti-thyroglobulin antibody		<40 KIU/L	<40 IU/mL
Anti-thyroid peroxidase antibody		<35 KIU/L	<35 IU/mL
B-type natriuretic peptide (BNP)	P	Age and gender specific: <100 ng/L	Age and gender specific: <100 pg/mL
Bence Jones protein, serum qualitative	S	Not applicable	None detected
Bence Jones protein, serum quantitative	S		
Free kappa		3.3–19.4 mg/L	0.33–1.94 mg/dL
Free lambda		5.7–26.3 mg/L	0.57–2.63 mg/dL
K/L ratio		0.26–1.65	0.26–1.65
Beta-2-microglobulin	S	1.1–2.4 mg/L	1.1–2.4 mg/L
Bilirubin	S		
Total		5.1–22 µmol/L	0.3–1.3 mg/dL
Direct		1.7–6.8 µmol/L	0.1–0.4 mg/dL
Indirect		3.4–15.2 µmol/L	0.2–0.9 mg/dL

(*continued*)

TABLE 2

CLINICAL CHEMISTRY AND IMMUNOLOGY (*CONTINUED*)

ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
C peptide	S	0.27–1.19 nmol/L	0.8–3.5 ng/mL
C1-esterase-inhibitor protein	S	210–390 mg/L	21–39 mg/dL
CA 125	S	<35 kU/L	<35 U/mL
CA 19-9	S	<37 kU/L	<37 U/mL
CA 15-3	S	<33 kU/L	<33 U/mL
CA 27-29	S	0–40 kU/L	0–40 U/mL
Calcitonin	S		
Male		0–7.5 ng/L	0–7.5 pg/mL
Female		0–5.1 ng/L	0–5.1 pg/mL
Calcium	S	2.2–2.6 mmol/L	8.7–10.2 mg/dL
Calcium, ionized	WB	1.12–1.32 mmol/L	4.5–5.3 mg/dL
Carbon dioxide content (TCO_2)	P (sea level)	22–30 mmol/L	22–30 meq/L
Carboxyhemoglobin (carbon monoxide content)	WB		
Nonsmokers		0.0–0.015	0–1.5%
Smokers		0.04–0.09	4–9%
Loss of consciousness and death		>0.50	>50%
Carcinoembryonic antigen (CEA)	S		
Nonsmokers		0.0–3.0 µg/L	0.0–3.0 ng/mL
Smokers		0.0–5.0 µg/L	0.0–5.0 ng/mL
Ceruloplasmin	S	250–630 mg/L	25–63 mg/dL
Chloride	S	102–109 mmol/L	102–109 meq/L
Cholesterol: see Table 5			
Cholinesterase	S	5–12 kU/L	5–12 U/mL
Chromogranin A	S	0–50 µg/L	0–50 ng/mL
Complement	S		
C3		0.83–1.77 g/L	83–177 mg/dL
C4		0.16–0.47 g/L	16–47 mg/dL
Complement total		60–144 CAE units	60–144 CAE units
Cortisol	S		
Fasting, 8 A.M.–12 noon		138–690 nmol/L	5–25 µg/dL
12 noon–8 P.M.		138–414 nmol/L	5–15 µg/dL
8 P.M.–8 A.M.		0–276 nmol/L	0–10 µg/dL
C-reactive protein	S	<10 mg/L	<10 mg/L
C-reactive protein, high sensitivity	S	Cardiac risk Low: <1.0 mg/L Average: 1.0–3.0 mg/L High: >3.0 mg/L	Cardiac risk Low: <1.0 mg/L Average: 1.0–3.0 mg/L High: >3.0 mg/L
Creatine kinase (total)	S		
Females		0.66–4.0 µkat/L	39–238 U/L
Males		0.875.0 µkat/L	51–294 U/L
Creatine kinase-MB	S		
Mass		0.0–5.5 µg/L	0.0–5.5 ng/mL
Fraction of total activity (by electrophoresis)		0–0.04	0–4.0%
Creatinine	S		
Female		44–80 µmol/L	0.5–0.9 mg/dL
Male		53–106 µmol/L	0.6–1.2 mg/dL
Cryoglobulins	S	Not applicable	None detected
Cystatin C	S	0.5–1.0 mg/L	0.5–1.0 mg/L

(*continued*)

TABLE 2

CLINICAL CHEMISTRY AND IMMUNOLOGY (*CONTINUED*)

ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Dehydroepiandrosterone (DHEA) (adult)	S		
Male		6.2–43.4 nmol/L	180–1250 ng/dL
Female		4.5–34.0 nmol/L	130–980 ng/dL
Dehydroepiandrosterone (DHEA) sulfate	S		
Male (adult)		100–6190 µg/L	10–619 µg/dL
Female (adult, premenopausal)		120–5350 µg/L	12–535 µg/dL
Female (adult, postmenopausal)		300–2600 µg/L	30–260 µg/dL
11-Deoxycortisol (adult)(compound S)	S	0.34–4.56 nmol/L	12–158 ng/dL
Dihydrotestosterone	S, P		
Male		1.03–2.92 nmol/L	30–85 ng/dL
Female		0.14–0.76 nmol/L	4–22 ng/dL
Dopamine	P	0–130 pmol/L	0–20 pg/mL
Epinephrine	P		
Supine (30 min)		<273 pmol/L	<50 pg/mL
Sitting		<328 pmol/L	<60 pg/mL
Standing (30 min)		<491 pmol/L	<90 pg/mL
Erythropoietin	S	4–27 U/L	4–27 U/L
Estradiol	S, P		
Female			
Menstruating			
Follicular phase		74–532 pmol/L	<20–145 pg/mL
Midcycle peak		411–1626 pmol/L	112–443 pg/mL
Luteal phase		74–885 pmol/L	<20–241 pg/mL
Postmenopausal		217 pmol/L	<59 pg/mL
Male		74 pmol/L	<20 pg/mL
Estrone	S, P		
Female			
Menstruating			
Follicular phase		<555 pmol/L	<150 pg/mL
Luteal phase		<740 pmol/L	<200 pg/mL
Postmenopausal		11–118 pmol/L	3–32 pg/mL
Male		33–133 pmol/L	9–36 pg/mL
Fatty acids, free (nonesterified)	P	0.1–0.6 mmol/L	2.8–16.8 mg/dL
Ferritin	S		
Female		10–150 µg/L	10–150 ng/mL
Male		29–248 µg/L	29–248 ng/mL
Follicle-stimulating hormone (FSH)	S, P		
Female			
Menstruating			
Follicular phase		3.0–20.0 IU/L	3.0–20.0 mIU/mL
Ovulatory phase		9.0–26.0 IU/L	9.0–26.0 mIU/mL
Luteal phase		1.0–12.0 IU/L	1.0–12.0 mIU/mL
Postmenopausal		18.0–153.0 IU/L	18.0–153.0 mIU/mL
Male		1.0–12.0 IU/L	1.0–12.0 mIU/mL
Fructosamine	S	<285 umol/L	<285 umol/L
Gamma glutamyltransferase	S	0.15–0.99 µkat/L	9–58 U/L
Gastrin	S	<100 ng/L	<100 pg/mL
Glucagon	P	40–130 ng/L	40–130 pg/mL

(*continued*)

TABLE 2

CLINICAL CHEMISTRY AND IMMUNOLOGY (*CONTINUED*)

ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Glucose	WB	3.6–5.3 mmol/L	65–95 mg/dL
Glucose (fasting)	P		
Normal		4.2–5.6 mmol/L	75–100 mg/dL
Increased risk for diabetes		5.6–6.9 mmol/L	100–125 mg/dL
Diabetes mellitus		Fasting >7.0 mmol/L A 2-hour level of >11.1 mmol/L during an oral glucose tolerance test A random glucose level of ≥11.1 mmol/L in patients with symptoms of hyperglycemia	Fasting >126 mg/dL A 2-hour level of ≥200 mg/dL during an oral glucose tolerance test A random glucose level of ≥200 mg/dL in patients with symptoms of hyperglycemia
Growth hormone	S	0–5 µg/L	0–5 ng/mL
Hemoglobin A_{Ic}	WB	0.04–0.06 HgB fraction	4.0–5.6%
Pre-diabetes		0.057–0.064 HgB fraction	5.7–6.4%
Diabetes mellitus		A hemoglobin A_{1c} level of ≥0.065 Hgb fraction as suggested by the American Diabetes Association	A hemoglobin A_{1c} level of ≥6.5% as suggested by the American Diabetes Association
Hemoglobin A_{1c} with estimated average glucose (eAg)	WB	eAg mmoL/L = 1.59 × HbA_{1c} – 2.59	eAg (mg/dL) = 28.7 × HbA_{1c} – 46.7
High-density lipoprotein (HDL) (see Table 5)			
Homocysteine	P	4.4–10.8 µmol/L	4.4–10.8 µmol/L
Human chorionic gonadotropin (HCG)	S		
Nonpregnant female		<5 IU/L	<5 mIU/ml
1–2 weeks postconception		9–130 IU/L	9–130 mIU/mL
2–3 weeks postconception		75–2600 IU/L	75–2600 mIU/mL
3–4 weeks postconception		850–20,800 IU/L	850–20,800 mIU/mL
4–5 weeks postconception		4000–100,200 IU/L	4000–100,200 mIU/mL
5–10 weeks postconception		11,500–289,000 IU/L	11,500–289,000 mIU/mL
10–14 weeks post conception		18,300–137,000 IU/L	18,300–137,000 mIU/mL
Second trimester		1400–53,000 IU/L	1400–53,000 mIU/mL
Third trimester		940–60,000 IU/L	940–60,000 mIU/mL
β-Hydroxybutyrate	P	60–170 µmol/L	0.6–1.8 mg/dL
17-Hydroxyprogesterone (adult)	S		
Male		<4.17 nmol/L	<139 ng/dL
Female			
Follicular phase		0.45–2.1 nmol/L	15–70 ng/dL
Luteal phase		1.05–8.7 nmol/L	35–290 ng/dL
Immunofixation	S	Not applicable	No bands detected
Immunoglobulin, quantitation (adult)			
IgA	S	0.70–3.50 g/L	70–350 mg/dL
IgD	S	0–140 mg/L	0–14 mg/dL
IgE	S	1–87 KIU/L	1–87 IU/mL
IgG	S	7.0–17.0 g/L	700–1700 mg/dL
IgG_1	S	2.7–17.4 g/L	270–1740 mg/dL
IgG_2	S	0.3–6.3 g/L	30–630 mg/dL
IgG_3	S	0.13–3.2 g/L	13–320 mg/dL
IgG_4	S	0.11–6.2 g/L	11–620 mg/dL
IgM	S	0.50–3.0 g/L	50–300 mg/dL
Insulin	S, P	14.35–143.5 pmol/L	2–20 µU/mL
Iron	S	7–25 µmol/L	41–141 µg/dL

(*continued*)

TABLE 2

CLINICAL CHEMISTRY AND IMMUNOLOGY (*CONTINUED*)

ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Iron-binding capacity	S	45–73 µmol/L	251–406 µg/dL
Iron-binding capacity saturation	S	0.16–0.35	16–35%
Ischemia modified albumin	S	<85 KU/L	<85 U/mL
Joint fluid crystal	JF	Not applicable	No crystals seen
Joint fluid mucin	JF	Not applicable	Only type I mucin present
Ketone (acetone)	S	Negative	Negative
Lactate	P, arterial P, venous	0.5–1.6 mmol/L 0.5–2.2 mmol/L	4.5–14.4 mg/dL 4.5–19.8 mg/dL
Lactate dehydrogenase	S	2.0–3.8 µkat/L	115–221 U/L
Lipase	S	0.51–0.73 µkat/L	3–43 U/L
Lipids: see Table 5			
Lipoprotein (a)	S	0–300 mg/L	0–30 mg/dL
Low-density lipoprotein (LDL) (see Table 5)			
Luteinizing hormone (LH) Female Menstruating Follicular phase Ovulatory phase Luteal phase Postmenopausal Male	S, P 	 2.0–15.0 U/L 22.0–105.0 U/L 0.6–19.0 U/L 16.0–64.0 U/L 2.0–12.0 U/L	 2.0–15.0 mIU/mL 22.0–105.0 mIU/mL 0.6–19.0 mIU/mL 16.0–64.0 mIU/mL 2.0–12.0 mIU/mL
Magnesium	S	0.62–0.95 mmol/L	1.5–2.3 mg/dL
Metanephrine	P	<0.5 nmol/L	<100 pg/mL
Methemoglobin	WB	0.0–0.01	0–1%
Myoglobin Male Female	S 	 20–71 µg/L 25–58 µg/L	 20–71 µg/L 25–58 µg/L
Norepinephrine Supine (30 min) Sitting Standing (30 min)	P 	 650–2423 pmol/L 709–4019 pmol/L 739–4137 pmol/L	 110–410 pg/mL 120–680 pg/mL 125–700 pg/mL
N-telopeptide (cross-linked), NTx Female, premenopausal Male BCE = bone collagen equivalent	S 	 6.2–19.0 nmol BCE 5.4–24.2 nmol BCE	 6.2–19.0 nmol BCE 5.4–24.2 nmol BCE
NT-Pro BNP	S, P	<125 ng/L up to 75 years <450 ng/L >75 years	<125 pg/mL up to 75 years <450 pg/mL >75 years
5′ Nucleotidase	S	0.00–0.19 µkat/L	0–11 U/L
Osmolality	P	275–295 mOsmol/kg serum water	275–295 mOsmol/kg serum water
Osteocalcin	S	11–50 µg/L	11–50 ng/mL
Oxygen content Arterial (sea level) Venous (sea level)	WB 	 17–21 10–16	 17–21 vol% 10–16 vol%
Oxygen saturation (sea level) Arterial Venous, arm	WB 	Fraction: 0.94–1.0 0.60–0.85	Percent: 94–100% 60–85%
Parathyroid hormone (intact)	S	8–51 ng/L	8–51 pg/mL

(*continued*)

TABLE 2

CLINICAL CHEMISTRY AND IMMUNOLOGY (*CONTINUED*)

ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Phosphatase, alkaline	S	0.56–1.63 μkat/L	33–96 U/L
Phosphorus, inorganic	S	0.81–1.4 mmol/L	2.5–4.3 mg/dL
Potassium	S	3.5–5.0 mmol/L	3.5–5.0 meq/L
Prealbumin	S	170–340 mg/L	17–34 mg/dL
Procalcitonin	S	<0.1 μg/L	<0.1 ng/mL
Progesterone	S, P		
Female: Follicular		<3.18 nmol/L	<1.0 ng/mL
Midluteal		9.54–63.6 nmol/L	3–20 ng/mL
Male		<3.18 nmol/L	<1.0 ng/mL
Prolactin	S		
Male		53–360 mg/L	2.5–17 ng/mL
Female		40–530 mg/L	1.9–25 ng/mL
Prostate-specific antigen (PSA)	S	0.0–4.0 μg/L	0.0–4.0 ng/mL
Prostate-specific antigen, free	S	With total PSA between 4 and 10 μg/L and when the free PSA is: >0.25 decreased risk of prostate cancer <0.10 increased risk of prostate cancer	With total PSA between 4 and 10 ng/mL and when the free PSA is: >25% decreased risk of prostate cancer <10% increased risk of prostate cancer
Protein fractions:	S		
Albumin		35–55 g/L	3.5–5.5 g/dL (50–60%)
Globulin		20–35 g/L	2.0–3.5 g/dL (40–50%)
$Alpha_1$		2–4 g/L	0.2–0.4 g/dL (4.2–7.2%)
$Alpha_2$		5–9 g/L	0.5–0.9 g/dL (6.8–12%)
Beta		6–11 g/L	0.6–1.1 g/dL (9.3–15%)
Gamma		7–17 g/L	0.7–1.7 g/dL (13–23%)
Protein, total	S	67–86 g/L	6.7–8.6 g/dL
Pyruvate	P	40–130 μmol/L	0.35–1.14 mg/dL
Rheumatoid factor	S	<15 kIU/L	<15 IU/mL
Serotonin	WB	0.28–1.14 umol/L	50–200 ng/mL
Serum protein electrophoresis	S	Not applicable	Normal pattern
Sex hormone–binding globulin (adult)	S		
Male		11–80 nmol/L	11–80 nmol/L
Female		30–135 nmol/L	30–135 nmol/L
Sodium	S	136–146 mmol/L	136–146 meq/L
Somatomedin-C (IGF-1) (adult)	S		
16 years		226–903 μg/L	226–903 ng/mL
17 years		193–731 μg/L	193–731 ng/mL
18 years		163–584 μg/L	163–584 ng/mL
19 years		141–483 μg/L	141–483 ng/mL
20 years		127–424 μg/L	127–424 ng/mL
21–25 years		116–358 μg/L	116–358 ng/mL
26–30 years		117–329 μg/L	117–329 ng/mL
31–35 years		115–307 μg/L	115–307 ng/mL
36–40 years		119–204 μg/L	119–204 ng/mL
41–45 years		101–267 μg/L	101–267 ng/mL
46–50 years		94–252 μg/L	94–252 ng/mL
51–55 years		87–238 μg/L	87–238 ng/mL
56–60 years		81–225 μg/L	81–225 ng/mL
61–65 years		75–212 μg/L	75–212 ng/mL

(*continued*)

TABLE 2

CLINICAL CHEMISTRY AND IMMUNOLOGY (*CONTINUED*)

ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
66–70 years		69–200 µg/L	69–200 ng/mL
71–75 years		64–188 µg/L	64–188 ng/mL
76–80 years		59–177 µg/L	59–177 ng/mL
81–85 years		55–166 µg/L	55–166 ng/mL
Somatostatin	P	<25 ng/L	<25 pg/mL
Testosterone, free	S		
Female, adult		10.4–65.9 pmol/L	3–19 pg/mL
Male, adult		312–1041 pmol/L	90–300 pg/mL
Testosterone, total,	S		
Female		0.21–2.98 nmol/L	6–86 ng/dL
Male		9.36–37.10 nmol/L	270–1070 ng/dL
Thyroglobulin	S	1.3–31.8 µg/L	1.3–31.8 ng/mL
Thyroid-binding globulin	S	13–30 mg/L	1.3–3.0 mg/dL
Thyroid-stimulating hormone	S	0.34–4.25 mIU/L	0.34–4.25 µIU/mL
Thyroxine, free (fT4)	S	9.0–16 pmol/L	0.7–1.24 ng/dL
Thyroxine, total (T4)	S	70–151 nmol/L	5.4–11.7 µg/dL
Thyroxine index (free)	S	6.7–10.9	6.7–10.9
Transferrin	S	2.0–4.0 g/L	200–400 mg/dL
Triglycerides (see Table 5)	S	0.34–2.26 mmol/L	30–200 mg/dL
Triiodothyronine, free (fT3)	S	3.7–6.5 pmol/L	2.4–4.2 pg/mL
Triiodothyronine, total (T3)	S	1.2–2.1 nmol/L	77–135 ng/dL
Troponin I (method dependent)	S, P		
99th percentile of a healthy population		0–0.04 µg/L	0–0.04 ng/mL
Troponin T	S, P		
99th percentile of a healthy population		0–0.01 µg/L	0–0.01 ng/mL
Urea nitrogen	S	2.5–7.1 mmol/L	7–20 mg/dL
Uric acid	S		
Females		0.15–0.33 mmol/L	2.5–5.6 mg/dL
Males		0.18–0.41 mmol/L	3.1–7.0 mg/dL
Vasoactive intestinal polypeptide	P	0–60 ng/L	0–60 pg/mL
Zinc protoporphyrin	WB	0–400 µg/L	0–40 µg/dL
Zinc protoporphyrin (ZPP)-to-heme ratio	WB	0–69 µmol ZPP/mol heme	0–69 µmol ZPP/mol heme

Abbreviations: P, plasma; S, serum; WB, whole blood.

TABLE 3

TOXICOLOGY AND THERAPEUTIC DRUG MONITORING

	THERAPEUTIC RANGE		TOXIC LEVEL	
DRUG	**SI UNITS**	**CONVENTIONAL UNITS**	**SI UNITS**	**CONVENTIONAL UNITS**
Acetaminophen	66–199 µmol/L	10–30 µg/mL	>1320 µmol/L	>200 µg/mL
Amikacin				
Peak	34–51 µmol/L	20–30 µg/mL	>60 µmol/L	>35 µg/mL
Trough	0–17 µmol/L	0–10 µg/mL	>17 µmol/L	>10 µg/mL
Amitriptyline/nortriptyline (total drug)	430–900 nmol/L	120–250 ng/mL	>1800 nmol/L	>500 ng/mL
Amphetamine	150–220 nmol/L	20–30 ng/mL	>1500 nmol/L	>200 ng/mL
Bromide	9.4–18.7 mmol/L	75–150 mg/dL	>18.8 mmol/L	>150 mg/dL
Mild toxicity			6.4–18.8 mmol/L	51–150 mg/dL
Severe toxicity			>18.8 mmol/L	>150 mg/dL
Lethal			>37.5 mmol/L	>300 mg/dL
Caffeine	25.8–103 µmol/L	5–20 µg/ml	>206 µmol/L	>40 µg/mL
Carbamazepine	17–42 µmol/L	4–10 µg/mL	>85 µmol/L	>20 µg/mL
Chloramphenicol				
Peak	31–62 µmol/L	10–20 µg/mL	>77 µmol/L	>25 µg/mL
Trough	15–31 µmol/L	5–10 µg/mL	>46 µmol/L	>15 µg/mL
Chlordiazepoxide	1.7–10 µmol/L	0.5–3.0 µg/mL	>17µmol/L	>5.0 µg/mL
Clonazepam	32–240 nmol/L	10–75 ng/mL	>320 nmol/L	>100 ng/mL
Clozapine	0.6–2.1 µmol/L	200–700 ng/mL	>3.7 µmol/L	>1200 ng/mL
Cocaine			>3.3 µmol/L	>1.0 µg/mL
Codeine	43–110 nmol/mL	13–33 ng/mL	>3700 nmol/mL	>1100 ng/mL (lethal)
Cyclosporine				
Renal transplant				
0–6 months	208–312 nmol/L	250–375 ng/mL	>312 nmol/L	>375 ng/mL
6–12 months after transplant	166–250 nmol/L	200–300 ng/mL	>250 nmol/L	>300 ng/mL
>12 months	83–125 nmol/L	100–150 ng/mL	>125 nmol/L	>150 ng/mL
Cardiac transplant				
0–6 months	208–291 nmol/L	250–350 ng/mL	>291 nmol/L	>350 ng/mL
6–12 months after transplant	125–208 nmol/L	150–250 ng/mL	>208 nmol/L	>250 ng/mL
>12 months	83–125 nmol/L	100–150 ng/mL	>125 nmol/L	150 ng/mL
Lung transplant				
0–6 months	250–374 nmol/L	300–450 ng/mL	>374 nmol/L	>450 ng/mL
Liver transplant				
Initiation	208–291 nmol/L	250–350 ng/mL	>291 nmol/L	>350 ng/mL
Maintenance	83–166 nmol/L	100–200 ng/mL	>166 nmol/L	>200 ng/mL
Desipramine	375–1130 nmol/L	100–300 ng/mL	>1880 nmol/L	>500 ng/mL
Diazepam (and metabolite)				
Diazepam	0.7–3.5 µmol/L	0.2–1.0 µg/mL	>7.0 µmol/L	>2.0 µg/mL
Nordiazepam	0.4–6.6 µmol/L	0.1–1.8 µg/mL	>9.2 µmol/L	>2.5 µg/mL
Digoxin	0.64–2.6 nmol/L	0.5–2.0 ng/mL	>5.0 nmol/L	>3.9 ng/mL
Disopyramide	5.3–14.7 µmol/L	2–5 µg/mL	>20.6 µmol/L	>7 µg/mL
Doxepin and nordoxepin				
Doxepin	0.36–0.98 µmol/L	101–274 ng/mL	>1.8 µmol/L	>503 ng/mL
Nordoxepin	0.38–1.04 µmol/L	106–291 ng/mL	>1.9 µmol/L	>531 ng/mL
Ethanol				
Behavioral changes			>4.3 mmol/L	>20 mg/dL
Legal limit			≥17 mmol/L	≥80 mg/dL
Critical with acute exposure			>54 mmol/L	>250 mg/dL
Ethylene glycol				
Toxic			>2 mmol/L	>12 mg/dL
Lethal			>20 mmol/L	>120 mg/dL

(*continued*)

TABLE 3

TOXICOLOGY AND THERAPEUTIC DRUG MONITORING (*CONTINUED*)

	THERAPEUTIC RANGE		TOXIC LEVEL	
DRUG	**SI UNITS**	**CONVENTIONAL UNITS**	**SI UNITS**	**CONVENTIONAL UNITS**
Ethosuximide	280–700 µmol/L	40–100 µg/mL	>700 µmol/L	>100 µg/mL
Everolimus	3.13–8.35 nmol/L	3–8 ng/mL	>12.5 nmol/L	>12 ng/mL
Flecainide	0.5–2.4 µmol/L	0.2–1.0 µg/mL	>3.6 µmol/L	>1.5 µg/mL
Gentamicin				
Peak	10–21 µmol/mL	5–10 µg/mL	>25 µmol/mL	>12 µg/mL
Trough	0–4.2 µmol/mL	0–2 µg/mL	>4.2 µmol/mL	>2 µg/mL
Heroin (diacetyl morphine)			>700 µmol/L	>200 ng/mL (as morphine)
Ibuprofen	49–243 µmol/L	10–50 µg/mL	>970 µmol/L	>200 µg/mL
Imipramine (and metabolite)				
Desimipramine	375–1130 nmol/L	100–300 ng/mL	>1880 nmol/L	>500 ng/mL
Total imipramine + desimipramine	563–1130 nmol/L	150–300 ng/mL	>1880 nmol/L	>500 ng/mL
Lamotrigine	11.7–54.7 µmol/L	3–14 µg/mL	>58.7 µmol/L	>15 µg/mL
Lidocaine	5.1–21.3 µmol/L	1.2–5.0 µg/mL	>38.4 µmol/L	>9.0 µg/mL
Lithium	0.5–1.3 mmol/L	0.5–1.3 meq/L	>2 mmol/L	>2 meq/L
Methadone	1.0–3.2 µmol/L	0.3–1.0 µg/mL	>6.5 µmol/L	>2 µg/mL
Methamphetamine	0.07–0.34 µmol/L	0.01–0.05 µg/mL	>3.35 µmol/L	>0.5µg/mL
Methanol			>6 mmol/L	>20 mg/dL
Methotrexate				
Low-dose	0.01–0.1 µmol/L	0.01–0.1 µmol/L	>0.1 mmol/L	>0.1 mmol/L
High-dose (24h)	<5.0 µmol/L	<5.0 µmol/L	>5.0 µmol/L	>5.0 µmol/L
High-dose (48h)	<0.50 µmol/L	<0.50 µmol/L	>0.5 µmol/L	>0.5 µmol/L
High-dose (72h)	<0.10 µmol/L	<0.10 µmol/L	>0.1 µmol/L	>0.1 µmol/L
Morphine	232–286 µmol/L	65–80 ng/mL	>720 µmol/L	>200 ng/mL
Mycophenolic acid	3.1–10.9 µmol/L	1.0–3.5 ng/mL	>37 µmol/L	>12 ng/mL
Nitroprusside (as thiocyanate)	103–499 µmol/L	6–29 µg/mL	860 µmol/L	>50 µg/mL
Nortriptyline	190–569 nmol/L	50–150 ng/mL	>1900 nmol/L	>500 ng/mL
Phenobarbital	65–172 µmol/L	15–40 µg/mL	>258 µmol/L	>60 µg/mL
Phenytoin	40–79 µmol/L	10–20 µg/mL	>158 µmol/L	>40 µg/mL
Phenytoin, free	4.0–7.9 µg/mL	1–2 µg/mL	>13.9 µg/mL	>3.5 µg/mL
% Free	0.08–0.14	8–14%		
Primidone and metabolite				
Primidone	23–55 µmol/L	5–12 µg/mL	>69 µmol/L	>15 µg/mL
Phenobarbital	65–172 µmol/L	15–40 µg/mL	>215 µmol/L	>50 µg/mL
Procainamide				
Procainamide	17–42 µmol/L	4–10 µg/mL	>43 µmol/L	>10 µg/mL
NAPA (*N*-acetylprocainamide)	22–72 µmol/L	6–20µg/mL	>126 µmol/L	>35 µg/mL
Quinidine	6.2–15.4 µmol/L	2.0–5.0 µg/mL	>19 µmol/L	>6 µg/mL
Salicylates	145–2100 µmol/L	2–29 mg/dL	>2900 µmol/L	>40 mg/dL
Sirolimus (trough level)				
Kidney transplant	4.4–15.4 nmol/L	4–14 ng/mL	>16 nmol/L	>15 ng/mL
Tacrolimus (FK506) (trough)				
Kidney and liver	12–19 nmol/L	10–15 ng/mL	>25 nmol/L	>20 ng/mL
Initiation				
Maintenance	6–12 nmol/L	5–10 ng/mL	>25 nmol/L	>20 ng/mL
Heart				
Initiation	19–25 nmol/L	15–20 ng/mL		
Maintenance	6–12 nmol/L	5–10 ng/mL		

(*continued*)

TABLE 3

TOXICOLOGY AND THERAPEUTIC DRUG MONITORING (*CONTINUED*)

	THERAPEUTIC RANGE		TOXIC LEVEL	
DRUG	**SI UNITS**	**CONVENTIONAL UNITS**	**SI UNITS**	**CONVENTIONAL UNITS**
Theophylline	56–111 µg/mL	10–20 µg/mL	>168 µg/mL	>30 µg/mL
Thiocyanate				
After nitroprusside infusion	103–499 µmol/L	6–29 µg/mL	860 µmol/L	>50 µg/mL
Nonsmoker	17–69 µmol/L	1–4 µg/mL		
Smoker	52–206 µmol/L	3–12 µg/mL		
Tobramycin				
Peak	11–22 µg/L	5–10 µg/mL	>26 µg/L	>12 µg/mL
Trough	0–4.3 µg/L	0–2 µg/mL	>4.3 µg/L	>2 µg/mL
Valproic acid	346–693 µmol/L	50–100 µg/mL	>693 µmol/L	>100 µg/mL
Vancomycin				
Peak	14–28 µmol/L	20–40 µg/mL	>55µmol/L	>80 µg/mL
Trough	3.5–10.4µmol/L	5–15 µg/mL	>14 µmol/L	>20 µg/mL

TABLE 4

VITAMINS AND SELECTED TRACE MINERALS

		REFERENCE RANGE	
SPECIMEN	**ANALYTE**	**SI UNITS**	**CONVENTIONAL UNITS**
Aluminum	S	<0.2 µmol/L	<5.41 µg/L
Arsenic	WB	0.03–0.31 µmol/L	2–23 µg/L
Cadmium	WB	<44.5 nmol/L	<5.0 µg/L
Coenzyme Q10 (ubiquinone)	P	433–1532 µg/L	433–1532 µg/L
β-Carotene	S	0.07–1.43 µmol/L	4–77 µg/dL
Copper	S	11–22 µmol/L	70–140 µg/dL
Folic acid	RC	340–1020 nmol/L cells	150–450 ng/mL cells
Folic acid	S	12.2–40.8 nmol/L	5.4–18.0 ng/mL
Lead (adult)	S	<0.5 µmol/L	<10 µg/dL
Mercury	WB	3.0–294 nmol/L	0.6–59 µg/L
Selenium	S	0.8–2.0 umol/L	63–160 µg/L
Vitamin A	S	0.7–3.5 µmol/L	20–100 µg/dL
Vitamin B_1 (thiamine)	S	0–75 nmol/L	0–2 µg/dL
Vitamin B_2 (riboflavin)	S	106–638 nmol/L	4–24 µg/dL
Vitamin B_6	P	20–121 nmol/L	5–30 ng/mL
Vitamin B_{12}	S	206–735 pmol/L	279–996 pg/mL
Vitamin C (ascorbic acid)	S	23–57 µmol/L	0.4–1.0 mg/dL
Vitamin D_3,1,25-dihydroxy, total	S, P	36–180 pmol/L	15–75 pg/mL
Vitamin D_3,25-hydroxy, total	P	75–250 nmol/L	30–100 ng/mL
Vitamin E	S	12–42 µmol/L	5–18 µg/mL
Vitamin K	S	0.29–2.64 nmol/L	0.13–1.19 ng/mL
Zinc	S	11.5–18.4 µmol/L	75–120 µg/dL

Abbreviations: P, plasma; RC, red cells; S, serum; WB, whole blood.

TABLE 5

CLASSIFICATION OF LDL, TOTAL, AND HDL CHOLESTEROL

LDL Cholesterol	
<70 mg/dL	Therapeutic option for very high-risk patients
<100 mg/dL	Optimal
100–129 mg/dL	Near optimal/above optimal
130–159 mg/dL	Borderline high
160–189 mg/dL	High
≥190 mg/dL	Very high
Total Cholesterol	
<200 mg/dL	Desirable
200–239 mg/dL	Borderline high
≥240 mg/dL	High
HDL Cholesterol	
<40 mg/dL	Low
≥60 mg/dL	High

Abbreviations: LDL, low-density lipoprotein; HDL, high-density lipoprotein.

Source: Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). JAMA 2001; 285:2486–97. Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. SM Grundy et al for the Coordinating Committee of the National Cholesterol Education Program: Circulation 110:227, 2004.

REFERENCE VALUES FOR SPECIFIC ANALYTES

TABLE 6

CEREBROSPINAL FLUID[a]

	REFERENCE RANGE	
CONSTITUENT	**SI UNITS**	**CONVENTIONAL UNITS**
Osmolarity	292–297 mmol/kg water	292–297 mOsm/L
Electrolytes		
Sodium	137–145 mmol/L	137–145 meq/L
Potassium	2.7–3.9 mmol/L	2.7–3.9 meq/L
Calcium	1.0–1.5 mmol/L	2.1–3.0 meq/L
Magnesium	1.0–1.2 mmol/L	2.0–2.5 meq/L
Chloride	116–122 mmol/L	116–122 meq/L
CO_2 content	20–24 mmol/L	20–24 meq/L
P_{CO_2}	6–7 kPa	45–49 mmHg
pH	7.31–7.34	
Glucose	2.22–3.89 mmol/L	40–70 mg/dL
Lactate	1–2 mmol/L	10–20 mg/dL
Total protein		
Lumbar	0.15–0.5 g/L	15–50 mg/dL
Cisternal	0.15–0.25 g/L	15–25 mg/dL
Ventricular	0.06–0.15 g/L	6–15 mg/dL
Albumin	0.066–0.442 g/L	6.6–44.2 mg/dL
IgG	0.009–0.057 g/L	0.9–5.7 mg/dL
IgG index[b]	0.29–0.59	
Oligoclonal bands (OGB)	<2 bands not present in matched serum sample	
Ammonia	15–47 µmol/L	25–80 µg/dL
Creatinine	44–168 µmol/L	0.5–1.9 mg/dL
Myelin basic protein	<4 µg/L	
CSF pressure		50–180 mmH_2O
CSF volume (adult)	~150 mL	
Red blood cells	0	0
Leukocytes		
Total	0–5 mononuclear cells per µL	
Differential		
Lymphocytes	60–70%	
Monocytes	30–50%	
Neutrophils	None	

[a]Since cerebrospinal fluid concentrations are equilibrium values, measurements of the same parameters in blood plasma obtained at the same time are recommended. However, there is a time lag in attainment of equilibrium, and cerebrospinal levels of plasma constituents that can fluctuate rapidly (such as plasma glucose) may not achieve stable values until after a significant lag phase.

[b]IgG index = CSF IgG (mg/dL) × serum albumin (g/dL)/serum IgG (g/dL) × CSF albumin (mg/dL).

TABLE 7A

DIFFERENTIAL NUCLEATED CELL COUNTS OF BONE MARROW ASPIRATES[a]

	OBSERVED RANGE (%)	95% RANGE (%)	MEAN (%)
Blast cells	0–3.2	0–3.0	1.4
Promyelocytes	3.6–13.2	3.2–12.4	7.8
Neutrophil myelocytes	4–21.4	3.7–10.0	7.6
Eosinophil myelocytes	0–5.0	0–2.8	1.3
Metamyelocytes	1–7.0	2.3–5.9	4.1
Neutrophils			
Males	21.0–45.6	21.9–42.3	32.1
Females	29.6–46.6	28.8–45.9	37.4
Eosinophils	0.4–4.2	0.3–4.2	2.2
Eosinophils plus eosinophil myelocytes	0.9–7.4	0.7–6.3	3.5
Basophils	0–0.8	0–0.4	0.1
Erythroblasts			
Males	18.0–39.4	16.2–40.1	28.1
Females	14.0–31.8	13.0–32.0	22.5
Lymphocytes	4.6–22.6	6.0–20.0	13.1
Plasma cells	0–1.4	0–1.2	0.6
Monocytes	0–3.2	0–2.6	1.3
Macrophages	0–1.8	0–1.3	0.4
M:E ratio			
Males	1.1–4.0	1.1–4.1	2.1
Females	1.6–5.4	1.6–5.2	2.8

[a]Based on bone marrow aspirate from 50 healthy volunteers (30 men, 20 women).
Abbreviation: M:E, myeloid to erythroid ratio.
Source: BJ Bain: Br J Haematol 94:206, 1996.

TABLE 7B

BONE MARROW CELLULARITY

AGE	OBSERVED RANGE	95% RANGE	MEAN
Under 10 years	59.0–95.1%	72.9–84.7%	78.8%
10–19 years	41.5–86.6%	59.2–69.4%	64.3%
20–29 years	32.0–83.7%	54.1–61.9%	58.0%
30–39 years	30.3–81.3%	41.1–54.1%	47.6%
40–49 years	16.3–75.1%	43.5–52.9%	48.2%
50–59 years	19.7–73.6%	41.2–51.4%	46.3%
60–69 years	16.3–65.7%	40.8–50.6%	45.7%
70–79 years	11.3–47.1%	22.6–35.2%	28.9%

Source: From RJ Hartsock et al: Am J Clin Pathol 1965; 43:326, 1965.

TABLE 8

STOOL ANALYSIS

	REFERENCE RANGE	
	SI UNITS	CONVENTIONAL UNITS
Alpha-1-antitrypsin	≤540 mg/L	≤54 mg/dL
Amount	0.1–0.2 kg/d	100–200 g/24 h
Coproporphyrin	611–1832 nmol/d	400–1200 µg/24 h
Fat		
Adult		<7 g/d
Adult on fat-free diet		<4 g/d
Fatty acids	0–21 mmol/d	0–6 g/24 h
Leukocytes	None	None
Nitrogen	<178 mmol/d	<2.5 g/24 h
pH	7.0–7.5	
Potassium	14–102 mmol/L	14–102 mmol/L
Occult blood	Negative	Negative
Osmolality	280–325 mosmol/kg	280–325 mosmol/kg
Sodium	7–72 mmol/L	7–72 mmol/L
Trypsin		20–95 U/g
Urobilinogen	85–510 µmol/d	50–300 mg/24 h
Uroporphyrins	12–48 nmol/d	10–40 µg/24 h
Water	<0.75	<75%

Source: Modified from: FT Fishbach, MB Dunning III: *A Manual of Laboratory and Diagnostic Tests*, 7th ed. Philadelphia, Lippincott Williams & Wilkins, 2004.

TABLE 9

URINE ANALYSIS AND RENAL FUNCTION TESTS

	REFERENCE RANGE	
	SI UNITS	**CONVENTIONAL UNITS**
Acidity, titratable	20–40 mmol/d	20–40 meq/d
Aldosterone	Normal diet: 6–25 µg/d Low-salt diet: 17–44 µg/d High-salt diet: 0–6 µg/d	Normal diet: 6–25 µg/d Low-salt diet: 17–44 µg/d High-salt diet: 0–6 µg/d
Aluminum	0.19–1.11 µmol/L	5–30 µg/L
Ammonia	30–50 mmol/d	30–50 meq/d
Amylase		4–400 U/L
Amylase/creatinine clearance ratio $[(Cl_{am}/Cl_{cr}) \times 100]$	1–5	1–5
Arsenic	0.07–0.67 µmol/d	5–50 µg/d
Bence Jones protein, urine, qualitative	Not applicable	None detected
Bence Jones protein, urine, quantitative		
Free Kappa	1.4–24.2 mg/L	0.14–2.42 mg/dL
Free Lambda	0.2–6.7 mg/L	0.02–0.67 mg/dL
K/L ratio	2.04–10.37	2.04–10.37
Calcium (10 meq/d or 200 mg/d dietary calcium)	<7.5 mmol/d	<300 mg/d
Chloride	140–250 mmol/d	140–250 mmol/d
Citrate	320–1240 mg/d	320–1240 mg/d
Copper	<0.95 µmol/d	<60 µg/d
Coproporphyrins (types I and III)	0–20 µmol/mol creatinine	0–20 µmol/mol creatinine
Cortisol, free	55–193 nmol/d	20–70 µg/d
Creatine, as creatinine		
Female	<760 µmol/d	<100 mg/d
Male	<380 µmol/d	<50 mg/d
Creatinine	8.8–14 mmol/d	1.0–1.6 g/d
Dopamine	392–2876 nmol/d	60–440 µg/d
Eosinophils	<100 eosinophils/mL	<100 eosinophils/mL
Epinephrine	0–109 nmol/day	0–20 µg/day
Glomerular filtration rate	>60 mL/min/1.73 m^2 For African Americans multiply the result by 1.21	>60 mL/min/1.73 m^2 For African Americans multiply the result by 1.21
Glucose (glucose oxidase method)	0.3–1.7 mmol/d	50–300 mg/d
5-Hydroindoleacetic acid [5-HIAA]	0–78.8 µmol/d	0–15 mg/d
Hydroxyproline	53–328 µmol/d	53–328 µmol/d
Iodine, spot urine		
WHO classification of iodine deficiency		
Not iodine deficient	>100 µg/L	>100 µg/L
Mild iodine deficiency	50–100 µg/L	50–100 µg/L
Moderate iodine deficiency	20–49 µg/L	20–49 µg/L
Severe iodine deficiency	<20 µg/L	<20 µg/L
Ketone (acetone)	Negative	Negative
17 Ketosteroids	3–12 mg/d	3–12 mg/d
Metanephrines		
Metanephrine	30–350 µg/d	30–350 µg/d
Normetanephrine	50–650 µg/d	50–650 µg/d

(*continued*)

TABLE 9

URINE ANALYSIS AND RENAL FUNCTION TESTS (*CONTINUED*)

	REFERENCE RANGE	
	SI UNITS	**CONVENTIONAL UNITS**
Microalbumin		
Normal	0.0–0.03 g/d	0–30 mg/d
Microalbuminuria	0.03–0.30 g/d	30–300 mg/d
Clinical albuminuria	>0.3 g/d	>300 mg/d
Microalbumin/creatinine ratio		
Normal	0–3.4 g/mol creatinine	0–30 μg/mg creatinine
Microalbuminuria	3.4–34 g/mol creatinine	30–300 μg/mg creatinine
Clinical albuminuria	>34 g/mol creatinine	>300 μg/mg creatinine
β_2-Microglobulin	0–160μg/L	0–160μg/L
Norepinephrine	89–473 nmol/d	15–80 μg/d
N-telopeptide (cross-linked), NTx		
Female, premenopausal	17–94 nmol BCE/mmol creatinine	17–94 nmol BCE/mmol creatinine
Female, postmenopausal	26–124 nmol BCE/mmol creatinine	26–124 nmol BCE/mmol creatinine
Male	21–83 nmol BCE/mmol creatinine	21–83 nmol BCE/mmol creatinine
BCE = bone collagen equivalent		
Osmolality	100–800 mosm/kg	100–800 mosm/kg
Oxalate		
Male	80–500 μmol/d	7–44 mg/d
Female	45–350 μmol/d	4–31 mg/d
pH	5.0–9.0	5.0–9.0
Phosphate (phosphorus) (varies with intake)	12.9–42.0 mmol/d	400–1300 mg/d
Porphobilinogen	None	None
Potassium (varies with intake)	25–100 mmol/d	25–100 meq/d
Protein	<0.15 g/d	<150 mg/d
Protein/creatinine ratio	Male: 15–68 mg/g Female: 10–107 mg/g	Male: 15–68 mg/g Female: 10–107 mg/g
Sediment		
Red blood cells	0–2/high-power field	
White blood cells	0–2/high-power field	
Bacteria	None	
Crystals	None	
Bladder cells	None	
Squamous cells	None	
Tubular cells	None	
Broad casts	None	
Epithelial cell casts	None	
Granular casts	None	
Hyaline casts	0–5/low-power field	
Red blood cell casts	None	
Waxy casts	None	
White cell casts	None	
Sodium (varies with intake)	100–260 mmol/d	100–260 meq/d
Specific gravity		
After 12-h fluid restriction	>1.025	>1.025
After 12-h deliberate water intake	≤1.003	≤1.003
Tubular reabsorption, phosphorus	0.79–0.94 of filtered load	79–94% of filtered load
Urea nitrogen	214–607 mmol/d	6–17 g/d
Uric acid (normal diet)	1.49–4.76 mmol/d	250–800 mg/d
Vanillylmandelic acid (VMA)	<30 μmol/d	<6 mg/d

TABLE 10

NORMAL PRESSURES IN HEART AND GREAT VESSELS

PRESSURE (mmHg)	AVERAGE	RANGE
Right Atrium		
Mean	2.8	1–5
a wave	5.6	2.5–7
c wave	3.8	1.5–6
x wave	1.7	0–5
v wave	4.6	2–7.5
y wave	2.4	0–6
Right Ventricle		
Peak systolic	25	17–32
End-diastolic	4	1–7
Pulmonary Artery		
Mean	15	9–19
Peak systolic	25	17–32
End-diastolic	9	4–13
Pulmonary Artery Wedge		
Mean	9	4.5–13
Left Atrium		
Mean	7.9	2–12
a wave	10.4	4–16
v wave	12.8	6–21
Left Ventricle		
Peak systolic	130	90–140
End-diastolic	8.7	5–12
Brachial Artery		
Mean	85	70–105
Peak systolic	130	90–140
End-diastolic	70	60–90

Source: Reproduced from MJ Kern: *The Cardiac Catheterization Handbook*, 4th ed., Philadelphia, Mosby, 2003.

TABLE 11

CIRCULATORY FUNCTION TESTS

	RESULTS: REFERENCE RANGE	
TEST	**SI UNITS (RANGE)**	**CONVENTIONAL UNITS (RANGE)**
Arteriovenous oxygen difference	30–50 mL/L	30–50 mL/L
Cardiac output (Fick)	2.5–3.6 L/m^2 of body surface area per min	2.5–3.6 L/m^2 of body surface area per min
Contractility indexes		
Max. left ventricular *dp/dt* (*dp/dt*)	220 kPa/s (176–250 kPa/s)	1650 mmHg/s (1320–1880 mmHg/s)
DP when DP = 5.3 kPa (40 mmHg) (DP, developed LV pressure)	(37.6 ± 12.2)/s	(37.6 ± 12.2)/s
Mean normalized systolic ejection rate (angiography)	3.32 ± 0.84 end-diastolic volumes per second	3.32 ± 0.84 end-diastolic volumes per second
Mean velocity of circumferential fiber shortening (angiography)	1.83 ± 0.56 circumferences per second	1.83 ± 0.56 circumferences per second
Ejection fraction: stroke volume/end-diastolic volume (SV/EDV)	0.67 ± 0.08 (0.55–0.78)	0.67 ± 0.08 (0.55–0.78)
End-diastolic volume	70 ± 20.0 mL/m^2 (60–88 mL/m^2)	70 ± 20.0 mL/m^2 (60–88 mL/m^2)
End-systolic volume	25 ± 5.0 mL/m^2 (20–33 mL/m^2)	25 ± 5.0 mL/m^2 (20–33 mL/m^2)
Left ventricular work		
Stroke work index	50 ± 20.0 (g·m)/m^2 (30–110)	50 ± 20.0 (g·m)/m^2 (30–110)
Left ventricular minute work index	1.8–6.6 [(kg·m)/m^2]/min	1.8–6.6 [(kg·m)/m^2]/min
Oxygen consumption index	110–150 mL	110–150 mL
Maximum oxygen uptake	35 mL/min (20–60 mL/min)	35 mL/min (20–60 mL/min)
Pulmonary vascular resistance	2–12 (kPa·s)/L	20–130 (dyn·s)/cm^5
Systemic vascular resistance	77–150 (kPa·s)/L	770–1600 (dyn·s)/cm^5

Source: E Braunwald et al: *Heart Disease*, 6th ed. Philadelphia, W.B. Saunders Co., 2001.

TABLE 12

NORMAL ECHOCARDIOGRAPHIC REFERENCE LIMITS AND PARTITION VALUES IN ADULTS

	WOMEN REFERENCE RANGE	MILDLY ABNORMAL	MODERATELY ABNORMAL	SEVERELY ABNORMAL	MEN REFERENCE RANGE	MILDLY ABNORMAL	MODERATELY ABNORMAL	SEVERELY ABNORMAL
Left ventricular dimensions								
Septal thickness, cm	0.6–0.9	1.0–1.2	1.3–1.5	≥1.6	0.6–1.0	1.1–1.3	1.4–1.6	≥1.7
Posterior wall thickness, cm	0.6–0.9	1.0–1.2	1.3–1.5	≥1.6	0.6–1.0	1.1–1.3	1.4–1.6	≥1.7
Diastolic diameter, cm	3.9–5.3	5.4–5.7	5.8–6.1	≥6.2	4.2–5.9	6.0–6.3	6.4–6.8	≥6.9
Diastolic diameter/BSA, cm/m^2	2.4–3.2	3.3–3.4	3.5–3.7	≥3.8	2.2–3.1	3.2–3.4	3.5–3.6	≥3.7
Diastolic diameter/height, cm/m	2.5–3.2	3.3–3.4	3.5–3.6	≥3.7	2.4–3.3	3.4–3.5	3.6–3.7	≥3.8
Left ventricular volumes								
Diastolic, mL	56–104	105–117	118–130	≥131	67–155	156–178	179–201	≥202
Diastolic/BSA, mL/m^2	35–75	76–86	87–96	≥97	35–75	76–86	87–96	≥97
Systolic, mL	19–49	50–59	60–69	≥70	22–58	59–70	71–82	≥83
Systolic/BSA, mL/m^2	12–30	31–36	37–42	≥43	12–30	31–36	37–42	≥43
Left ventricular mass, 2D method								
Mass, g	66–150	151–171	172–182	≥183	96–200	201–227	228–254	≥255
Mass/BSA, g/m^2	44–88	89–100	101–112	≥113	50–102	103–116	117–130	≥131
Left ventricular function								
Endocardial fractional shortening (%)	27–45	22–26	17–21	≤16	25–43	20–24	15–19	≤14
Midwall fractional shortening (%)	15–23	13–14	11–12	≤10	14–22	12–13	10–11	≤9
Ejection fraction, 2D method (%)	≥55	45–54	30–44	≤29	≥55	45–54	30–44	≤29
Right heart dimensions (cm)								
Basal RV diameter	2.0–2.8	2.9–3.3	3.4–3.8	≥3.9	2.0–2.8	2.9–3.3	3.4–3.8	≥3.9
Mid-RV diameter	2.7–3.3	3.4–3.7	3.8–4.1	≥4.2	2.7–3.3	3.4–3.7	3.8–4.1	≥4.2
Base-to-apex length	7.1–7.9	8.0–8.5	8.6–9.1	≥9.2	7.1–7.9	8.0–8.5	8.6–9.1	≥9.2
RVOT diameter above aortic valve	2.5–2.9	3.0–3.2	3.3–3.5	≥3.6	2.5–2.9	3.0–3.2	3.3–3.5	≥3.6
RVOT diameter above pulmonic valve	1.7–2.3	2.4–2.7	2.8–3.1	≥3.2	1.7–2.3	2.4–2.7	2.8–3.1	≥3.2
Pulmonary artery diameter below pulmonic valve	1.5–2.1	2.2–2.5	2.6–2.9	≥3.0	1.5–2.1	2.2–2.5	2.6–2.9	≥3.0
Right ventricular size and function in 4-chamber view								
Diastolic area, cm^2	11–28	29–32	33–37	≥38	11–28	29–32	33–37	≥38
Systolic area, cm^2	7.5–16	17–19	20–22	≥23	7.5–16	17–19	20–22	≥23
Fractional area change, %	32–60	25–31	18–24	≤17	32–60	25–31	18–24	≤17
Atrial sizes								
LA diameter, cm	2.7–3.8	3.9–4.2	4.3–4.6	≥4.7	3.0–4.0	4.1–4.6	4.7–5.2	≥5.3
LA diameter/BSA, cm/m^2	1.5–2.3	2.4–2.6	2.7–2.9	≥3.0	1.5–2.3	2.4–2.6	2.7–2.9	≥3.0
RA minor axis, cm	2.9–4.5	4.6–4.9	5.0–5.4	≥5.5	2.9–4.5	4.6–4.9	5.0–5.4	≥5.5
RA minor axis/BSA, cm/m^2	1.7–2.5	2.6–2.8	2.9–3.1	≥3.2	1.7–2.5	2.6–2.8	2.9–3.1	≥3.2

(*continued*)

TABLE 12

NORMAL ECHOCARDIOGRAPHIC REFERENCE LIMITS AND PARTITION VALUES IN ADULTS (*CONTINUED*)

	WOMEN REFERENCE RANGE	MILDLY ABNORMAL	MODERATELY ABNORMAL	SEVERELY ABNORMAL	MEN REFERENCE RANGE	MILDLY ABNORMAL	MODERATELY ABNORMAL	SEVERELY ABNORMAL
Atrial sizes (*continued*)								
LA area, cm^2	<20	20–30	30–40	≥41	<20	20–30	30–40	≥41
LA volume, mL	22–52	53–62	63–72	≥73	18–58	59–68	69–78	≥79
LA volume/BSA, mL/m^2	16–28	29–33	34–39	≥40	16–28	29–33	34–39	≥40
Aortic stenosis, classification of severity								
Aortic jet velocity, m/s		2.6–2.9	3.0–4.0	>4.0		2.6–2.9	3.0–4.0	>4.0
Mean gradient, mmHg		<20	20–40	>40		<20	20–40	>40
Valve area, cm^2		>1.5	1.0–1.5	<1.0		>1.5	1.0–1.5	<1.0
Indexed valve area, cm^2/m^2		>0.85	0.60–0.85	<0.6		>0.85	0.60–0.85	<0.6
Velocity ratio		>0.50	0.25–0.50	<0.25		>0.50	0.25–0.50	<0.25
Mitral stenosis, classification of severity								
Valve area, cm^2		>1.5	1.0–1.5	<1.0		>1.5	1.0–1.5	<1.0
Mean gradient, mmHg		<5	5–10	>10		<5	5–10	>10
Pulmonary artery pressure, mmHg		<30	30–50	>50		<30	30–50	>50
Aortic regurgitation, indices of severity								
Vena contracta width, cm		<0.30	0.30–0.60	≥0.60		<0.30	0.30–0.60	≥0.60
Jet width/LVOT width, %		<25	25–64	≥65		<25	25–64	≥65
Jet CSA/LVOT CSA, %		<5	5–59	≥60		<5	5–59	≥60
Regurgitant volume, mL/beat		<30	30–59	≥60		<30	30–59	≥60
Regurgitant fraction, %		<30	30–49	≥50		<30	30–49	≥50
Effective regurgitant orifice area, cm^2		<0.10	0.10–0.29	≥0.30		<0.10	0.10–0.29	≥0.30
Mitral regurgitation, indices of severity								
Vena contracta width, cm		<0.30	0.30–0.69	≥0.70		<0.30	0.30–0.69	≥0.70
Regurgitant volume, mL/beat		<30	30–59	≥60		<30	30–59	≥60
Regurgitant fraction, %		<30	30–49	≥50		<30	30–49	≥50
Effective regurgitant orifice area, cm^2		<0.20	0.20–0.39	≥0.40		<0.20	0.20–0.39	≥0.40

Abbreviations: BSA, body surface area; CSA, cross-sectional area; LA, left atrium; LVOT, left ventricular outflow tract; RA, right atrium; RV, right ventricle; RVOT, right ventricular outflow tract; 2D, 2-dimensional.

Source: Values adapted from: American Society of Echocardiography, Guidelines and Standards. *http://www.asecho.org/i4a/pages/index.cfm?pageid=3317*. Accessed Feb 23, 2010.

TABLE 13

SUMMARY OF VALUES USEFUL IN PULMONARY PHYSIOLOGY

	SYMBOL	TYPICAL VALUES: MAN AGED 40, 75 kg, 175 cm TALL	TYPICAL VALUES: WOMAN AGED 40, 60 kg, 160 cm TALL
Pulmonary Mechanics			
Spirometry—volume-time curves			
Forced vital capacity	FVC	5.0 L	3.4 L
Forced expiratory volume in 1 s	FEV_1	4.0 L	2.8 L
FEV_1/FVC	FEV_1%	80%	78%
Maximal midexpiratory flow rate	MMEF (FEF 25–75)	4.1 L/s	3.2 L/s
Maximal expiratory flow rate	MEFR (FEF 200–1200)	9.0 L/s	6.1 L/s
Spirometry—flow-volume curves			
Maximal expiratory flow at 50% of expired vital capacity	V_{max} 50 (FEF 50%)	5.0 L/s	4.0 L/s
Maximal expiratory flow at 75% of expired vital capacity	V_{max} 75 (FEF 75%)	2.1 L/s	2.0 L/s
Resistance to airflow			
Pulmonary resistance	RL (R_L)	<3.0 (cmH_2O/s)/L	
Airway resistance	Raw	<2.5 (cmH_2O/s)/L	
Specific conductance	SGaw	>0.13 cmH_2O/s	
Pulmonary compliance			
Static recoil pressure at total lung capacity	Pst TLC	25 ± 5 cmH_2O	
Compliance of lungs (static)	CL	0.2 L cmH_2O	
Compliance of lungs and thorax	C(L + T)	0.1 L cmH_2O	
Dynamic compliance of 20 breaths per minute	C dyn 20	0.25 ± 0.05 L/cmH_2O	
Maximal static respiratory pressures			
Maximal inspiratory pressure	MIP	>110 cmH_2O	>70 cmH_2O
Maximal expiratory pressure	MEP	>200 cmH_2O	>140 cmH_2O
Lung Volumes			
Total lung capacity	TLC	6.9 L	4.9 L
Functional residual capacity	FRC	3.3 L	2.6 L
Residual volume	RV	1.9 L	1.5 L
Inspiratory capacity	IC	3.7 L	2.3 L
Expiratory reserve volume	ERV	1.4 L	1.1 L
Vital capacity	VC	5.0 L	3.4 L
Gas Exchange (Sea Level)			
Arterial O_2 tension	Pa_{O_2}	12.7 ± 0.7 kPa (95 ± 5 mmHg)	
Arterial CO_2 tension	Pa_{CO_2}	5.3 ± 0.3 kPa (40 ± 2 mmHg)	
Arterial O_2 saturation	Sa_{O_2}	0.97 ± 0.02 (97 ± 2%)	
Arterial blood pH	pH	7.40 ± 0.02	
Arterial bicarbonate	HCO_3^-	24 + 2 meq/L	
Base excess	BE	0 ± 2 meq/L	
Diffusing capacity for carbon monoxide (single breath)	DL_{CO}	37 mL CO/min/mmHg	27 mL CO/min/mmHg
Dead space volume	V_D	2 mL/kg body wt	
Physiologic dead space; dead space-tidal volume ratio	V_D/V_T		
Rest		≤35% V_T	
Exercise		≤20% V_T	
Alveolar-arterial difference for O_2	$P(A - a)_{O2}$	≤2.7 kPa ≤20 kPa (≤24 mmHg)	

Source: Based on AH Morris et al: *Clinical Pulmonary Function Testing. A Manual of Uniform Laboratory Procedures*, 2nd ed. Salt Lake City, Utah, Intermountain Thoracic Society, 1984.

TABLE 14

GASTROINTESTINAL TESTS

TEST	RESULTS	
	SI UNITS	CONVENTIONAL UNITS
Absorption tests		
D-Xylose: after overnight fast, 25 g xylose given in oral aqueous solution		
Urine, collected for following 5 h	25% of ingested dose	25% of ingested dose
Serum, 2 h after dose	2.0–3.5 mmol/L	30–52 mg/dL
Vitamin A: a fasting blood specimen is obtained and 200,000 units of vitamin A in oil is given orally	Serum level should rise to twice fasting level in 3–5 h	Serum level should rise to twice fasting level in 3–5 h
Bentiromide test (pancreatic function): 500 mg bentiromide (chymex) orally; *p*-aminobenzoic acid (PABA) measured		
Plasma		>3.6 (±1.1) µg/mL at 90 min
Urine	>50% recovered in 6 h	>50% recovered in 6 h
Gastric juice		
Volume		
24 h	2–3 L	2–3 L
Nocturnal	600–700 mL	600–700 mL
Basal, fasting	30–70 mL/h	30–70 mL/h
Reaction		
pH	1.6–1.8	1.6–1.8
Titratable acidity of fasting juice	4–9 µmol/s	15–35 meq/h
Acid output		
Basal		
Females (mean ± 1 SD)	0.6 ± 0.5 µmol/s	2.0 ± 1.8 meq/h
Males (mean ± 1 SD)	0.8 ± 0.6 µmol/s	3.0 ± 2.0 meq/h
Maximal (after SC histamine acid phosphate, 0.004 mg/kg body weight, and preceded by 50 mg promethazine, or after betazole, 1.7 mg/kg body weight, or pentagastrin, 6 µg/kg body weight)		
Females (mean ± 1 SD)	4.4 ± 1.4 µmol/s	16 ± 5 meq/h
Males (mean ± 1 SD)	6.4 ± 1.4 µmol/s	23 ± 5 meq/h
Basal acid output/maximal acid output ratio	≤0.6	≤0.6
Gastrin, serum	0–200 µg/L	0–200 pg/mL
Secretin test (pancreatic exocrine function): 1 unit/kg body weight, IV		
Volume (pancreatic juice) in 80 min	>2.0 mL/kg	>2.0 mL/kg
Bicarbonate concentration	>80 mmol/L	>80 meq/L
Bicarbonate output in 30 min	>10 mmol	>10 meq

MISCELLANEOUS

TABLE 15
BODY FLUIDS AND OTHER MASS DATA

	REFERENCE RANGE	
	SI UNITS	CONVENTIONAL UNITS
Body fluid,		
Total volume (lean) of body weight	50% (in obese) to 70%	
Intracellular	30-40% of body weight	
Extracellular	20-30% of body weight	
Blood		
Total volume		
Males	69 mL/kg body weight	
Females	65 mL/kg body weight	
Plasma volume		
Males	39 mL/kg body weight	
Females	40 mL/kg body weight	
Red blood cell volume		
Males	30 mL/kg body weight	1.15–1.21 L/m^2 of body surface area
Females	25 mL/kg body weight	0.95–1.00 L/m^2 of body surface area
Body mass index	18.5–24.9 kg/m^2	18.5–24.9 kg/m^2

TABLE 16
RADIATION-DERIVED UNITS

QUANTITY	MEASURES	OLD UNIT	SI UNIT	SPECIAL NAME FOR SI UNIT (ABBREVIATION)	CONVERSION
Activity	Rate of radioactive decay	curie (Ci)	Disintegrations per second (dps)	becquerel (Bq)	1 Ci = 3.7×10^{10} Bq 1 mCi = 37 MBq 1 Bq = 2.703×10^{-11} Ci
Exposure	Amount of ionizations produced in dry air by x-rays or gamma rays, per unit of mass	roentgen (R)	Coulomb per kilogram (C/kg)	none	1 C/kg = 3876 R 1 R = 2.58×10^{-4} C/kg 1 mR = 258 pC/kg
Air kerma	Sum of initial energies of charged particles liberated by ionizing radiation in air, per unit of mass	rad	Joule per kilogram (J/kg)	gray (Gy)	1 Gy = 100 rad 1 rad = 0.01 Gy 1 mrad = 10 μGy
Absorbed dose	Energy deposited per unit of mass in a medium, e.g. an organ/tissue	rad	Joule per kilogram (J/kg)	gray (Gy)	1 Gy = 100 rad 1 rad = 0.01 Gy 1 mrad = 10 μGy
Equivalent dose	Energy deposited per unit of mass in a medium (e.g., an organ/tissue), weighted to reflect type(s) of radiation	rem	Joule per kilogram (J/kg)	sievert (Sv)	1 Sv = 100 rem 1 rem = 0.01 Sv 1 mrem = 10 μSv
Effective dose	Energy deposited per unit of mass in a reference individual, doubly weighted to reflect type(s) of radiation and organ(s) irradiated	rem	Joule per kilogram (J/kg)	sievert (Sv)	1 Sv = 100 rem 1 rem = 0.01 Sv 1 mrem = 10 μSv

ACKNOWLEDGMENTS

The contributions of Drs. Daniel J. Fink, Patrick M. Sluss, James L. Januzzi, and Kent B. Lewandrowski to this chapter in previous editions of Harrison's Principles of Internal Medicine are gratefully acknowledged. We also express our gratitude to Drs. Amudha Palanisamy and Scott Fink for careful review of tables and helpful suggestions.

REVIEW AND SELF-ASSESSMENT*

Charles M. Wiener ■ Cynthia D. Brown ■ Anna R. Hemnes

QUESTIONS

DIRECTIONS: Choose the **one best** response to each question.

1. Deficits in the complement membrane attack complex (C5-8) are associated with infections of what variety?

A. Catalase-positive bacteria
B. *Neisseria meningitis*
C. *Pseudomonas aeruginosa*
D. *Salmonella* spp.
E. *Streptococcus pneumoniae*

2. One goal of immunization programs is to eliminate a specific disease. In 2010, indigenous transmission of which of the following diseases had been eliminated in the United States?

A. Diphtheria
B. Mumps
C. Pertussis
D. Varicella
E. None of the above

3. A 63-year-old man has chronic obstructive pulmonary disease and presents to your office for routine follow-up. He has no complaints currently and feels well. He is being managed with tiotropium 18 μg once daily with albuterol metered-dose inhaler as needed. His most recent forced expiratory volume in 1 second (FEV_1) was 55% predicted, and he is not on oxygen. He has received one dose of pneumococcal vaccine 5 years previously. He is asking if he should receive another dose of pneumococcal vaccine. According to the guidelines of the Centers for Disease Control and Prevention, what is your recommendation?

A. He does not require further vaccination unless his FEV_1 drops below 50% predicted.
B. He does not require further vaccination until he reaches age 65 years.
C. He should be revaccinated today.
D. He should be revaccinated 10 years after his initial vaccine.
E. No further vaccination is recommended because a single dose is all that is required.

4. A 48-year-old woman is traveling to Haiti with a humanitarian aid group. What is the recommended prophylaxis against malaria for this patient?

A. Atovaquone–proguanil
B. Chloroquine
C. Doxycycline
D. Mefloquine
E. Any of the above can be used

5. Ten individuals in Arizona are hospitalized over a 4-week period with fever and rapidly enlarging and painful lymph nodes. Seven of these individuals experience severe sepsis, and three die. While reviewing the epidemiologic characteristics of these individuals, you note that they are all illegal immigrants and have recently stayed in the same immigrant camp. Blood cultures are growing gram-negative rods that are identified as *Yersinia pestis*. You notify local public health officials and the Centers for Disease Control and Prevention. Which of the following factors indicate that this is NOT likely to be an act of bioterrorism?

A. The area affected was limited to a small immigrant camp.
B. The individuals presented with symptoms of bubonic plague rather than pneumonic plague.
C. The individuals were in close contact with one another, suggesting possible person-to-person transmission.
D. The mortality rate was less than 50%.
E. *Yersinia pestis* is not environmentally stable for longer than 1 hour.

6. A 37-year-old woman is brought to the ICU after her elective laparoscopic cholecystectomy is complicated by a temperature of 105°F, tachycardia, and systemic hypotension. Examination is notable for diffuse muscular rigidity. Which of the following drugs should be administered immediately?

A. Acetaminophen
B. Dantrolene
C. Haloperidol
D. Hydrocortisone
E. Ibuprofen

*Questions and answers were taken from Wiener C et al (eds): *Harrison's Principles of Internal Medicine Self-Assessment and Board Review*, 18th ed. New York: McGraw-Hill, 2012.

7. A 23-year-old woman with a chronic lower extremity ulcer related to prior trauma presents with rash, hypotension, and fever. She has had no recent travel or outdoor exposure and is up to date on all of her vaccinations. She does not use IV drugs. On examination, the ulcer looks clean with a well-granulated base and no erythema, warmth, or pustular discharge. However, the patient does have diffuse erythema that is most prominent on her palms, conjunctiva, and oral mucosa. Other than profound hypotension and tachycardia, the remainder of the examination is nonfocal. Laboratory results are notable for a creatinine of 2.8 mg/dL, aspartate aminotransferase of 250 U/L, alanine aminotransferase of 328 U/L, total bilirubin of 3.2 mg/dL, direct bilirubin of 0.5 mg/dL, INR of 1.5, activated partial thromboplastin time of 1.6 × control, and platelets at 94,000/μL. Ferritin is 1300 μg/mL. The patient is started on broad-spectrum antibiotics after appropriate blood cultures are drawn and is resuscitated with IV fluid and vasopressors. Her blood cultures are negative at 72 hours; at this point, her fingertips start to desquamate. What is the most likely diagnosis?

A. Juvenile rheumatoid arthritis (JRA)
B. Leptospirosis
C. Staphylococcal toxic shock syndrome
D. Streptococcal toxic shock syndrome
E. Typhoid fever

8. A 50-year-old man is evaluated for fevers and weight loss of uncertain etiology. He first developed symptoms 3 months previously. He reports daily fevers to as high as 39.4°C (103°F) with night sweats and fatigue. Over this same period, his appetite has been decreased, and he has lost 50 lb compared with his weight at his last annual examination. Fevers have been documented in his primary care physician's office to as high as 38.7°C (101.7°F). He has no exposures or ill contacts. His medical history is significant for diabetes mellitus, obesity, and obstructive sleep apnea. He is taking insulin glargine 50 U daily. He works in a warehouse driving a forklift. He has not traveled outside of his home area in a rural part of Virginia. He has never received a blood transfusion and is married with one female sexual partner for the past 25 years. On examination, no focal findings are identified. Multiple laboratory studies have been performed that have shown nonspecific findings only with exception of an elevated calcium at 11.2 g/dL. A complete blood count showed a white blood cell count of 15,700/μL with 80% polymorphonuclear cells, 15% lymphocytes, 3% eosinophils, and 2% monocytes. The peripheral smear is normal. The hematocrit is 34.7%. His erythrocyte sedimentation rate (ESR) is elevated at 57 mm/hr. A rheumatologic panel is normal, and the ferritin is 521 ng/mL. Liver and kidney function

8. (*Continued*)
are normal. The serum protein electrophoresis demonstrated polyclonal gammopathy. HIV, Epstein-Barr virus (EBV), and cytomegalovirus (CMV) testing are negative. The urine *Histoplasma* antigen result is negative. Routine blood cultures for bacteria, chest radiograph, and purified protein derivative (PPD) testing results are negative. A CT scan of the chest, abdomen, and pelvis has borderline enlargement of lymph nodes in the abdomen and retroperitoneum to 1.2 cm. What would be the next best step in determining the etiology of fever in this patient?

A. Empiric treatment with glucocorticoids
B. Empiric treatment for *Mycobacterium tuberculosis*
C. Needle biopsy of enlarged lymph nodes
D. PET-CT imaging
E. Serum angiotensin-converting enzyme levels

9. A 66-year-old woman has chronic lymphocytic leukemia with a stable white blood cell count of between 60,000 and 70,000/μL. She is currently hospitalized with pneumococcal pneumonia. This is the patient's third episode of pneumonia within the past 12 months. What finding on laboratory testing would be most likely in this patient?

A. Granulocytopenia
B. Hypogammaglobulinemia
C. Impaired T-cell function with normal T-lymphocyte counts
D. Low CD4 count
E. No specific abnormality is expected.

10. During the first 2 weeks after solid organ transplantation, which family of infection is most common?

A. Cytomegalovirus and Epstein-Barr virus reactivation
B. Humoral immunodeficiency–associated infections (e.g., meningococcemia, invasive *Streptococcus pneumoniae* infection)
C. Neutropenia-associated infection (e.g., aspergillosis, candidemia)
D. T-cell deficiency–associated infections (e.g., *Pneumocystis jiroveci*, nocardiosis, cryptococcosis)
E. Typical hospital-acquired infections (e.g., central line infection, hospital-acquired pneumonia, urinary tract infection)

11. After leaving which of the following patients' room would the use of alcohol-based hand rub be inadequate?

A. A 54-year-old man with quadriplegia admitted with a urinary tract infection caused by extended-spectrum β-lactamase–producing bacteria
B. A 78-year-old nursing home resident with recent antibiotic use and *Clostridium difficile* infection

11. (*Continued*)

C. A 35-year-old woman with advanced HIV infection and cavitary pulmonary tuberculosis
D. A 20-year-old renal transplant recipient with varicella pneumonia
E. A 40-year-old man with MRSA furunculosis

12. A 32-year-old woman is admitted to the hospital complaining of right thigh pain. She is treated empirically with oxacillin intravenously for cellulitis. The admitting physician notes that the degree of pain appears to be disproportionate to the amount of overlying cellulitis. Over the course of the next 24 hours, the patient develops profound septic shock complicated by hypotension, acute renal failure, and evidence of disseminated intravascular coagulation. A CT scan of her right leg demonstrates a collection of fluid with gas in the deep fascia of her right leg. Emergent surgical evacuation is planned. What changes to the patient's antibiotic therapy would be recommended?

A. Continue oxacillin and add clindamycin.
B. Continue oxacillin and add clindamycin and gentamicin.
C. Discontinue oxacillin and add clindamycin, vancomycin, and gentamicin.
D. Discontinue oxacillin and add piperacillin/tazobactam and vancomycin.
E. Discontinue oxacillin and add vancomycin and gentamicin.

13. A 68-year-old woman is brought to the emergency department for fever and lethargy. She first felt ill yesterday and experienced generalized body aches. Overnight, she developed a fever of 39.6°C and had shaking chills. By this morning, she was feeling very fatigued. Her son feels that she has had periods of waxing and waning mental status. She denies cough, nausea, vomiting, diarrhea, and abdominal pain. She has a medical history of rheumatoid arthritis. She takes prednisone, 10 mg daily, and methotrexate, 15 mg weekly. On examination, she is lethargic but appropriate. Her vital signs are blood pressure of 85/50 mmHg, heart rate of 122 beats/min, temperature of 39.1°C, respiratory rate of 24 breaths/min, and oxygen saturation of 97% on room air. Physical examination shows clear lung fields and a regular tachycardia without murmur. There is no abdominal tenderness or masses. Stool is negative for occult blood. There are no rashes. Hematologic studies show a white blood cell count of 24,200/μL with a differential of 82% PMNs, 8% band forms, 6% lymphocytes, and 3% monocytes. Hemoglobin is 8.2 g/dL. Urinalysis shows numerous white blood cells with gram-negative bacteria on Gram stain. Chemistries reveal the following: bicarbonate of 16 meq/L, BUN of 60 mg/dL, and creatinine of 2.4 mg/dL. After fluid administration of 2 L, the patient has a blood pressure of 88/54 mmHg

13. (*Continued*)

and a heart rate of 112 beats/min with a central venous pressure of 18 cmH_2O. There is 25 mL of urine output in the first hour. The patient has been initiated on antibiotics with cefepime. What should be done next for the treatment of this patient's hypotension?

A. Dopamine, 3 μg/kg/min IV
B. Hydrocortisone, 50 mg IV every 6 hours
C. Norepinephrine, 2 μg/min IV
D. Ongoing colloid administration at 500–1000 mL/h
E. Transfusion of 2 units of packed red blood cells

14. A 28-year-old man seeks evaluation for sore throat for 2 days. He has not had a cough or rhinorrhea. He has no other medical conditions and works as a daycare provider. On examination, tonsillar hypertrophy with membranous exudate is present. What is the next step in the management of this patient?

A. Empiric treatment with amoxicillin 500 mg twice daily for 10 days
B. Rapid antigen detection test for *Streptococcus pyogenes* only
C. Rapid antigen detection test for *Streptococcus pyogenes* plus throat culture if the rapid test result is negative
D. Rapid antigen detection test for *Streptococcus pyogenes* plus a throat culture regardless of result
E. Throat culture only

15. Which of the following statements regarding the diagnosis of community-acquired pneumonia is TRUE?

A. Directed therapy specific to the causative organism is more effective than empirical therapy in hospitalized patients who are not in intensive care.
B. Five percent to 15% of patients hospitalized with community-acquired pneumonia will have positive blood cultures.
C. In patients who have bacteremia caused by *Streptococcus pneumoniae*, sputum cultures are positive in more than 80% of cases.
D. Polymerase chain reaction tests for identification of *Legionella pneumophila* and *Mycoplasma pneumoniae* are widely available and should be utilized for diagnosis in patients hospitalized with community-acquired pneumonia.
E. The etiology of community-acquired pneumonia is typically identified in about 70% of cases.

16. Which of the following is the most common cause of diffuse bronchiectasis worldwide?

A. Cystic fibrosis
B. Immunoglobulin deficiency
C. *Mycobacterium avium-intracellulare* infection
D. *Mycobacterium tuberculosis* infection
E. Rheumatoid arthritis

17. Which of the following patients should receive antibiotic prophylaxis to prevent infective endocarditis?

A. A 23-year-old woman with known mitral valve prolapse undergoing a gingival surgery
B. A 24-year-old woman who had an atrial septal defect completely corrected 22 years ago who is undergoing elective cystoscopy for painless hematuria
C. A 30-year-old man with a history of intravenous drug use and prior endocarditis undergoing operative drainage of a prostatic abscess
D. A 45-year-old man who received a prosthetic mitral valve 5 years ago undergoing routine dental cleaning
E. A 63-year-old woman who received a prosthetic aortic valve 2 years ago undergoing screening colonoscopy

18. Which of the following statements is true regarding pulsus paradoxus?

A. It consists of a greater than 15 mmHg increase in systolic arterial pressure with inspiration.
B. It may be found in patients with severe obstructive lung disease.
C. It is the reversal of a normal phenomenon during inspiration.
D. It results from right ventricular distention during expiration resulting in compression of the left ventricular volume and subsequent reduction in systolic pulse pressure.
E. All of the above are true.

19. All of the following organisms may cause bullae as a manifestation of their infection except:

A. *Clostridium perfringens*
B. *Sporothrix schenckii*
C. *Staphylococcus aureus*
D. *Streptococcus pyogenes*
E. *Vibrio vulnificus*

20. A 79-year-old man has had a diabetic foot ulcer overlying his third metatarsal head for 3 months but has not been compliant with his physician's request to offload the affected foot. He presents with dull, throbbing foot pain and subjective fevers. Examination reveals a putrid-smelling wound notable also for a pus-filled 2.5-cm-wide ulcer. A metal probe is used to probe the wound, and it detects bone as well as a 3-cm deep cavity. Gram stain of the pus shows gram-positive cocci in chains, gram-positive rods, gram-negative diplococci, enteric-appearing gram-negative rods, tiny pleomorphic gram-negative rods, and a predominance of neutrophils. Which of the following empirical antibiotic regimens is recommended while blood and drainage cultures are processed?

20. (*Continued*)
A. Ampicillin–sulbactam, 1.5 g IV q4h
B. Clindamycin, 600 mg PO tid
C. Linezolid, 600 mg IV bid
D. Metronidazole, 500 mg PO qid
E. Vancomycin, 1 g IV bid

21. A 66-year-old woman with a history of rheumatoid arthritis and frequent attacks of pseudogout in her left knee presents with night sweats and a 2-day history of left knee pain. Her medications include methotrexate 15 mg weekly, folate 1 mg daily, prednisone 5 mg daily, and ibuprofen 800 mg three times daily as needed for pain. On physical examination, her temperature is 38.6°C (101.5°F), heart rate is 110 beats/min, blood pressure is 104/78 mmHg, and oxygen saturation is 97% on room air. Her left knee is swollen, red, painful, and warm. With 5° of flexion or extension, she develops extreme pain. She has evidence of chronic joint deformity in her hands, knees, and spine. Peripheral white blood cell (WBC) count is 16,700 cells/μL with 95% neutrophils. A diagnostic tap of her left knee reveals 168,300 WBCs/μL and 99% neutrophils, and diffuse needle-shaped birefringent crystals are present. Gram stain shows rare gram-positive cocci in clusters. Management includes all of the following EXCEPT:

A. Blood cultures
B. Glucocorticoids
C. Needle aspiration of joint fluid
D. Orthopedic surgery consult
E. Vancomycin

22. A 45-year-old man with a history of alcoholism and presumed cirrhosis is brought to the emergency department by his friend complaining of 2 to 3 days of increasing lethargy and confusion. He has not consumed alcohol in the past 2 years. He currently takes no medications and works at home as a video game designer. He has no risk factors for HIV. He was referred by his primary care physician for a liver transplant evaluation and is scheduled to begin his evaluation next month. His vital signs included blood pressure of 90/60 mmHg, heart rate of 105 beats/min, temperature of 38.5°C, and respiratory rate of 10 breaths/min with O2 saturation of 97% on room air. He is somnolent but is able to answer questions accurately. His skin is notable for many spider telangiectasias and palmar erythema. He has a distended diffusely tender abdomen with a positive fluid wave. Paracentesis reveals slightly cloudy fluid with WBC 1000/μL and 40% neutrophils. His blood pressure increases to 100/65 mmHg, and his heart rate decreases to 95 beats/min after 1 L of intravenous fluids. Which of the following statements regarding his condition and treatment is true?

22. (*Continued*)
A. Fever is present in more than 50% of cases.
B. Initial empiric therapy should include metronidazole or clindamycin for anaerobes.
C. The diagnosis of primary (spontaneous) bacterial peritonitis is not confirmed because the percentage of neutrophils in the peritoneal fluid is less than 50%.
D. The mostly causative organism for his condition is enterococcus.
E. The yield of peritoneal fluid cultures for diagnosis is greater than 90%.

23. A 46-year-old woman travels to a rural area of Guatemala. Three days after arrival, she develops watery diarrhea with severe abdominal cramping. She reports two unformed stools daily for the past 2 days. She has noticed no blood in the stool and has not experienced a fever. What is the most likely cause of the patient's illness?

A. *Campylobacter jejuni*
B. Enterotoxigenic *Escherichia coli*
C. *Giardia lamblia*
D. Norovirus
E. *Shigella* spp.

24. For the case above, which of the following treatments would you recommend?

A. Azithromycin 10 mg/kg on day 1 with 5 mg/kg on days 2 and 3 if the diarrhea persists
B. Ciprofloxacin 500 mg three times daily for 5 days
C. Ciprofloxacin 750 mg once
D. Loperamide 4 mg once followed by 2 mg after passage of each unformed stool
E. Oral rehydration therapy only

25. Which of the following organisms is most likely to be causative in acute appendicitis?

A. *Clostridium* species
B. *Escherichia coli*
C. *Mycobacterium tuberculosis*
D. *Staphylococcus aureus*
E. *Yersinia enterocolitica*

26. Which of the following diagnostic features characterizes bacterial vaginosis?

A. Scant vaginal secretions, erythema of vaginal epithelium, and clue cells
B. Vaginal fluid pH >4.5, clue cells, and profuse mixed microbiota on microscopic examination
C. Vaginal fluid pH ≥5.0, motile trichomonads on microscopic exam, and fishy odor with 10% KOH
D. Vaginal fluid pH <4.5, lactobacilli predominant on microscopic examination, and scant clear secretions
E. Vaginal fluid pH <4.5, clue cells, and profuse mixed microbiota on microscopic examination

27. Which of the following groups of patients should receive empirical antibiotic therapy that includes coverage of *Listeria monocytogenes* in cases of presumed meningitis?

A. Immunocompromised patients
B. Elderly patients
C. Infants
D. All of the above

28. Which of the following medicines has been most commonly implicated in the development of noninfectious chronic meningitis?

A. Acetaminophen
B. Acyclovir
C. β-Lactam antibiotics
D. Ibuprofen
E. Phenobarbital

29. In the CDC diagnostic criteria for chronic fatigue syndrome, in addition to clearly delineated findings of fatigue, all of the following symptoms or findings must be concurrently present for at least 6 months EXCEPT:

A. Delusional disorder
B. Impaired memory or concentration
C. Muscle pain
D. Sore throat
E. Tender cervical or axillary lymph nodes

30. A 23-year-old college student is admitted to the hospital with a fever and painful, erythematous purulent nodules on his forearm. He is an avid weightlifter and other than depression treated with citalopram has been healthy. These lesions have been present for approximately 1 week, and his primary care physician attempted to treat him with clindamycin as an outpatient. After admission, he develops hypotension and evidence of systemic inflammatory response syndrome, prompting transfer to the medical intensive care unit. There, dopamine is started, linezolid is administered, and hydrocortisone and fludrocortisone are given for possible adrenal insufficiency in the context of septic shock. After 6 hours, he develops an agitated delirium with diaphoresis, tachycardia, a temperature of 103.4°F, and diarrhea. His examination is notable for tremor; muscular rigidity; hyperreflexia; and clonus, especially in the lower extremities. Which of the following drug–drug interactions is most likely the culprit of this clinical syndrome?

A. Citalopram–dopamine
B. Citalopram–linezolid
C. Dopamine–fludrocortisone
D. Dopamine–linezolid
E. Fludrocortisone–linezolid

31. All of the following statements regarding *Streptococcus pneumoniae* (the pneumococcus) are true EXCEPT:

A. Asymptomatic colonization does not occur.
B. Infants (younger than 2 years old) and elderly adults are at greatest risk of invasive disease.
C. Pneumococcal vaccination has impacted the epidemiology of disease.
D. The likelihood of death within 24 hours of hospitalization for patients with invasive pneumococcal pneumonia has not changed since the introduction of antibiotics.
E. There is a clear association between prior viral upper respiratory infection and secondary pneumococcal pneumonia.

32. Which of the following biochemical tests distinguishes *S. aureus* from *S. epidermidis*?

A. Catalase
B. Coagulase
C. Lactose fermentation
D. Oxidase
E. Urease

33. A 19-year-old woman from Guatemala presents to your office for a routine screening physical examination. At age 4 years, she was diagnosed with acute rheumatic fever. She does not recall the specifics of her illness and remembers only that she was required to be on bed rest for 6 months. She has remained on penicillin V orally at a dose of 250 mg bid since that time. She asks if she can safely discontinue this medication. She has had only one other flare of her disease, at age 8 years, when she stopped taking penicillin at the time of her emigration to the United States. She is currently working as a day care provider. Her physical examination is notable for normal point of maximal impulse (PMI) with a grade III/VI holosystolic murmur that is heard best at the apex of the heart and radiates to the axilla. What do you advise the patient to do?

A. An echocardiogram should be performed to determine the extent of valvular damage before deciding if penicillin can be discontinued.
B. Penicillin prophylaxis can be discontinued because she has had no flares in 5 years.
C. She should change her dosing regimen to IM benzathine penicillin every 8 weeks.
D. She should continue on penicillin indefinitely because she had a previous recurrence, has presumed rheumatic heart disease, and is working in a field with high occupational exposure to group A streptococcus.
E. She should replace penicillin prophylaxis with polyvalent pneumococcal vaccine every 5 years.

34. A 74-year-old man with a recent history of diverticulitis is admitted to the hospital with 1 week of fever, malaise, and generalized weakness. His physical examination is notable for a temperature of 38.5°C, a new mitral heart murmur, and splinter hemorrhages. Three blood cultures grow *Enterococcus faecalis*, and an echocardiogram shows a small vegetation on the mitral valve. The organism is reported as being sensitive to ampicillin with no high-level resistance to aminoglycosides. Based on this information, which of the following is recommended therapy?

A. Ampicillin
B. Ampicillin plus gentamicin
C. Daptomycin
D. Linezolid
E. Tigecycline

35. Which of the following is the most common clinical presentation of acute rheumatic fever (ARF)?

A. Carditis
B. Chorea
C. Erythema marginatum
D. Polyarthritis
E. Subcutaneous nodules

36. A 42-year-old man with HIV has been developing worsening disease because of HAART resistance and worsening viremia. Over the past 6 months, his CD4 T-cell count has fallen below 100/μL. He has not been compliant with prophylactic medication because he is tired of taking pills. He comes to clinic reporting 3 weeks of productive cough and low-grade fever. A chest radiograph shows multiple small necrotizing nodules in the bilateral lower lobes. A percutaneous needle biopsy reveals some neutrophils and small gram-positive coccobacilli that the laboratory says looks like corynebacterium. A culture grows *Rhodococcus equi*. All of the following are effective therapy EXCEPT:

A. Azithromycin
B. Cefotaxime
C. Linezolid
D. Tigecycline
E. Vancomycin

37. A 26-year-old woman presents late in the third trimester of her pregnancy with high fevers, myalgias, backache, and malaise. She is admitted and started on empirical broad-spectrum antibiotics. Blood cultures return positive for *Listeria monocytogenes*. She delivers a 5-lb infant 24 hours after admission. Which of the following statements regarding antibiotic treatment for this infection is true?

37. (*Continued*)

A. Clindamycin should be used in patients with penicillin allergy.
B. Neonates should receive weight-based ampicillin and gentamicin.
C. Penicillin plus gentamicin is first-line therapy for the mother.
D. Quinolones should be used for *Listeria* bacteremia in late-stage pregnancy.
E. Trimethoprim–sulfamethoxazole has no efficacy against *Listeria* spp.

38. A 64-year-old man with a long history of heroin abuse is brought to the hospital because of fever and worsening muscle spasms and pain over the past day. Because of long-standing venous sclerosis, he no longer injects intravenously but "skin pops," often with dirty needles. On examination, he is extremely sweaty and febrile to 101.4°F. There are widespread muscle spasms, including the face. He is unable to open his jaw because of muscle spasm and has severe back pain because of diffuse spasm. On his leg, there is a skin wound that is tender and erythematous. All of the following statements regarding this patient are true EXCEPT:

A. Culture of the wound may reveal *Clostridium tetani*.
B. Intrathecal antitoxin administration is recommended therapy.
C. Metronidazole is the recommended therapy.
D. Permanent muscle dysfunction is likely after recovery.
E. Strychnine poisoning and antidopaminergic drug toxicity should be ruled out.

39. A 34-year-old injection drug user presents with a 2-day history of slurred speech, blurry vision that is worse with bilateral gaze deviation, dry mouth, and difficulty swallowing both liquids and solids. He states that his arms feel weak as well but denies any sensory deficits. He has had no recent illness but does describe a chronic ulcer on his left lower leg that has felt slightly warm and tender of late. He frequently injects heroin into the edges of the ulcer. On review of systems, he reports mild shortness of breath but denies any gastrointestinal symptoms, urinary retention, or loss of bowel or bladder continence. Physical examination reveals a frustrated, nontoxic appearing man who is alert and oriented but noticeably dysarthric. He is afebrile with stable vital signs. Cranial nerve examination reveals bilateral cranial nerve VI deficits and an inability to maintain medial gaze in both eyes. He has mild bilateral ptosis, and both pupils are reactive but sluggish. His strength is 5/5 in all extremities except for his shoulder shrug, which is 4/5.

39. (*Continued*)

Sensory examination and deep tendon reflexes are within normal limits in all four extremities. His oropharynx is dry. Cardiopulmonary and abdominal examination findings are normal. He has a 4 cm × 5 cm well-granulated lower-extremity ulcer with redness, warmth, and erythema noted on the upper margin of the ulcer. What is the treatment of choice?

A. Glucocorticoids
B. Equine antitoxin to *Clostridium botulinum* neurotoxin
C. Intravenous heparin
D. Naltrexone
E. Plasmapheresis

40. A 19-year-old man presents to the emergency department with 4 days of watery diarrhea, nausea, vomiting, and low-grade fever. He recalls no unusual meals, sick contacts, or travel. He is hydrated with IV fluid, given antiemetics, and discharged home after feeling much better. Three days later, two of three blood cultures are positive for *Clostridium perfringens*. He is called at home and says that he feels fine and is back at work. What should your next instruction to the patient be?

A. Return for IV penicillin therapy.
B. Return for IV penicillin therapy plus echocardiography.
C. Return for IV penicillin therapy plus colonoscopy.
D. Return for surveillance blood culture.
E. Reassurance

41. Which of the following is a common manifestation of *Clostridium difficile* infection?

A. Fever
B. Nonbloody diarrhea
C. Adynamic ileus
D. Recurrence after therapy
E. All of the above

42. A 21-year-old college student is admitted to the hospital with meningitis. CSF cultures reveal *N. meningitidis* type B. The patient lives in a dormitory suite with five other students. Which of the following is recommended for the close household contacts?

A. Culture all close contacts and offer prophylaxis to those with positive culture results
B. Immediate administration of ceftriaxone to all close contacts
C. Immediate administration of rifampin to all close contacts
D. Immediate vaccination with conjugate vaccine
E. No therapy necessary

43. A 19-year-old man comes to clinic complaining of 2 days of severe dysuria and urethral discharge. Urine analysis shows pyuria. He reports unprotected sexual contact with a new partner within the past week. DNA probe is positive for *N. gonorrheae*. Which of the following is the recommended therapy?

A. Intramuscular ceftriaxone plus oral azithromycin
B. Intramuscular penicillin
C. Oral azithromycin
D. Oral cefixime
E. Oral levofloxacin

44. A 44-year-old man presents to the emergency department for evaluation of a severe sore throat. His symptoms began this morning with mild irritation on swallowing and have gotten progressively severe over the course of 12 hours. He has been experiencing a fever to as high as 39°C at home and reports progressive shortness of breath. He denies antecedent rhinorrhea and tooth and jaw pain. He has had no ill contacts. On physical examination, the patient appears flushed and in respiratory distress with use of accessory muscles of respiration. Inspiratory stridor is present. He is sitting leaning forward and is drooling with his neck extended. His vital signs are as follows: temperature of 39.5°C, blood pressure of 116/60 mmHg, heart rate of 118 beats/min, respiratory rate of 24 breaths/min, and oxygen saturation of 95% on room air. Examination of his oropharynx shows erythema of the posterior oropharynx without exudates or tonsillar enlargement. The uvula is midline. There is no sinus tenderness and no cervical lymphadenopathy. His lung fields are clear to auscultation, and cardiovascular examination reveals a regular tachycardia with a II/VI systolic ejection murmur heard at the upper right sternal border. Abdominal, extremity, and neurologic examinations are normal. Laboratory studies reveal a white blood cell count of 17,000/μL with a differential of 87% neutrophils, 8% band forms, 4% lymphocytes, and 1% monocytes. Hemoglobin is 13.4 g/dL with a hematocrit of 44.2%. An arterial blood gas on room air has a pH of 7.32, a P_{CO_2} of 48 mmHg, and a P_{O_2} of 92 mmHg. A lateral neck radiograph shows an edematous epiglottis. What is the next most appropriate step in evaluation and treatment of this individual?

A. Ampicillin, 500 mg IV q6h
B. Ceftriaxone, 1 g IV q24h
C. Endotracheal intubation and ampicillin, 500 mg IV q6h
D. Endotracheal intubation, 1 g IV q24h of ceftriaxone, and 600 mg IV q6h of clindamycin
E. Laryngoscopy and close observation

45. A 75-year-old patient presents with fevers and wasting. He describes fatigue and malaise over the past several months and is concerned that he has been losing weight. On examination, he is noted to have a low-grade fever, and a soft diastolic heart murmur is appreciated. Laboratory tests reveal a normocytic, normochromic anemia. Three separate blood cultures grow *Cardiobacterium hominis*. Which of the following statements is true about this patient's clinical condition?

A. Antibiotics are not likely to improve his condition.
B. Echocardiography findings will likely be normal.
C. He has a form of endocarditis with a high risk of emboli.
D. He will likely need surgery.
E. The positive blood culture results are likely because of a skin contaminant.

46. All of the following are risk factors for the development of *Legionella* pneumonia EXCEPT:

A. Glucocorticoid use
B. HIV infection
C. Neutropenia
D. Recent surgery
E. Tobacco use

47. An 18-year-old man seeks attention for a severe cough. He reports no past medical history and excellent health. Approximately 7 days ago, he developed an upper respiratory syndrome with low-grade fever, coryza, some cough, and malaise. The fever and coryza have improved, but over the past 2 days, he has had an episodic cough that often is severe enough to result in vomiting. He reports receiving all infant vaccinations but only tetanus in the past 12 years. He is afebrile, and while not coughing, his chest examination is normal. During a coughing episode, there is an occasional inspiratory whoop. Chest radiography findings are unremarkable. Which of the following is true regarding his likely illness?

A. A fluoroquinolone is recommended therapy.
B. Cold agglutinin results may be positive.
C. Nasopharyngeal aspirate for DNA testing is likely to be diagnostic.
D. Pneumonia is a common complication.
E. Urinary antigen testing results remain positive for up to 3 months.

48. All of the following statements regarding intestinal disease caused by strains of Shiga toxin–producing and enterohemorrhagic *E. coli* are true EXCEPT:

A. Antibiotic therapy lessens the risk of developing hemolytic uremic syndrome.
B. Ground beef is the most common source of contamination.
C. Gross bloody diarrhea without fever is the most common clinical manifestation.

48. (*Continued*)
D. Infection is more common in industrialized than developing countries.
E. O157:H7 is the most common serotype.

49. A 63-year-old man has been in the ICU for 3 weeks with slowly resolving ARDS after an episode of acute pancreatitis. He remains on mechanical ventilation through a tracheostomy. Over the past week, he has had gradual lessening of his mechanical ventilator needs and slight improvement of his radiograph. He has been afebrile with a normal WBC for the past 10 days. Over the past 24 hours, his Fi_{O_2} has been increased from 0.60 to 0.80 to maintain adequate oxygenation. In addition, he has developed newly purulent sputum with a right lower lobe infiltrate, fever to 101.5°C, and a rising WBC count. Sputum gram stain shows gram-negative plump coccobacilli that are identified as *Acinetobacter baumannii*. All of the following are true about this organism EXCEPT:

A. Mortality from bloodstream infection approaches 40%.
B. Multidrug resistance is characteristic.
C. They are a growing cause of hospital-acquired pneumonia and bloodstream infections in the United States.
D. They are not yet a significant problem in Asia or Australia.
E. Tigecycline is treatment of choice for bloodstream infection.

50. *Helicobacter pylori* colonization increases the odds ratio of developing all of the following conditions EXCEPT:

A. Duodenal ulcer disease
B. Esophageal adenocarcinoma
C. Gastric adenocarcinoma
D. Gastric mucosa-associated lymphoid tissue (MALT) lymphoma
E. Peptic ulcer disease

51. Which single clinical feature has the most specificity in differentiating *Pseudomonas aeruginosa* sepsis from other causes of severe sepsis in a hospitalized patient?

A. Ecthyma gangrenosum
B. Hospitalization for severe burn
C. Profound bandemia
D. Recent antibiotic exposure
E. Recent mechanical ventilation for >14 days

52. Five healthy college roommates develop a rapid (<8 hours) onset of abdominal pain, cramping, fever to 38.5°C, vomiting, and copious nonbloody diarrhea while camping. They immediately return for hydration and diagnosis. A stool culture grows *Salmonella enteritidis*. All of the statements regarding their clinical syndrome are true EXCEPT:

52. (*Continued*)
A. Antibiotic therapy is not indicated.
B. Bacteremia occurs in fewer than 10% of cases.
C. The most likely source was undercooked eggs.
D. There is no vaccine available for this illness.
E. They have enteric (typhoid) fever.

53. Two days after returning from a trip to Thailand, a 36-year-old woman develops severe crampy abdominal pain, fever to 40°C, nausea, and malaise. The next day, she begins having bloody mucopurulent diarrhea with worsening abdominal pain and continued fever. She reports she was in Bangkok during monsoonal flooding and ate fresh food from stalls. A stool examination shows many neutrophils, and culture grows *Shigella flexneri*. Which of the following statements regarding her clinical syndrome is true?

A. An effective vaccine for travelers is available.
B. Antibiotic therapy prolongs the carrier state and should not be administered unless she develops bacteremia.
C. Antimotility agents are effective in reducing the risk of dehydration.
D. Ciprofloxacin is recommended therapy.
E. Her disease can be distinguished from illness caused by *Campylobacter jejuni* on clinical grounds by the presence of fever.

54. A previously healthy 32-year-old graduate student at the University of Wisconsin describes 1 to 2 days of fever, myalgia, and headache followed by abdominal pain and diarrhea. He has experienced up to 10 bowel movements over the past day. He has noted mucus and blood in the stool. The patient notes that 3 days ago, he was at a church barbecue, where several people contracted a diarrheal illness. He has not traveled in more than 6 months and has no history of GI illness. Physical examination is unremarkable except for a temperature of 38.8°C and diffuse abdominal tenderness. Laboratory findings are notable only for a slightly elevated leukocyte count and an elevated erythrocyte sedimentation rate. Wright's stain of a fecal sample reveals the presence of neutrophils. Colonoscopy reveals inflamed mucosa. Biopsy of an affected area discloses mucosal infiltration with neutrophils, monocytes, and eosinophils; epithelial damage, including loss of mucus; glandular degeneration; and crypt abscesses. Which of the following microbial pathogens is most likely to be responsible for his illness?

A. *Campylobacter*
B. *Escherichia coli*
C. Norwalk agent
D. Rotavirus
E. *Staphylococcus aureus*

55. In the patient described in question 54, which of the following is recommended therapy?

55. (*Continued*)
A. Azithromycin
B. Ceftriaxone
C. Lomotil only for symptoms
D. Metronidazole
E. Tinidazole

56. While working for a relief mission in Haiti, you are asked to see a 19-year-old patient with profuse watery diarrhea as shown in Figure 56. The patient is mildly hypotensive and tachycardic and is afebrile. There is no abdominal tenderness. All of the statements regarding this patient's illness are true EXCEPT:

FIGURE 56

A. Antibiotic therapy shortens the duration of disease and hastens clearance of the organism from stool.
B. Morbidity or death is mediated by bacteremia and multiorgan failure.
C. Point of care antigen testing is available.
D. The diarrhea is toxin mediated.
E. Vaccines with moderate efficacy are available outside the United States.

57. A 45-year-old man from western Kentucky presents to the emergency department in September complaining of fevers, headaches, and muscle pains. He recently had been on a camping trip with several friends during which they hunted for their food, including fish, squirrels, and rabbits. He did not

57. (*Continued*)
recall any tick bites during the trip but does recall having several mosquito bites. For the past week, he has had an ulceration on his right hand with redness and pain surrounding it. He also has noticed some pain and swelling near his right elbow. None of the friends he camped with have been similarly ill. His vital signs are blood pressure of 106/65 mmHg, heart rate of 116 beats/min, respiratory rate of 24 breaths/min, and temperature of 38.7°C. His oxygen saturation is 93% on room air. He appears mildly tachypneic and flushed. His conjunctiva are not injected, and his mucous membranes are dry. The chest examination reveals crackles in the right mid-lung field and left base. His heart rate is tachycardic but regular. There is a II/VI systolic ejection murmur heard best at the lower left sternal border. His abdominal examination is unremarkable. On the right hand, there is an erythematous ulcer with a punched-out center covered by a black eschar. He has no cervical lymphadenopathy, but there are markedly enlarged and tender lymph nodes in the right axillae and epitrochlear regions. The epitrochlear node has some fluctuance with palpation. A chest radiograph shows fluffy bilateral alveolar infiltrates. Over the first 12 hours of his hospitalization, the patient becomes progressively hypotensive and hypoxic, requiring intubation and mechanical ventilation. What is the most appropriate therapy for this patient?

A. Ampicillin, 2 g IV q6h
B. Ceftriaxone, 1 g IV daily
C. Ciprofloxacin, 400 mg IV twice daily
D. Doxycycline, 100 mg IV twice daily
E. Gentamicin, 5 mg/kg twice daily

58. A 35-year-old man comes to the emergency department complaining of an acute-onset high fever, malaise, and a tender lymph node. The patient returned from a camping trip in the Four Corners region of the United States (junction area of New Mexico, Arizona, Colorado, and Utah) 4 days ago and reports being bitten by fleas. He has no past medical history and works as a university professor. He denies illicit drug use. On physical examination, he is lethargic but oriented and has a temperature 39.4°C, heart rate of 105 beats/min, and blood pressure of 100/65 mmHg. There are numerous crusted flea bites on the upper legs. In the right inguinal region, there is an exquisitely tender 3- to 4-cm tense lymph node with surrounding edema but no lymphangitis. An aspirate of the node reveals small gram-negative coccobacilli that appear bipolar on Wright's stain. Which of the following is the most likely causative organism?

A. *Bartonella henselae*
B. Epstein-Barr virus

58. (*Continued*)
C. *Rickettsia rickettsii*
D. *Staphylococcus aureus*
E. *Yersinia pestis*

59. In the patient in question 58, which of the following therapeutic options is recommended?

A. Azithromycin
B. Gentamicin
C. No therapy; it is a self-limited disease
D. Vancomycin
E. Voriconazole

60. A 38-year-old homeless man presents to the emergency department with a transient ischemic attack characterized by a facial droop and left arm weakness lasting 20 minutes and left upper quadrant pain. He reports intermittent subjective fevers, diaphoresis, and chills for the past 2 weeks. He has had no recent travel or contact with animals. He has taken no recent antibiotics. Physical examination reveals a slightly distressed man with disheveled appearance. His temperature is 38.2°C, heart rate is 90 beats/min, and blood pressure is 127/74 mmHg. He has poor dentition. Cardiac examination reveals an early diastolic murmur over the left third intercostal space. His spleen is tender and 2 cm descended below the costal margin. He has tender painful red nodules on the tips of the third finger of his right hand and on the fourth finger of his left hand that are new. He has nits evident on his clothes consistent with body louse infection. White blood cell count is 14,500/μL, with 5% band forms and 93% polymorphonuclear cells. Blood cultures are drawn followed by empirical vancomycin therapy. These culture results remain negative for growth 5 days later. He remains febrile but hemodynamically stable but does develop a new lesion on his toe similar to those on his fingers on hospital day 3. A transthoracic echocardiogram reveals a 1-cm mobile vegetation on the cusp of his aortic valve and moderate aortic regurgitation. A CT scan of the abdomen shows an enlarged spleen with wedge-shaped splenic and renal infarctions. What test should be sent to confirm the most likely diagnosis?

A. *Bartonella* serology
B. Epstein-Barr virus heterophile antibody
C. HIV polymerase chain reaction
D. Peripheral blood smear
E. Q fever serology

61. A 24-year-old man seeks evaluation for painless penile ulcerations. He noted the first lesion about 2 weeks ago, and since that time, two adjacent areas have also developed ulceration. He states that there has been blood staining his underwear from slight

61. (*Continued*)
oozing of the ulcers. He has no past medical history and takes no medication. He returned 5 weeks ago from a vacation in Brazil, where he did have unprotected sexual intercourse with a local woman. He denies other high-risk sexual behaviors and has never had sex with prostitutes. He was last tested for HIV 2 years ago. He has never had a chlamydial or gonococcal infection. On examination, there are three well-defined red, friable lesions measuring 5 mm or less on the penile shaft. They bleed easily with any manipulation. There is no pain with palpation. There is shotty inguinal lymphadenopathy. On biopsy of one lesion, there is a prominent intracytoplasmic inclusion of bipolar organisms in an enlarged mononuclear cell. Additionally, there is epithelial cell proliferation with an increased number of plasma cells and few neutrophils. A rapid plasma reagin test result is negative. Cultures grow no organisms. What is the most likely causative organism?

A. *Calymmatobacterium granulomatis* (donovanosis)
B. *Chlamydia trachomatis* (lymphogranuloma venereum)
C. *Haemophilus ducreyi* (chancroid)
D. *Leishmania amazonensis* (cutaneous leishmaniasis)
E. *Treponema pallidum* (secondary syphilis)

62. A 67-year-old woman with a history of systemic hypertension presents to her local emergency department with 2 weeks of right jaw pain that now has developed an area of purulent drainage into her mouth. She reports an accompanying fever. She denies recent dental work. Aside from osteoporosis, she is healthy. Her only medications are alendronate and lisinopril. Physical examination is notable for a temperature of 101.1°F, right-sided facial swelling, diffuse mandibular tenderness, and an area of yellow purulent drainage through the buccal mucosa on the right side. Microscopic examination of the purulent secretions is likely to show which of the following?

A. Auer rods
B. Sialolith
C. Squamous cell carcinoma
D. Sulfur granules
E. Weakly acid-fast branching, beaded filaments

63. In the patient described above, what is the most appropriate therapy?

A. Amphotericin B
B. Itraconazole
C. Penicillin
D. Surgical debridement
E. Tobramycin

64. Which of the following is a major reservoir for anaerobic organisms in the human body?

A. Duodenum
B. Female genital tract
C. Gallbladder
D. Lung
E. Prostate

65. All of the following individuals receiving tuberculin skin purified protein derivative (PPD) reactions should be treated for latent tuberculosis EXCEPT:

A. A 23-year-old injection drug user who is HIV negative has a 12-mm PPD reaction.
B. A 38-year-old fourth grade teacher has a 7-mm PPD reaction and no known exposures to active tuberculosis. She has never been tested with a PPD previously.
C. A 43-year-old individual in the Peace Corps working in sub-Saharan Africa has a 10-mm PPD reaction. Eighteen months ago, the PPD reaction was 3 mm.
D. A 55-year-old man who is HIV positive has a negative PPD result. His partner was recently diagnosed with cavitary tuberculosis.
E. A 72-year-old man who is receiving chemotherapy for non-Hodgkin's lymphoma has a 16-mm PPD reaction.

66. A 76-year-old woman is brought into the clinic by her son. She complains of a chronic nonproductive cough and fatigue. Her son adds that she has had low-grade fevers, progressive weight loss over months, and "just doesn't seem like herself." A representative slice from her chest CT is shown in Figure 66. She was treated for tuberculosis when she was in her 20s. A sputum sample is obtained, as are blood cultures. Two weeks later, both culture sets grow acid-fast bacilli consistent with *Mycobacterium avium* complex. Which of the following is the best treatment option?

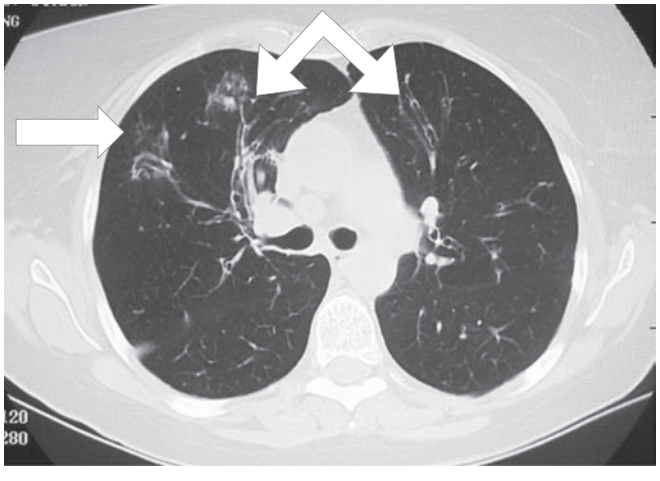


FIGURE 66

66. (*Continued*)
A. Bronchodilators and pulmonary toilet
B. Clarithromycin, ethambutol, and rifampin
C. Clarithromycin and rifampin
D. Moxifloxacin and rifampin
E. Pyrazinamide, isoniazid, rifampin, and ethambutol

67. All of the following statements regarding antituberculosis therapeutic agents are true EXCEPT:

A. In the United States, *M. tuberculosis* resistance to isoniazid remains below 10%.
B. Optic neuritis is the most severe adverse effect of ethambutol.
C. Pyrazinamide has utility in the therapy of *M. avium* complex and *M. kansasii* infections.
D. Rifabutin should be used instead of rifampin in patients receiving concurrent treatment with protease inhibitors or nevirapine.
E. Rifampin can decrease the half-life of warfarin, cyclosporine, prednisone, oral contraceptives, clarithromycin, and other important drugs.

68. Which of the following patients with latent syphilis should undergo lumbar puncture for assessment of possible neurosyphilis?

A. A 24-year-old woman with an RPR titer of 1:128
B. A 38-year-old man with an RPR titer of 1:32 who was treated with benzathine G penicillin 2.4 million units intramuscularly. Repeat RPR titer 12 months after treatment is 1:16.
C. A 46-year-old man with HIV and a CD4 count of 150/μL
D. A 62-year-old woman with Bell's palsy and a recent change in mental status
E. All of the above

69. A 46-year-old man presents to the emergency department in Honolulu, Hawaii, with myalgias, malaise, and fevers. He is homeless and has alcoholism and frequently sleeps in alleys that are infested with rats. He recalls blacking out from alcohol ingestion and waking with his legs in a fetid pool. He noted scratches and bites around his ankles about 2 weeks ago. Since that time, he has felt increasingly ill. For the past day, he has also noted that his skin is increasingly yellow. In addition to alcohol abuse, he has a medical history of schizophrenia and smokes 1 to 2 packs of cigarettes daily. He currently receives olanzapine as an intramuscular injection at a dose of 300 mg monthly. On initial evaluation, his temperature is 38.6°C, pulse is 105 beats/min, respiratory rate is 24/min, and blood pressure is 98/59 mmHg with O_2 saturations of 92% on room air. He appears acutely ill and markedly jaundiced. His conjunctivae are injected bilaterally without discharge. Bibasilar crackles are present. His liver is enlarged

69. (*Continued*)
and tender, but no splenomegaly is present. Laboratory results are notable for a BUN of 64 mg/dL, creatinine of 3.6 mg/dL, total bilirubin of 32.4 mg/dL, direct bilirubin of 29.8 mg/dL, AST of 80 U/L, ALT of 184 U/L, and alkaline phosphatase of 168 U/L. His complete blood count shows a white blood cell count of 12,500/μL with 13% bands and 80% polymorphonuclear forms, hematocrit of 33%, and platelets of 82,000/μL. Urinalysis reveals 20 white blood cells per high-power field, 3+ protein, and no casts. Coagulation study results are within normal limits. CT scan of the chest shows diffuse flame-like infiltrates consistent with pulmonary hemorrhage. What is the likely diagnosis?

A. Acute alcoholic hepatitis
B. Disseminated intravascular coagulation due to *Streptococcus pneumoniae* infection
C. Microscopic polyangiitis
D. Rat bite fever (*Streptobacillus moniliformis* infection)
E. Weil's syndrome (*Leptospira interrogans* infection)

70. A 26-year-old man presents to your office complaining of recurrent episodes of fever and malaise. He returned from a camping trip in the northwestern part of Montana about 3 weeks ago. While he was hiking, he denies eating or drinking any unpasteurized milk products. He sterilized all of his water before drinking. He had multiple insect bites, but did not identify any ticks. He primarily slept in cabins or tents and did not notice any rodent droppings in the areas where he camped. Two friends that accompanied him on the trip have not been ill. He initially experienced fevers as high as 104.7°F (40.4°C) with myalgias, headache, nausea, vomiting, and diarrhea beginning 5 days after his return home. These symptoms lasted for about 3 days and resolved spontaneously. He attributed his symptoms to the "flu" and returned to his normal functioning. Seven days later, the fevers returned with temperatures to 105.1°F (40.6°C). With these episodes, his family noted him to have intermittent confusion. Today is day 4 of his current illness, and the patient feels that his fevers have again subsided. What is the most likely cause of the patient's recurrent fevers?

A. Brucellosis
B. Colorado tick fever
C. Leptospirosis
D. Lymphocytic choriomeningitis
E. Tick-borne relapsing fever

71. *Borrelia burgdorferi* serologic testing is indicated for which of the following patients, all of whom reside in Lyme-endemic regions?

71. (*Continued*)
A. 19-year-old female camp counselor who presents with her second episode of an inflamed, red, and tender left knee and right ankle
B. A 23-year-old male house painter who presents with a primary erythema migrans lesion at the site of a witnessed tick bite
C. A 36-year-old female state park ranger who presents with a malar rash; diffuse arthralgias or arthritis of her shoulders, knees, and metacarpophalangeal and proximal interphalangeal joints; pericarditis; and acute glomerulonephritis
D. A 42-year-old woman with chronic fatigue, myalgias, and arthralgias
E. A 46-year-old male gardener who presents with fevers, malaise, migratory arthralgias or myalgias, and three erythema migrans lesions

72. A 27-year-old woman who lives in North Carolina presents to her primary care physician complaining of fever, headache, myalgias, nausea, and anorexia 7 days after returning from hiking on the Appalachian Trail. Physical examination is remarkable for a temperature of 101.5°F (38.6°C). She appears generally fatigued but not toxic. She does not have a rash. She is reassured by her primary care physician that this likely represents a viral illness. She returns to clinic 3 days later with a progressive rash and ongoing fevers. She states that small red spots began to appear on her wrists and ankles within 24 hours of her previous visit and have now progressed up her extremities and onto her trunk. She also is noting increasing headache, and her husband thinks she has had some confusion. On physical examination, the patient is noted to be lethargic and answers questions slowly. What would be a reasonable course of action?

A. Admit the patient to the hospital for treatment with intravenous ceftriaxone 1 g twice daily and vancomycin 1 g twice daily.
B. Admit the patient to the hospital for treatment with doxycycline 100 mg twice daily.
C. Initiate treatment with doxycycline 100 mg orally twice daily as an outpatient.
D. Initiate treatment with trimethoprim–sulfamethoxazole DS twice daily.
E. Order rickettsial serologies and withhold treatment until a firm diagnosis is made.

73. A previously healthy 20-year-old college student presents in September with several days of headache, extensive cough with scant sputum, and fever of 101.5°F (38.6°C). Several individuals in his dormitory have also been ill with a similar illness. On examination, pharyngeal erythema is noted, and lung examination reveals bilateral expiratory wheezing and scattered crackles in the lower lung zones. He coughs frequently during

73. (*Continued*)
the examination. Chest radiography reveals bilateral peribronchial pneumonia with increased interstitial markings. No lobar consolidation is seen. Which organism is most likely to cause the patient's presentation?

A. Adenovirus
B. *Chlamydia pneumoniae*
C. *Legionella pneumophila*
D. *Mycoplasma pneumoniae*
E. *Streptococcus pneumoniae*

74. A 19-year-old man presents to an urgent care clinic with urethral discharge. He reports three new female sexual partners over the past 2 months. What should his management be?

A. Nucleic acid amplification test for *Neisseria gonorrhoeae* and *Chlamydia trachomatis* and return to clinic in 2 days
B. Ceftriaxone 250 mg IM × 1 and azithromycin 1 g PO × 1 for the patient and his recent partners
C. Nucleic acid amplification test for *N. gonorrhoeae* and *C. trachomatis* plus ceftriaxone 250 mg IM × 1 and azithromycin 1 g PO × 1 for the patient
D. Nucleic acid amplification test for *N. gonorrhoeae* and *C. trachomatis* plus ceftriaxone 250 mg IM × 1 and azithromycin 1 g PO × 1 for the patient and his recent partners
E. Nucleic acid amplification test for *N. gonorrhoeae* and *C. trachomatis* plus ceftriaxone 250 mg IM × 1, azithromycin 1 g PO × 1, and Flagyl 2 g PO × 1 for the patient and his partners

75. All of the following viruses have been implicated as a cause of human cancer EXCEPT:

A. Dengue fever virus
B. Epstein-Barr virus
C. Hepatitis B virus
D. Hepatitis C virus
E. Human papillomavirus

76. All of the following antiviral medications are correctly matched with a significant side effect EXCEPT:

A. Acyclovir—thrombotic thrombocytopenic purpura
B. Amantadine—anxiety and insomnia
C. Foscarnet—acute renal failure
D. Ganciclovir—bone marrow suppression
E. Interferon—fevers and myalgias

77. A 23-year-old woman is newly diagnosed with genital herpes simplex virus-2 (HSV-2) infection. What can you tell her that the chance of reactivation disease will be during the first year after infection?

77. (*Continued*)
A. 5%
B. 25%
C. 50%
D. 75%
E. 90%

78. Which of the following statements regarding administration of varicella-zoster vaccine to patients above the age of 60 is true?

A. It is a killed virus vaccine, so it is safe in immunocompromised patients.
B. It is not recommended for patients in this age group.
C. It will decrease the risk of developing postherpetic neuralgia.
D. It will not decrease the risk of developing shingles.
E. It will not decrease the burden of disease.

79. A 19-year-old college student comes to clinic reporting that he has been ill for 2 weeks. About 2 weeks ago, he developed notable fatigue and malaise that prevented him from his usual exercise regimen and caused him to miss some classes. Last week, he developed low-grade fevers, sore throat, and swollen lymph nodes in his neck. He has a history of strep pharyngitis, so 3 days ago, he took some ampicillin that he had in his possession. Over the past 2 days, he has developed a worsening slightly itchy rash as shown in Figure 79. His physical examination is notable for a temperature of 38.1°C, pharyngeal erythema, bilateral tonsillar enlargement without exudates, bilateral tender cervical adenopathy, and a palpable spleen. All of the following statements regarding his illness are true EXCEPT:

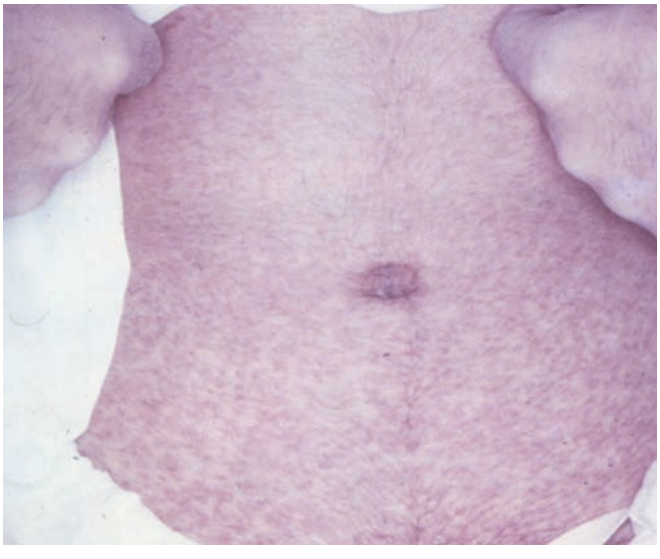


FIGURE 79

79. (*Continued*)
A. Greater than 10% atypical lymphocytosis is likely.
B. Heterophile antibody testing will likely be diagnostic.
C. If the heterophile antibody test result is negative, testing for IgG antibodies against viral capsid antigen will likely be diagnostic.
D. It is spread via contaminated saliva.
E. The patient can receive ampicillin in the future if indicated.

80. In the patient described above, which of the following is indicated treatment?

A. Acyclovir
B. Acyclovir plus prednisone
C. Ganciclovir
D. Prednisone
E. Rest, supportive measures, and reassurance

81. All of the following statements regarding human herpes virus-8 (HHV-8) are true EXCEPT:

A. It has been implicated causally in invasive cervical carcinoma.
B. It has been implicated causally in Kaposi's sarcoma.
C. It has been implicated causally in multicentric Castleman's disease.
D. It has been implicated causally in primary pleural lymphoma.
E. Primary infection may manifest with fever and maculopapular rash.

82. All of the following clinical findings are consistent with the diagnosis of molluscum contagiosum EXCEPT:

A. Involvement of the genitals
B. Involvement of the soles of the feet
C. Lack of inflammation or necrosis at the site of the rash
D. Rash associated with an eczematous eruption
E. Rash spontaneously resolving over 3 to 4 months

83. A 22-year-old woman presents with diffuse arthralgias and morning stiffness in her hands, knees, and wrists. Two weeks earlier, she had a self-limited febrile illness notable for a red facial rash and lacy reticular rash on her extremities. On examination, her bilateral wrists, metacarpophalangeal joints, and proximal interphalangeal joints are warm and slightly boggy. Which of the following tests is most likely to reveal her diagnosis?

A. Antinuclear antibody
B. *Chlamydia trachomatis* ligase chain reaction of the urine
C. Joint aspiration for crystals and culture
D. Parvovirus B19 IgM
E. Rheumatoid factor

84. Which of the following statements regarding the currently licensed human papillomavirus (HPV) vaccines is true?

A. Both protect against genital warts.
B. After becoming sexually active, women will derive little protective benefit from vaccination.
C. They are inactivated live virus vaccines.
D. They are targeted toward all oncogenic strains of HPV but are only 70% effective at decreasing infection in an individual.
E. Vaccinees should continue to receive standard Pap smear testing.

85. All of the following respiratory viruses is a cause of the common cold syndrome in children or adults EXCEPT:

A. Adenoviruses
B. Coronaviruses
C. Enteroviruses
D. Human respiratory syncytial viruses
E. Rhinoviruses

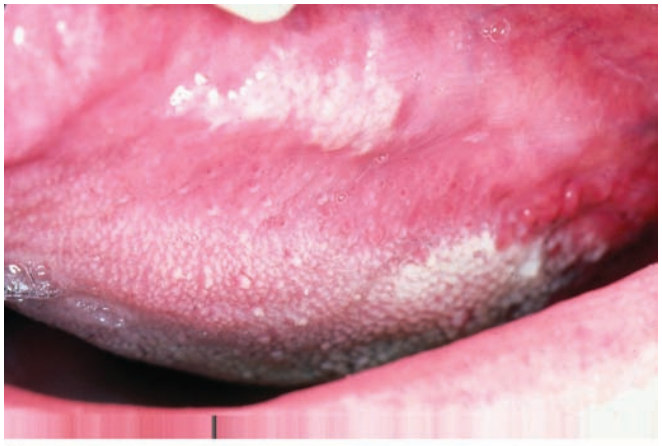
86. A 17-year-old woman with a medical history of mild intermittent asthma presents to your clinic in February with several days of cough, fever, malaise, and myalgias. She notes that her symptoms started 3 days earlier with a headache and fatigue and that several students and teachers at her high school have been diagnosed recently with "the flu." She did not receive a flu shot this year. Which of the following medication treatment plans is the best option for this patient?

A. Aspirin and a cough suppressant with codeine
B. Oseltamivir, 75 mg PO bid for 5 days
C. Rimantadine, 100 mg PO bid for 1 week
D. Symptom-based therapy with over-the-counter agents
E. Zanamivir, 10 mg inhaled bid for 5 days

87. Per-coital rate of HIV acquisition in a man who has unprotected sexual intercourse with an HIV-infected female partner is likely to increase under which of the following circumstances?

A. Acute HIV infection in the female partner
B. Female herpes simplex virus (HSV-2)–positive serostatus
C. Male nongonococcal urethritis at the time of intercourse
D. Uncircumcised male status
E. All of the above

88. A 47-year-old woman with known HIV/AIDS (CD4+ lymphocytes, 106/μL; viral load, 35,000/mL) presents with painful growths on the side of her tongue as shown in Figure 88. What is the most likely diagnosis?



B

FIGURE 88

88. (*Continued*)
A. Aphthous ulcers
B. Hairy leukoplakia
C. Herpes stomatitis
D. Oral candidiasis
E. Oral Kaposi's sarcoma

89. Which of the following patients should receive HIV antiretroviral therapy?

A. A 24-year-old man with newly diagnosed acute HIV infection by viral PCR
B. A 44-year-old man who reports having unprotected anal intercourse with another man who has active HIV infection
C. A 26-year-old pregnant women found at screening to have HIV infection of unknown duration and a CD4 lymphocyte count of 700/μL
D. A 51-year-old man found at screening to have HIV infection of unknown duration and a CD4 lymphocyte count of 150/μL
E. All of the patients should receive antiretroviral therapy.

90. All of the following statements regarding Norwalk virus gastroenteritis are true EXCEPT:

A. Fever is common.
B. Incubation period is typically 5 to 7 days.
C. Infection is common worldwide.
D. It is a major cause of nonbacterial diarrhea outbreaks in the United States.
E. Transmission is typically fecal–oral.

91. A 26-year-old woman presents to your clinic and is interested in getting pregnant. She seeks your advice regarding vaccines she should obtain, and in particular asks about the hepatitis B vaccine. She works as a receptionist for a local business, denies alcohol or illicit drug use, and is in a monogamous relationship. Which of the following is true regarding hepatitis B vaccination?

91. (*Continued*)
A. Hepatitis B vaccine consists of two IM doses 1 month apart.
B. Only patients with defined risk factors need to be vaccinated.
C. Pregnancy is not a contraindication to the hepatitis B vaccine.
D. This patient's hepatitis serologies should be checked before vaccination.
E. Vaccination should not be administered to children under 2 years old.

92. A 46-year-old man is known to have chronic hepatitis C virus (HCV) infection. He is a former IV drug user for more than 20 years who has been abstinent from drug use for 1 year. He is asking whether he should receive treatment for his HCV infection. He has a prior history of hepatitis B virus (HBV) and has positive antibody to HBV surface antigen. He was treated for tricuspid valve endocarditis 3 years previously. He has no other medical history. He does not know when he acquired HCV. His laboratory studies show a positive HCV IgG antibody with a viral load of greater than 1 million copies. The virus is genotype 1. His AST is 62 U/L, and his ALT is 54 U/L. He undergoes liver biopsy, which demonstrates a moderate degree of bridging fibrosis. What do you tell him regarding his likelihood of progression and possibilities regarding treatment?

A. As he is infected with genotype 1, the likelihood of response to pegylated interferon and ribavirin is less than 40%.
B. Following 12 weeks of treatment, the expected viral load should be undetectable.
C. Given his normal liver enzymes on laboratory testing, he is unlikely to develop progressive liver injury.
D. If the patient elects to undergo treatment, the best regimen for individuals with genotype 1 disease is pegylated interferon and ribavirin for 24 weeks.
E. The presence of bridging fibrosis on liver biopsy is the most predictive factor of the development of cirrhosis over the next 10–20 years.

93. The human enterovirus family includes poliovirus, coxsackieviruses, enteroviruses, and echovirus. Which of the following statements regarding viral infection with one of the members of this group is true?

A. Among children infected with poliovirus, paralysis is common.
B. Enteroviruses are not transmitted via blood transfusions and insect bites.
C. In utero exposure to maternal enteroviral antibodies is not protective.
D. Infections are most common in adolescents and adults, although serious illness is most common in young children.
E. Paralysis from poliovirus infection was more commonly seen in developing countries.

94. A 23-year-old previously healthy female letter carrier works in a suburb in which the presence of rabid foxes and skunks has been documented. She is bitten by a bat, which then flies away. Initial examination reveals a clean break in the skin in the right upper forearm. She has no history of receiving treatment for rabies and is unsure about vaccination against tetanus. The physician should:

A. Clean the wound with a 20% soap solution.
B. Clean the wound with a 20% soap solution and administer tetanus toxoid.
C. Clean the wound with a 20% soap solution, administer tetanus toxoid, and administer human rabies immune globulin intramuscularly.
D. Clean the wound with a 20% soap solution, administer tetanus toxoid, administer human rabies immune globulin IM, and administer human diploid cell vaccine.
E. Clean the wound with a 20% soap solution and administer human diploid cell vaccine.

95. While working at a new medical school in Kuala Lumpur, Malaysia, a 35-year-old previously healthy man from Baltimore develops a sudden onset of malaise, fever, headache, retro-orbital pain, backache, and myalgias. On examination, his temperature is 39.6°C with normal blood pressure and slight tachycardia. He has some vesicular lesions on his palate and scleral injection. Laboratory studies are notable for a platelet count of 100,000/μL. All of the following are true regarding his illness EXCEPT:

A. A second infection could result in hemorrhagic fever.
B. After resolution, he has lifelong immunity.
C. IgM ELISA may be diagnostic.
D. In equatorial areas, year-round transmission occurs.
E. The disease is transmitted by mosquitoes.

96. Variant Creutzfeldt-Jakob disease (vCJD) has been diagnosed in which of the following populations?

A. Family members with well-defined germ-line mutations leading to autosomal dominant inheritance of a fatal neurodegenerative disease
B. New Guinea natives practicing cannibalism
C. Patients accidentally inoculated with infected material during surgical procedures
D. Worldwide, in sporadic cases, mostly during the fifth and sixth decades of life
E. Young adults in Europe thought to have been exposed to tainted beef products

97. All of the following antifungal medications are approved for the treatment of *Candida albicans* fungemia EXCEPT:

A. Caspofungin
B. Fluconazole

97. (*Continued*)
C. Micafungin
D. Posaconazole
E. Voriconazole

98. A 24-year-old female student at the Ohio State University is seen in the emergency department for shortness of breath and chest pain. She has no significant past medical history. Her only medication is an oral contraceptive. As a component of her evaluation, she receives a contrast-enhanced CT scan of the chest. Fortunately, there is no pulmonary embolism (she is diagnosed with viral pleuritis), but there are numerous lung, mediastinal, and splenic calcifications. Based on these findings, which of the following remote infections was most likely?

A. Blastomycosis
B. Coccidioidomycosis
C. Cryptococcosis
D. Histoplasmosis
E. Tuberculosis

99. A 62-year-old man returns from a vacation to Arizona with fever, pleurisy, and a nonproductive cough. All of the following factors on history and laboratory examination favor a diagnosis of pulmonary coccidioidomycosis rather than community-acquired pneumonia EXCEPT:

A. Eosinophilia
B. Erythema nodosum
C. Mediastinal lymphadenopathy on chest radiography
D. Positive *Coccidioides* complement fixation titer result
E. Travel limited to northern Arizona (Grand Canyon area)

100. A 43-year-old man comes to the physician complaining of 1 month of low-grade fever, malaise, shortness of breath, and a growing skin lesion. He resides in the upper peninsula of Michigan and works as a landscaper. He avoids medical care as much as possible. He is on no medications and smokes 2 packs per day of cigarettes. Over the past month, he notices that his daily productive cough has worsened and the phlegm in dark yellow. He also reports that he has developed a number of skin lesions that start as a painful nodule and then over 1 week ulcerate and discharge pus (see Figure 100). His physical examination is notable for egophony and bronchial breath sounds in the right lower lobe, and approximately 5 to 10 ulcerating 4- to 8-cm skin lesions on the lower extremities consistent with the one shown in the figure. His chest radiograph shows right lower lobe consolidation with no pleural effusion and no evidence of hilar or mediastinal adenopathy. After obtaining sputum for cytology and culture and a biopsy of the skin lesion, which is the next most likely diagnostic or therapeutic intervention?

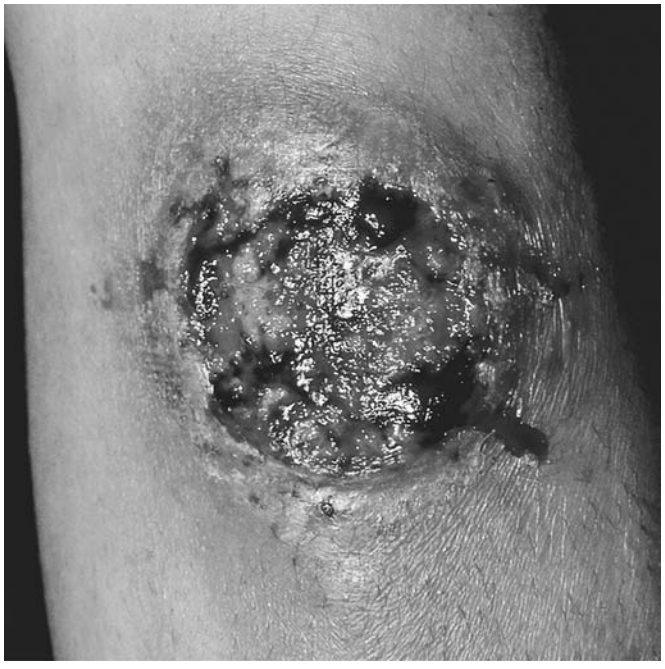


FIGURE 100
(Used with permission from Elizabeth M. Spiers, MD.)

100. (*Continued*)
A. Colonoscopy to evaluate for inflammatory bowel disease
B. INH, rifampin, PZA, and ethambutol
C. Itraconazole
D. PET scan to evaluate for metastatic malignant disease
E. Vancomycin

101. An HIV-positive patient with a CD4 count of 110/μL who is not taking any medications presents to an urgent care center with complaints of a headache for the past week. He also notes nausea and intermittently blurred vision. Examination is notable for normal vital signs without fever but mild papilledema. Head CT does not show dilated ventricles. The definitive diagnostic test for this patient is:

A. Cerebrospinal fluid culture
B. MRI with gadolinium imaging
C. Ophthalmologic examination, including visual field testing
D. Serum cryptococcal antigen testing
E. Urine culture

102. *Candida albicans* is isolated from the following patients. Rate the likelihood in order from greatest to least that the positive culture represents true infection rather than contaminant or noninfectious colonization.

Patient X: A 63-year-old man admitted to the intensive care unit (ICU) with pneumonia who has recurrent fevers after receiving 5 days of levofloxacin for pneumonia. A urinalysis drawn from a Foley catheter shows positive leukocyte esterase, negative

102. (*Continued*)
nitrite, 15 white blood cells/hpf, 10 red blood cells/hpf, and 10 epithelial cells/hpf. Urine culture grows *Candida albicans*.

Patient Y: A 38-year-old woman on hemodialysis presents with low-grade fevers and malaise. Peripheral blood cultures grow *C. albicans* in one of a total of three sets of blood cultures in the aerobic bottle only.

Patient Z: A 68-year-old man presents with a 2-day history of fever, productive cough, and malaise. Chest radiography reveals a left lower lobe infiltrate. A sputum Gram stain shows many PMNs, few epithelial cells, moderate gram-positive cocci in chains, and yeast consistent with *Candida* spp.

A. Patient X > patient Z > patient Y
B. Patient Y > patient Z > patient X
C. Patient Y > patient X > patient Z
D. Patient X > patient Y > patient Z
E. Patient Z > patient X > patient Y

103. Patients with which of the following have the lowest risk of invasive pulmonary *Aspergillus* infection?

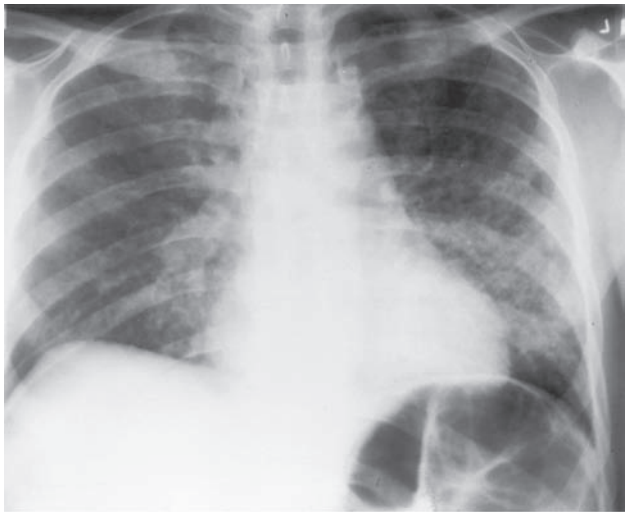
A. Allogeneic stem cell transplant with graft-versus-host disease
B. HIV infection
C. Long-standing high-dose glucocorticoids
D. Post-solid organ transplant with multiple episodes of rejection
E. Relapsed or uncontrolled leukemia

104. Patients with all of the following conditions have increased risk of developing mucormycosis EXCEPT:

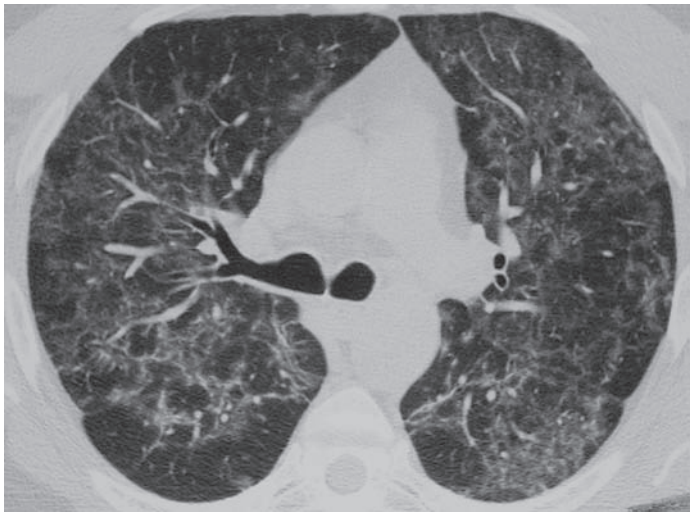
A. Deferoxamine therapy
B. Factitious hypoglycemia
C. Glucocorticoid therapy
D. Metabolic acidosis
E. Neutropenia

105. A 21-year-old college student seeks your opinion because of a lesion on his head. He has no significant medical history and reports a solitary lesion on the crown of his head for more than month that has been growing slowly. He has had no fever and reports that although the area is itchy, he feels well. On examination, you note a 3-cm round area of alopecia without redness, pain, or inflammation. It is well demarcated with central clearing, scaling, and broken hair shafts at the edges. There is no redness or pain. Which of the following should you recommend?

A. Caspofungin
B. Clindamycin
C. Doxycycline
D. Minoxidil
E. Terbinafine



A



B

FIGURE 106

106. A 35-year-old woman with long-standing rheumatoid arthritis has been treated with infliximab for the past 6 months with improvement of her joint disease. She has a history of positive PPD and takes INH prophylaxis. For the past week, she reports worsening dyspnea on exertion with low-grade fevers and a nonproductive cough. On examination, her vital signs are notable for normal blood pressure, temperature of 38.0°C, heart rate of 105 beats/min, respiratory rate of 22 breaths/min, and SaO_2 of 91% on room air. Her lungs are clear. Within one flight of steps, she becomes dyspneic, and her SaO_2 falls to 80%. A chest CT scan is shown in Figure 106. Which of the following is the most likely diagnosis?

A. *Aspergillus fumigatus* pneumonia
B. *Nocardia asteroides* pneumonia
C. *Pneumocystis jiroveci* pneumonia
D. Rheumatoid nodules
E. Staphylococcal bacteremia and septic pulmonary emboli

107. All of the following statements regarding the drug mefloquine are true EXCEPT:

A. Dose adjustment is necessary in patients with renal insufficiency.
B. It is only available in oral form.
C. It is the preferred drug for prophylaxis of chloroquine-resistant malaria.
D. It should not be administered concurrently with halofantrine.
E. Psychiatric side effects limit its use in certain patients.

108. A 45-year-old migrant worker originally from Mexico is evaluated for right upper quadrant pain, fever, and hepatic tenderness. He reports no diarrhea or bloody stool. He is found to have a large hepatic abscess on

108. (*Continued*)
CT scan of the abdomen. Of note, he has been in the United States for approximately 10 years and was well until approximately 10 days ago. Which of the following tests can be used to confirm the diagnosis?

A. Examination of stool for trophozoites
B. Liver biopsy
C. PCR of stool for *Campylobacter* spp.
D. Response to empiric trial of iodoquinol
E. Serologic test for antibody to *E. histolytica*

109. A 28-year-old woman presents with fevers, headache, diaphoresis, and abdominal pain 2 days after returning from an aid mission to the coast of Papua New Guinea. Several of her fellow aid workers developed malaria while abroad, and she stopped her doxycycline prophylaxis because of a photosensitivity reaction 5 days earlier. You send blood cultures, routine labs, and a thick and thin smear to evaluate the source of her fevers. Which of the following statements is accurate in reference to diagnosis of malaria?

A. A thick smear is performed to increase sensitivity compared with a thin smear but can only be performed in centers with experienced laboratory personnel and has a longer processing time.
B. Careful analysis of the thin blood film allows for prognostication based on estimation of parasitemia and morphology of the erythrocytes.
C. In the absence of rapid diagnostic information, empirical treatment for malaria should be strongly considered.
D. Morphology on blood smear is the current criterion used to differentiate the four species of *Plasmodium* that infect humans.
E. All of the above are true.

110. A 19-year-old college student is employed during the summer months on Nantucket Island in Massachusetts. She is evaluated in the local emergency department with 5 days of fever, malaise, and generalized weakness. Although she does recall a tick bite approximately 6 weeks ago, she denies rash around that time or presently. Physical examination is unremarkable with the exception of a temperature of 39.3°C. Which of the following statements is true regarding her most likely illness?

A. *B. duncani* is the most likely organism to be found in her peripheral blood smear.
B. First-line therapy for severe disease in this patient is immediate complete RBC exchange transfusion in addition to clindamycin and quinine.
C. If babesiosis is not demonstrated on thick or thin preparations of peripheral blood, PCR amplification of babesial 18S rRNA is recommended.
D. The ring form of *B. microti* seen in red blood cells on microscopy is indistinguishable from *Plasmodium falciparum*.
E. Without a current or historical rash, she is unlikely to have babesiosis.

111. A 35-year-old man from India is seen for evaluation of several weeks of fever that has decreased in intensity, but he now has developed abdominal swelling. He has no significant past medical history. Physical examination shows palpable splenomegaly and hepatomegaly and diffuse lymphadenopathy. Diffuse hyperpigmentation is present in his skin. Visceral leishmaniasis is suspected. Which of the following diagnostic techniques is most commonly used?

A. Culture of peripheral blood for *Leishmania* spp.
B. PCR for *L. infantum* nucleic acid in peripheral blood
C. Rapid immunochromatographic test for recombinant antigen rK39 from *L. infantum*
D. Smear of stool for amastigotes
E. Splenic aspiration to demonstrate amastigotes

112. A 36-year-old man is admitted to the hospital with 3 months of worsening dyspnea on exertion and orthopnea. Over the past 2 weeks, he has been sleeping upright. He denies any chest pain with exertion or syncope. There is no history of hypertension, hyperlipidemia, or diabetes. He is a lifelong nonsmoker and since arriving to the United States from rural Mexico 16 years ago works as an electrician. His physical examination is notable for being afebrile with a heart rate 105 beats/min, blood pressure of 100/80 mmHg, respiratory rate of 22 breaths/min, and oxygen saturation of 88% on room air. He has notable jugular venous distension upright with no Kussmaul sign, 3+ pitting edema to the knees, and bilateral crackles two-thirds up the lung fields. Cardiac examination shows a laterally displaced PMI, a 2/6 systolic murmur at the apex and axilla, an S3, and no friction rub or pericardial knock. Which of the following is likely to reveal the most likely diagnosis?

A. Coronary angiography
B. Right heart catheterization
C. Serum PCR for *T. cruzi* DNA
D. Serum *T. cruzi* IgG antibodies
E. Serum troponin

113. A 36-year-old man with HIV/AIDS is brought to the hospital after a grand mal seizure at home. He has a history of ongoing IV drug use and is not taking HAART. His last CD4 T-cell count was below 50/μL more than 1 month ago. Further medical history is unavailable. Vital signs are normal. On examination, he is barely arousable and disoriented. He is cachectic. There is no nuchal rigidity or focal motor deficits. Serum creatinine is normal. An urgent head MRI with gadolinium is performed, and the results of the T1-gated images are shown in Figure 113. Which of the following will be the most effective therapy?

A. Caspofungin
B. INH, rifampin, PZA, and ethambutol

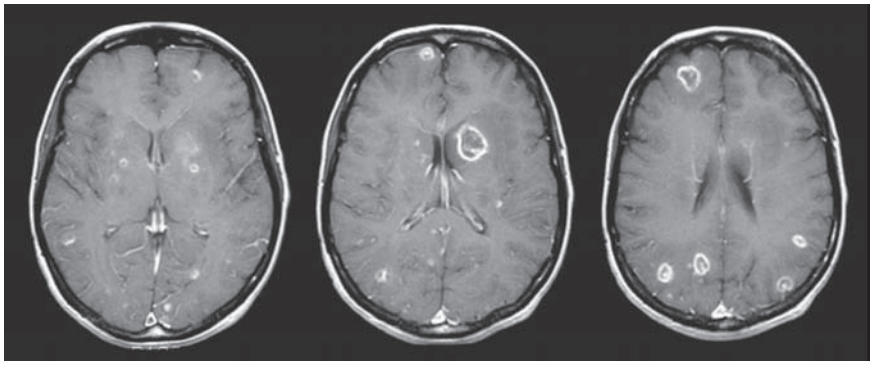


FIGURE 113

113. (*Continued*)
C. Pyrimethamine plus sulfadiazine
D. Streptokinase
E. Voriconazole

114. Which of the following intestinal protozoal infections can be diagnosed with stool ova and parasite examination?

A. *Cryptosporidium* spp.
B. *Cyclospora* spp.
C. *Giardia* spp.
D. *Isospora* spp.
E. Microsporidia
F. All of the above

115. A patient comes into the clinic and describes progressive muscle weakness over several weeks. He has also experienced nausea, vomiting, and diarrhea. One month ago, he had been completely healthy and describes a bear hunting trip in Alaska, where they ate some of the game they killed. Soon after he returned, his gastrointestinal symptoms began followed by muscle weakness in his jaw and neck that has now spread to his arms and lower back. Examination confirms decreased muscle strength in the upper extremities and neck. He also has slowed extraocular movements. Laboratory examination shows panic values for elevated eosinophils and serum creatine phosphokinase. Which of the following organisms is most likely the cause of his symptoms?

A. *Campylobacter* spp.
B. Cytomegalovirus
C. *Giardia* spp.
D. *Taenia solium*
E. *Trichinella* spp.

116. While attending the University of Georgia, a group of friends go on a 5-day canoeing and camping trip in rural southern Georgia. A few weeks later, one of the campers develops a serpiginous, raised, pruritic, erythematous eruption on the buttocks. *Strongyloides* larvae are found in his stool. Three of his companions, who are asymptomatic, are also found to have *Strongyloides* larvae in their stool. Which of the following is indicated in the asymptomatic carriers?

A. Fluconazole
B. Ivermectin
C. Mebendazole
D. Mefloquine
E. Treatment only for symptomatic illness

117. While participating in a medical missionary visit to Indonesia, you are asked to see a 22-year-old man with new onset of high fever, groin pain, and a swollen scrotum. His symptoms have been present for about 1 week and worsening steadily. His temperature is 38.8°C, and his examination is notable for tender inguinal lymphadenopathy, scrotal swelling with a hydrocele, and lymphatic streaking. All of the following may be useful in diagnosing his condition EXCEPT:

A. Examination of blood
B. Examination of hydrocele fluid
C. Scrotal ultrasonography
D. Serum ELISA
E. Stool O&P

118. The patient described above should be treated with which of the following medications?

A. Albendazole
B. Diethylcarbamazine (DEC)
C. Doxycycline
D. Ivermectin
E. Praziquantel

119. A person with liver disease caused by *Schistosoma mansoni* would be most likely to have what condition?

A. Ascites
B. Esophageal varices
C. Gynecomastia
D. Jaundice
E. Spider nevi

120. A 44-year-old woman presents to the emergency department with recurrent episodes of right upper quadrant pain, typically soon after meals. These episodes have been present for at least 1 month and seem to be worsening. The patient emigrated from Lebanon more than 20 years ago and works as an attorney. She takes no medications and is physically active. On examination, she is jaundiced and in obvious discomfort because of right upper quadrant pain. She is afebrile and tachycardic. Her physical examination is notable for an enlarged liver. Ultrasound examination confirms the large liver and demonstrates a complex 14-cm cyst with daughter cysts extending to the liver edge with associated biliary tract dilation. Which of the following is the most appropriate management approach to this patient?

A. Albendazole medical therapy
B. Albendazole followed by surgical resection
C. Needle biopsy of the cystic lesion

120. (*Continued*)

D. PAIR (percutaneous aspiration, infusion of scolicidal agent, and reaspiration)
E. Serologic testing for *E. granulosus*

121. A 39-year-old man comes to clinic reporting a 4-day illness that began while he was in the Caribbean on vacation. A few hours after attending a large seafood buffet, he developed abdominal pain, chills, nausea, and diarrhea. Soon thereafter, he noticed diffused paresthesias, throat numbness, and fatigue. The symptoms slowly improved over 2 days, and he returned home yesterday. Today he noticed while washing

121. (*Continued*)

that cold water felt hot and warm water felt cold. He is concerned about this new symptom. All of the following are true regarding his illness EXCEPT:

A. His symptoms should improve over weeks to months.
B. It is likely caused by ingestion of contaminated snapper or grouper.
C. It is likely caused by ingestion of undercooked oysters or clams.
D. Subsequent episodes may be more severe.
E. No diagnostic laboratory test is available.

ANSWERS

1. The answer is B.

(Chap. 1) Deficiencies in the complement system predispose patients to a variety of infections. Most of these deficits are congenital. Patients with sickle cell disease have acquired functional defects in the alternative complement pathway. They are at risk of infection from *Streptococcus pneumoniae* and *Salmonella* spp. Patients with liver disease, nephrotic syndrome, and systemic lupus erythematosus may have defects in C3. They are at particular risk for infections with *Staphylococcus aureus, S. pneumoniae, Pseudomonas* spp., and *Proteus* spp. Patients with congenital or acquired (usually systemic lupus erythematosus) deficiencies in the terminal complement cascade (C5-8) are at particular risk of infection from *Neisseria* spp. such as *N. meningitis* or *N. gonorrhoeae*.

2. The answer is A.

(Chap. 4) Immunization programs have the goals to control, eliminate, and eradicate disease. *Disease control* refers to decreases the impact of a specific illness on both health-related and societal outcomes. Examples of vaccinations that have lead to improved control of disease include the pneumococcal and influenza vaccines. Elimination can have two meanings. The first definition is to have zero cases in a defined geographic area. A second meaning is to reduce or eliminate the indigenous sustained transmission of an infection in a specific geographic area. In 2010, vaccine programs had eliminated measles, rubella, poliomyelitis, and diphtheria in the United States, although increasing numbers of cases of measles have been reported is some parts of the United States because of incomplete vaccination in children. Disease eradication is the most difficult goal to achieve. A disease can be considered eradicated when its elimination can be sustained without ongoing interventions. The only disease that has been globally eradicated at this point is smallpox. Poliomyelitis has been eradicated in most of the world although Afghanistan, Pakistan, India, and Nigeria continue to have ongoing transmission of the disease.

3. The answer is B.

(Chap. 4) Pneumococcal vaccination has been recommended for all individuals at any age with a variety of chronic medical conditions, including chronic respiratory disease, chronic heart disease, chronic liver failure, diabetes mellitus, asplenia, and chronic kidney disease. Determining when to revaccinate individuals has been somewhat controversial. The current recommendations are to revaccinate individuals ages 19 to 64 5 years after the initial vaccine if they have chronic renal failure or nephrotic syndrome, asplenia, or other immunocompromising conditions. All other individuals should receive a one-time revaccination at age 65 years and older if they were vaccinated 5 or more years previously and younger than 65 years old at the time of original vaccination.

4. The answer is E.

(Chap. 5, http://wwwnc.cdc.gov/travel/destinations/haiti.htm). Malaria remains endemic in many parts of the world, and an estimated 30,000 travelers from the United States and Europe are infected with malaria during travel yearly. The areas of highest risk are in sub-Saharan Africa and Oceania with the lowest risk in South and Central America, including Haiti and the Dominican Republic. Chloroquine resistance is growing throughout the world and is especially notable in parts of South America, Africa, and Southeast Asia. However, in Haiti, the incidence of chloroquine resistant malaria is low. For a traveler to Haiti, the Centers for Disease Control and Prevention states that travelers have a choice of chloroquine, doxycycline, atovaquone–proguanil, or mefloquine. In addition, travelers should be cautioned to use appropriate techniques for malarial prevention, including protective clothing, DEET-containing insect repellants, permethrin-impregnated bednets, and screened sleeping accommodations, if possible.

5. The answer is B.

(Chap. 7) Yersinia pestis is a gram-negative rod that causes the plague and has been one of the most widely used bioweapons over the centuries. Although *Y. pestis* lacks

environmental stability, it is highly contagious and has a high mortality rate, making it an effective agent of bioterrorism. There are two major syndromes caused by *Y. pestis* that reflect the mode of infection. These patients presented with symptoms typical of bubonic plague, which still exists widely in nature. In the United States, the area with the greatest number of naturally occurring cases of bubonic plague is in the Southwest with transmission occurring via contact with infected animals or fleas. In this case, infected animals or fleas were present in the concentrated population of an immigrant camp that had poor sanitation. After an individual is bitten by an infected vector, the bacteria travel through the lymphatics to regional lymph nodes, where they are phagocytized but not destroyed. The organisms can then multiply with the cells, leading to inflammation, painful and markedly enlarged lymph nodes, and fever. The affected lymph nodes can develop necrosis and are characteristically called buboes. Infection can progress to severe sepsis and death. The mortality rate for treated bubonic plague is 1–15% and 40–60% in untreated cases. When *Y. pestis* is used as an agent of bioterrorism, it is aerosolized to a large area, and the affected cases present primarily with pneumonic plague. Pneumonic plague presents with fever, cough, hemoptysis, and gastrointestinal symptoms that occur 1–6 days after exposure. Without treatment, pneumonic plague has an 85% morality rate with death occurring rapidly within 2–6 days. The treatment for *Y. pestis* could include aminoglycosides or doxycycline.

6. The answer is B.

(Chap. 8) The patient has a classic presentation of malignant hyperthermia likely caused by succinylcholine or inhalational anesthetic administration as part of her anesthetic regimen. This syndrome occurs in individuals with inherited abnormality of skeletal muscle sarcoplasmic reticulum that causes a rise in intracellular calcium content after inhalational anesthetic or succinylcholine administration. The syndrome presents with hyperthermia, or an uncontrolled increase in body temperature that exceeds the ability of the body to lose heat; muscular rigidity; and acidosis, cardiovascular instability, and rhabdomyolysis. Because the temperature dysregulation is not attributable to alteration in hypothalamic set point, antipyretics such as acetaminophen, ibuprofen, and corticosteroids are ineffective at treating the condition. Haloperidol is associated with neuroleptic malignant syndrome and should not be used to treat this condition. Physical cooling in addition to dantrolene are the treatments of choice. Dantrolene disrupts excitation–contraction coupling in skeletal muscle, thereby diminishing thermogenesis. Dantrolene may also be used in neuroleptic malignant syndrome and occasionally the serotonin syndrome.

7. The answer is C.

(Chap. 9) This case is likely toxic shock syndrome, given the clinical appearance of septic shock with no positive blood cultures. The characteristic diffuse rash, as well as the lack of a primary infected site, make *Staphylococcus* the most likely inciting agent. Streptococcal toxic shock usually has a prominent primary site of infection, but the diffuse rash is usually much more subtle than in this case. Staphylococcal toxic shock can be associated with immunosuppression, surgical wounds, or retained tampons. Mere *Staphylococcus aureus* colonization (with an appropriate toxigenic strain) can incite toxic shock. Centers for Disease Control and Prevention guidelines state that measles, Rocky Mountain spotted fever, and leptospirosis need to be ruled out serologically to confirm the diagnosis. However, this patient is at very low risk for these diagnoses based on vaccination and travel history. Juvenile rheumatoid arthritis would become a consideration only if the fevers were more prolonged and there was documented evidence of organomegaly and enlarged lymph nodes.

8. The answer is C.

(Chap. 10) Fever of unknown origin (FUO) is defined as the presence of fevers to greater than 38.3°C (101.0°F) on several occasions occurring for more than 3 weeks without a defined cause after appropriate investigation into potential causes have failed to yield a diagnosis. Initial laboratory investigation into an FUO should include a complete blood count with differential, peripheral blood smear, ESR, C-reactive protein, electrolytes, creatinine, calcium, liver function tests, urinalysis, and muscle enzymes. In addition, specific testing for a variety of infections should be performed, including VDRL for syphilis, HIV, CMV, EBV, PPD testing, and blood, sputum, and urine cultures if appropriate. Finally, the workup should include evaluation for inflammatory disorders. These tests include antinuclear antibodies, rheumatoid factor, ferritin, iron, and transferrin. This patient has had a significant workup that has demonstrated primarily nonspecific findings, including elevation in the erythrocyte sedimentation rate and ferritin as well as borderline enlargement of multiple lymph nodes. The only finding that may help define further workup is the elevation in calcium levels. When combined with the clinical symptoms and prominent lymph nodes, this could suggest granulomatous diseases, including disseminated tuberculosis, fungal infections, or sarcoidosis. The next step in the work up of this patient would be to obtain a sample from an enlarged lymph node for cultures and pathology to confirm granulomatous inflammation and provide additional samples for microbiology. In recent studies, up to 30% of individuals will not have an identified cause of FUO, and infectious etiologies continue to comprise 25% of all FUO. The most common infection causing FUO is extrapulmonary tuberculosis, which may be difficult to diagnose because PPD is often negative in these individuals. However, one would not consider empirical therapy if the possibility to obtain definitive diagnosis exists through a procedure such as a needle biopsy because it is prudent to have not only the diagnosis but also the sensitivity profile of the organism to ensure

appropriate therapy. Even in the presence of granulomatous infection, sarcoidosis would be considered a diagnosis of exclusion and would require definitive negative mycobacterial cultures before considering therapy with glucocorticoids. Serum angiotensin-converting enzyme levels are neither appropriately sensitive nor specific for diagnosis of sarcoidosis and should not be used to determine if therapy is needed. PET-CT imaging would be unlikely to be helpful in this situation because the presence of granulomatous inflammation can lead to false-positive results or will confirm the presence of already characterized abnormal lymph nodes.

9. The answer is B.

(Chap. 12) Specific malignancies are associated with underlying immune dysfunction and infection with specific organisms. Chronic lymphocytic leukemia and multiple myeloma may have an associated hypogammaglobulinemia. Individuals with these disorders are at risk of infections with *Streptococcus pneumoniae, Haemophilus influenzae,* and *Neisseria meningitidis*. Although immunoglobulin therapy is effective, it is more cost effective to give prophylactic antibiotics in these patients. Acute myeloid or lymphocytic leukemias often have an associated neutropenia and may present with overwhelming infection from extracellular bacteria and fungi, especially if the duration of neutropenia is prolonged. Patients with lymphomatous disorders often have abnormal T-cell function despite normal numbers of T cells. Moreover, most patients also receive treatment with high doses of glucocorticoids that further impair T-cell function. These individuals have an increased risk of infection with intracellular pathogens and may contract pneumonia with *Pneumocystis jiroveci*.

10. The answer is E.

(Chap. 13) Ultimately, solid organ transplant patients are at highest risk for infection because of T-cell immunodeficiency from antirejection medicines. As a result, they are also at risk for reactivation of many of the viruses from the herpesvirus family, most notably cytomegalovirus, varicella-zoster virus, and Epstein-Barr virus. However, immediately after transplantation, these deficits have not yet developed in full. Neutropenia is not common after solid organ transplantation as in bone marrow transplantation. In fact, patients are most at risk of infections typical for all hospitalized patients, including wound infections, urinary tract infection, pneumonia, *Clostridium difficile* infection, and line-associated infection. Therefore, a standard evaluation of a febrile patient in the first weeks after a solid organ transplant should include a detailed physical examination, blood and urine cultures, urinalysis, chest radiography, and *C. difficile* stool antigen or toxin studies if warranted, in addition to a transplant-specific evaluation.

11. The answer is B.

(Chap. 14) Nosocomial infections have reservoirs and sources just as do community-acquired pathogens. In hospitalized patients, cross-contamination (i.e., indirect spread of organisms from one patient to the next) accounts for many nosocomial infections. Although hand hygiene is uniformly recommended for health care practitioners, adherence to hand washing is low often because of time pressure, inconvenience, and skin damage. Because of improved adherence, alcohol-based hand rubs are now recommended for all heath care workers except when hands are visibly soiled or after care of a patient with *Clostridium difficile* infection, whose spores may not be killed by alcohol and thus require thorough hand wash with soap and water.

12. The answer is C.

(Chap. 15) Necrotizing fasciitis is a life-threatening infection that leads to extensive necrosis of the subcutaneous tissue and fascia. It is most commonly caused by group A streptococci and a mixed facultative and anaerobic flora. Recently, there have been an increasing number of cases of necrotizing fasciitis caused by community-acquired methicillin-resistant *Staphylococcus aureus*. Risk factors include diabetes mellitus, intravenous drug use, and peripheral vascular disease. The infection often arises at a site of minimal trauma, and the physical findings initially are minimal compared with the severity of pain and fever. The mortality rate for necrotizing fasciitis is between 15% and 34% but rises to as high as 70% if toxic shock syndrome is present. Wide surgical debridement of the affected tissue is necessary, and without surgery, the mortality rate is near 100%. A high index of clinical suspicion is important for selecting the appropriate antibiotic therapy and early consultation of surgery. The initial antibiotics should cover the typical organisms and include vancomycin 1 g IV every 12 hours, clindamycin 600 mg IV every 6–8 hours, and gentamicin 5 mg/kg/day intravenously.

13. The answer is B.

(Chap. 16) Sepsis is a systemic inflammatory response that develops in response to a microbial source. To diagnose the systemic inflammatory response syndrome (SIRS), a patient should have two or more of the following conditions: (1) fever or hypothermia; (2) tachypnea; (3) tachycardia; or (4) leukocytosis, leukopenia, or greater than 10% band forms. This patient fulfills the criteria for sepsis with septic shock because she meets these criteria for SIRS with the presence of organ dysfunction and ongoing hypotension despite fluid resuscitation. The patient has received 2 L of intravenous colloid and now has a central venous pressure of 18 cmH_2O. Ongoing large-volume fluid administration may result in pulmonary edema as the central venous pressure is quite high. At this point, fluid administration should continue but at a lower infusion rate. In this patient, who is receiving chronic glucocorticoids for an underlying inflammatory condition, stress-dose steroids should be administered because adrenal suppression will prevent the patient from developing the normal stress response in the face of SIRS. If the patient fails to respond to glucocorticoids, she should be started on vasopressor therapy. The diagnosis of adrenal insufficiency may be very difficult in critically ill patients. Whereas a plasma cortisol level of

less than 15 μg/mL indicates adrenal insufficiency (inadequate production of cortisol), many experts now feel that the adrenocorticotropic hormone stimulation test is not useful for detecting less profound degrees of corticosteroid deficiency in patients who are critically ill. A single small study has suggested that norepinephrine may be preferred over dopamine for septic shock, but these data have not been confirmed in other trials. The "Surviving Sepsis" guidelines state that either norepinephrine or dopamine should be considered as a first-line agent for the treatment of septic shock. Transfusion of red blood cells in critically ill patients has been associated with a higher risk for development of acute lung injury, sepsis, and death. A threshold hemoglobin value of 7 g/dL has been shown to be as safe as a value of 10 g/dL and is associated with fewer complications. In this patient, a blood transfusion is not currently indicated, but it may be considered if the central venous oxygen saturation is below 70% to improve oxygen delivery to tissues. An alternative to blood transfusion in this setting is the use of dobutamine to improve cardiac output.

14. The answer is B.

(Chap. 17) Approximately 5–15% of all cases of acute pharyngitis in adults are caused by *Streptococcus pyogenes*. Appropriate identification and treatment of *S. pyogenes* infection is needed because antibiotic therapy is recommended to decrease the small risk of acute rheumatic fever. In addition, treatment with antibiotics within 48 hours of onset of symptoms decreases symptom duration and, importantly, decreases transmission of streptococcal pharyngitis. In adults, the recommended diagnostic procedure by the Centers for Disease Control and Prevention and the Infectious Disease Society of America is a rapid antigen detection test for group A streptococci only. In children, however, the recommendation is to perform a throat culture for confirmation if the rapid screen result is negative to limit spread of disease and minimize potential complications. Throat culture generally is regarded as the most appropriate diagnostic method but cannot discriminate between colonization and infection. In addition, it takes 24–48 hours to get a result. Because most cases of pharyngitis at all ages are viral in origin, empiric antibiotic therapy is not recommended.

15. The answer is B.

(Chap. 18) The diagnosis and treatment of community-acquired pneumonia (CAP) often incorporate a combination of clinical, radiographic, and laboratory features to determine the most likely etiology and treatment. In most instances of CAP, outpatient treatment is sufficient, and definitive etiologic diagnosis of the causative organism is not required, nor is it cost-effective. However, the outpatient diagnosis of CAP most often does require confirmation by chest radiograph, as the sensitivity and specificity of the findings on physical examination are about 58% and 67%, respectively. In addition, chest radiograph may identify risk factors for more severe clinical courses such as multifocal infiltrates. Moreover, outside of the 2% of individuals admitted to intensive care for treatment of CAP, there are no data that treatment directed against the specific causative organism is superior to empiric therapy. In some instances, one may decide to attempt to determine a causative organism for CAP, particularly in individuals who have risk factors for resistant organisms or if the patient fails to respond appropriately to initial antibiotic therapy. The most common way CAP is diagnosed is via sputum culture with Gram stain. The primary purpose of the Gram stain is to ensure that the sputum is an adequate lower respiratory sample for culture with fewer than 10 squamous epithelial cells and more than 25 neutrophils per high-powered field. However, at times it can suggest a specific diagnosis based on the appearance. Generally, the yield from sputum culture is 50% or less, even in cases of bacteremic pneumococcal pneumonia. The yield from blood cultures is also low, even when collected prior to initiation of antibiotics, at 5–14%. More recently, antigen tests or polymerase chain reaction (PCR) testing directed against specific organisms has gained favor. The most common antigen test that is performed is for *Legionella pneumophila*, as this organism does not grow in culture unless performed on specific media. Antigen and PCR tests are also available for *Streptococcus pneumoniae* and *Mycoplasma pneumoniae*, but given the costs they are not frequently performed

16. The answer is D.

(Chap. 19) Bronchiectasis occurs when there is irreversible dilation of the distal airways and can occur in a focal or diffuse fashion. The most common cause of diffuse bronchiectasis worldwide is prior granulomatous infection due to *Mycobacterium tuberculosis*. In the developed world, tuberculosis is a less common cause of bronchiectasis, with nontuberculous mycobacteria such as *Mycobacterium avium-intracellulare* complex being a more common cause, particularly in the midlung fields. Other potential etiologies of diffuse bronchiectasis include cystic fibrosis, postradiation pneumonitis, immunoglobulin deficiency, end-stage fibrotic lung disease, and recurrent aspiration. However, despite extensive workup, as many as 25–50% of cases remain idiopathic.

17. The answer is C.

(Chap. 20) The recommendations for prophylaxis to prevent infective endocarditis have undergone change recently with a change to recommending it for fewer patients. The most recent American Heart Association guidelines (*Circulation* 116:1736, 2007) reverse many of the former recommendations based on indirect evidence suggesting that benefit is minimal and is not supported by cost-benefit or cost-effectiveness studies. Current recommendations advise prophylactic antibiotics only for those at highest risk for severe morbidity or mortality from endocarditis undergoing manipulation of gingival tissue or periapical region of the teeth, perforation of the oral mucosa, or a procedure on an infected site. Prophylaxis is not advised for routine gastrointestinal or genitourinary procedures. High-risk patients include those with prior endocarditis, prosthetic heart valves, unrepaired cyanotic congenital heart disease lesions, recently (<6 months)

repaired congenital heart lesions, incompletely repaired congenital heart disease lesions, and valvulopathy after cardiac transplant. The British Society for Antimicrobial Chemotherapy does recommend prophylaxis for at-risk patients undergoing selected gastrointestinal or genitourinary procedures; however, the National Institute for Health and Clinical Excellence in the United Kingdom advised discontinuation of the practice (*http://www.nice.org.uk/guidance/cg64*).

18. The answer is B.

(Chap. 21) Pulsus paradoxus is an exaggeration of the normal phenomenon in which systolic blood pressure declines 10 mmHg or less with inspiration. Pulsus paradoxus is typically seen in patients with pericardial tamponade and in patients with severe obstructive lung disease (COPD, asthma). In pulsus paradoxus due to pericardial tamponade, the inspiratory systolic blood pressure decline is greater due to the tight incompressible pericardial sac. The right ventricle distends with inspiration, compressing the left ventricle and resulting in decreased systolic pulse pressure in the systemic circulation. In severe obstructive lung disease, the inspiratory decline of systolic blood pressure may be due to the markedly negative pleural pressure either causing left ventricular compression (due to increased RV venous return) or increased LV impedance to ejection (increased afterload).

19. The answer is B.

(Chap. 22) Bullae (Latin for bubbles) are skin lesions that are greater than 5 mm and fluid filled. They may be regular or irregularly shaped and filled with serous or seropurulent fluid. *Clostridium* spp., including *perfringens*, may cause bullae through myonecrosis. *Staphylococcus* causes scalded skin syndrome through elaboration of the exfoliatin toxin from phage group II, particularly in neonates. *Streptococcus pyogenes*, the causative agent of impetigo, may cause bullae initially that progress to crusted lesions. MRSA may also cause impetigo. The halophilic *Vibrio*, including *V. vulnificus*, may cause an aggressive fasciitis with bullae formation. Patients with cirrhosis exposed to Gulf of Mexico or Atlantic waters (or ingestion of raw seafood from those waters) are at greatest risk. Infection with the dimorphic fungus, *Sporothrix schenckii*, presents with discrete crusted lesions resembling ringworm. Lesions may progress to ulcerate. Patients often have a history of working with soil or roses.

20. The answer is A.

(*Chap. 23*) The therapy for osteomyelitis is challenging because of the multiplicity of potential causative organisms, the diagnostic difficulty, and the prolonged necessary therapy. Early surgical intervention may be beneficial diagnostically and therapeutically. In this case, the Gram stain is polymicrobial, and the putrid smell is very specific for anaerobic organisms. The diagnosis of acute osteomyelitis is also very likely based on the positive probe to bone test and wide ulcer. Broad-spectrum antibiotics are indicated. Vancomycin and linezolid cover methicillin-resistant *Staphylococcus aureus* (MRSA) and streptococcal isolates but would miss gram-negative rods and anaerobic bacteria. Metronidazole covers only anaerobes, missing gram-positive organisms that are key in the initiation of diabetic foot infections. Clindamycin covers gram-positive organisms and anaerobes but misses gram-negative rods. Ampicillin–sulbactam is broad-spectrum antibiotic and covers all three classes of organism except MRSA. If the patient has a history of MRSA or MRSA risk factors, then the addition of vancomycin or linezolid is a strong consideration. Recent studies have also suggested that daptomycin may be a promising therapy for MRSA osteomyelitis.

21. The answer is B.

(Chap. 24) Although the crystals suggest that the patient may have active pseudogout, the more important acute medical problem is septic arthritis. This is highly probable based on the joint leukocyte count above 100,000/μL, high percentage of PMNs, and positive Gram stain. Crystal-induced, rheumatoid, and other noninfectious causes of arthritis typically have WBC counts in the 30,000–50,000/μL range. WBC counts in indolent infections such as fungal or mycobacterial arthritis are commonly in the 10,000–30,000/μL range. The bacteria of septic arthritis usually enter the joint via hematogenous spread through synovial capillaries. Patients with rheumatoid arthritis are at high risk of a septic arthritis due to *Staphylococcus aureus* because of chronic inflammation and glucocorticoid therapy. The concurrent presence of pseudogout does not preclude the diagnosis of septic arthritis. In adults, the most common bacterial pathogens are *Neisseria gonorrhoeae* and *S. aureus*. Antibiotics, prompt surgical evaluation for drainage, and blood cultures to rule out bacteremia are all indicated. Prompt local and systemic treatment of infection can prevent the destruction of cartilage, joint instability, or deformity. Direct instillation of antibiotics into the joint fluid is not necessary. If the smear shows no organisms, a third-generation cephalosporin is reasonable empirical therapy. In the presence of gram-positive cocci in clusters, antistaphylococcal therapy should be instituted based on the community prevalence of methicillin resistance or recent hospitalization (which would favor empirical vancomycin). Typically, acute flairs of pseudogout can be addressed with glucocorticoids. However, this could portend a higher risk in the context of infection. Nonsteroidal anti-inflammatory agents might be a possibility depending on the patient's renal function and gastrointestinal history.

22. The answer is A.

(Chap. 25) Primary (spontaneous) bacterial peritonitis (PBP) occurs when the peritoneal cavity becomes infected without an apparent source of contamination. PBP occurs most often in patients with cirrhosis, usually with preexisting ascites. The bacterial likely invade the peritoneal fluid because of poor hepatic filtration in cirrhosis. Although fever is present in up to 80% of cases, abdominal pain, acute onset, and peritoneal signs are often absent. Patients may present with nonspecific findings such as malaise or worsening encephalopathy. A neutrophil count in peritoneal fluid of

greater than 250/μL is diagnostic; there is no % neutrophil differential threshold. Diagnosis is often difficult because peritoneal culture findings are often negative. Blood cultures may reveal the causative organism. The most common organisms are enteric gram-negative bacilli, but gram-positive cocci are often found. Anaerobes are not common (in contrast to secondary bacterial peritonitis), and empiric antibiotics targeting them are not necessary if PBP is suspected. Third-generation cephalosporins or piperacillin–tazobactam are reasonable initial empiric therapy. Diagnosis requires exclusion of a primary intraabdominal source of peritonitis.

23 and 24. The answers are B and D, respectively.
(Chap. 26) Traveler's diarrhea is common among individuals traveling to Asia, Africa, and Central and South America, affecting 25% to 50% of travelers to these areas. Most traveler's diarrhea begins within 3 to 5 days after arrival and is self-limited, lasting 1 to 5 days. Most individuals acquire traveler's diarrhea after consuming contaminated food or water. Although some organisms have a geographic association, enterotoxigenic and enteroaggregative *Escherichia coli* are found worldwide and are the most common causes of traveler's diarrhea. In Asia, *Campylobacter jejuni* is also common. This presentation would be uncommon for *Shigella* spp. because it most frequently causes bloody diarrhea. Norovirus is associated with a more profuse diarrhea. It has been the causative organism in large outbreaks on cruise ships. *Giardia lamblia* is a parasite that is responsible for 5% or less of traveler's diarrhea.

The approach to treatment of traveler's diarrhea should be tailored to the severity of the patient's symptoms. In general, most cases are self-limited. As long as an individual is able to maintain adequate fluid intake, no specific therapy may be required if there are no more than one or two unformed stools daily without distressing abdominal symptoms, bloody stools, or fever. In this scenario, the patient is not having a large number of stools, but in the presence of distressing abdominal symptoms, use of bismuth subsalicylate or loperamide is recommended. If loperamide is used, an initial dose of 4 mg is given followed by 2 mg after passage of each unformed stool. Antibacterial therapy is only recommended if there is evidence of inflammatory diarrhea (bloody stools or fever) or there are more than two unformed stools daily. The antibacterial agent of choice is usually a fluoroquinolone. Ciprofloxacin given as a single dose of 750 mg or 500 mg three times daily for 3 days is typically effective. In Thailand, *Campylobacter jejuni* is a common agent and has a high degree of fluoroquinolone resistance. For travelers to Thailand who require antibiotics, azithromycin is recommended with an initial dose of 10 mg/kg on the first day followed by 5 mg/kg on days 2 and 3 if diarrhea persists.

25. The answer is E.
(Chap. 27) Infection with *Yersinia* organisms may potentially cause acute appendicitis after obstruction occurs. High complement fixation antibody titers have been found in up to 30% of proven cases of acute appendicitis. Chronic appendicitis is quite rare, but may occur due to tuberculosis, amebiasis, and actinomycosis.

26. The answer is B.
(Chap. 30) Bacterial vaginosis is associated with *Gardnerella vaginalis* and various anaerobic or noncultured bacteria. It generally has malodorous discharge that is white or gray. There is no external irritation, and pH of vaginal fluid is usually above 4.5; a fishy odor is present with 10% KOH preparation; and microscopy shows clue cells, few leukocytes, and many mixed microbiota. Normal vaginal findings are described in patient D with pH below 4.5 and lactobacilli seen on microscopic examination. A high pH above 5 with external irritation is often found in vulvovaginal candidiasis, but the presence of motile trichomonads is diagnostic for trichomonal vaginitis.

27. The answer is D.
(Chap. 31) Listeria has become an increasingly important cause of bacterial meningitis in neonates (<1 month of age), pregnant women, individuals more than 60 years old, and immunocompromised individuals. Infection is acquired by eating contaminated foods such as unpasteurized dairy products, coleslaw, milk, soft cheeses, delicatessen meats, and uncooked hot dogs. Ampicillin is the agent most often added to the initial empirical regimen to cover *L. monocytogenes*.

28. The answer is D.
(Chap. 32) Ibuprofen, isoniazid, ciprofloxacin, tolmetin, sulfa-containing medicines, and phenazopyridine have been implicated in drug hypersensitivity leading to meningitis. The cerebrospinal fluid (CSF) will typically show neutrophils, but mononuclear cells or eosinophils are occasionally present. Most causes of chronic (not recurrent) meningitis cause a predominance of mononuclear cells. The differential for chronic meningitis is broad and a diagnosis is often difficult to make. The treating physician needs to consider a diverse array of viral, fungal, bacterial, mycobacterial, helminthic, and protozoal pathogens, both common and exotic, and therefore should obtain a detailed social history and consult an expert in the field. Recurrent meningitis is often due to herpes simplex virus type 2 infection and this should be ruled out, particularly if active genital ulcers develop concurrently. Malignancy, sarcoidosis, and vasculitis are all potential causes, and history, physical examination, and appropriate further testing should dictate the degree to which these possibilities are explored. Medications are often overlooked as a cause of chronic meningitis and should always be carefully considered. When CSF neutrophils predominate after 3 weeks of illness, *Nocardia*, *Actinomyces*, *Brucella*, tuberculosis (<10% of cases), and fungal and noninfectious causes of chronic meningitis should be considered.

29. The answer is A.
(Chap. 33) Chronic fatigue syndrome (CFS) is a disorder characterized by persistent and unexplained fatigue resulting in severe impairment in daily functioning. Besides intense fatigue, most patients with CFS report

concomitant symptoms such as pain, cognitive dysfunction, and unrefreshing sleep. Additional symptoms can include headache, sore throat, tender lymph nodes, muscle aches, joint aches, feverishness, difficulty sleeping, psychiatric problems, allergies, and abdominal cramps. Criteria for the diagnosis of CFS have been developed by the U.S. Centers for Disease Control and Prevention (see Table 33-1). CFS is seen worldwide, with adult prevalence rates varying between 0.2% and 0.4%. In the United States, the prevalence is higher in women, members of minority groups (African and Native Americans), and individuals with lower levels of education and occupational status. Approximately 75% of all CFS patients are women. The mean age of onset is between 29 and 35 years. It is probable that many patients go undiagnosed and/or do not seek help.

30. The answer is B.

(Chap. 36) The patient presents with evidence of methicillin-resistant *Staphylococcus aureus*–associated soft tissue infection that has failed therapy with clindamycin. Linezolid is an appropriate choice for antibiotic coverage in this situation. Subsequent development of neurologic symptoms, including agitated delirium, evidence of autonomic instability coupled with tremor, muscular rigidity, hyperreflexia, and clonus, suggests serotonin syndrome. Because linezolid is a monoamine oxidase inhibitor, it interacts with selective serotonin reuptake inhibitors and can cause serotonin syndrome. Other potential triggers include tyramine-rich foods and sympathomimetics such as phenylpropanolamine. The other drug–drug combinations in the answer choices are not described to be associated with serotonin syndrome.

31. The answer is A.

(Chap. 37) Pneumococcal infections, particularly pneumonia, remain a worldwide public health problem. Intermittent colonization of the nasopharynx by pneumococcus transmitted by respiratory droplet is common and is the likely reservoir for invasive disease. Infants and elderly adults are at greatest risk of developing invasive pneumococcal disease (IPD) and death. In the developed world, children are the most common source of pneumococcal transmission. By 1 year of age, 50% of children have had at least one episode of colonization. Prevalence studies show carriage rates of 20% to 50% in children up to 5 years old and up to 15% for adults. These numbers approach 90% for children and 40% for adults in the developing world. Pneumococcal vaccination has dramatically impacted the epidemiology with reduced IPD in the United States attributable to reductions in serotypes included in the vaccine. Similar reductions have been observed in other countries implementing routine childhood vaccinations; however, in certain populations (Alaska native populations and United Kingdom), the reduction in vaccine covered serotype cases has been offset by increases in nonvaccine serotypes. Case fatality rates caused by pneumococcal pneumonia vary by host factors, age, and access to care. Interestingly, there appears to be no reduction in case fatality during the first 24 hours of hospitalization since the introduction of antibiotics. This is likely because of the development of severe multiorgan failure as a result of severe infection. Appropriate care in an intensive setting can reduce case fatality rate for severe infection. Outbreaks of disease are well recognized in crowded settings with susceptible individuals, such as infant daycare facilities, military barracks, and nursing homes. Furthermore, there is a clear association between preceding viral respiratory disease (especially but not exclusively influenza) and risk of secondary pneumococcal infections. The significant role of pneumococcal pneumonia in the morbidity and mortality associated with seasonal and pandemic influenza is increasingly recognized.

32. The answer is B.

(Chap. 38) Although new genetic diagnostic kits for distinguishing microbes are becoming more common, basic biochemical characterization of bacterial pathogens is still widely used in microbiology laboratories. Clinicians should be familiar with the most common of these techniques when interpreting laboratory results. Whereas all staphylococci are catalase positive, streptococci are catalase negative. Whereas *S. aureus* are coagulase positive, *Staphylococcus epidermidis* (as well as *S. hominis, S. saprophyticus*, and others) are coagulase negative. This is the initial result that can make this important clinical distinction. Lactose fermentation is used to distinguish many gram-negative bacteria. *Salmonella, Proteus,* and *Shigella* spp. and *Pseudomonas aeruginosa* are unable to ferment lactose. The oxidase test is commonly used to identify *P. aeruginosa.* The urease test is used to identify *Proteus* spp., *Helicobacter* spp., and other gram-negative organisms.

33. The answer is D.

(Chap. 39) Recurrent episodes of rheumatic fever are most common in the first 5 years after the initial diagnosis. Penicillin prophylaxis is recommended for at least this period. After the first 5 years, secondary prophylaxis is determined on an individual basis. Ongoing prophylaxis is currently recommended for patients who have had recurrent disease, have rheumatic heart disease, or work in occupations that have a high risk for reexposure to group A streptococcal infection. Prophylactic regimens are penicillin V, PO 250 mg bid; benzathine penicillin, 1.2 million units IM every 4 weeks; and sulfadiazine, 1 g PO daily. Polyvalent pneumococcal vaccine has no cross-reactivity with group A *Streptococcus*.

34. The answer is B.

(Chap. 40) This patient has enterococcal endocarditis, which often occurs in patients with underlying gastrointestinal or genitourinary pathology. *Enterococcus faecalis* is a more common causative organism than *E. faecium* in community-acquired endocarditis. Patients tend to more commonly be men with underlying chronic disease. The typical presentation is one of subacute bacterial endocarditis and with involvement of the mitral or aortic valves. Prolonged therapy beyond 4 to 6 weeks is often necessary for organisms with drug resistance. Complications requiring valve replacement are common. Enterococci are

intrinsically resistant or tolerant to several antimicrobial agents (with *tolerance* defined as lack of killing by drug concentrations 16 times higher than the minimal inhibitory concentration). Monotherapy for endocarditis with a β-lactam antibiotic (to which many enterococci are tolerant) has produced disappointing results with low cure rates at the end of therapy. However, the addition of an aminoglycoside to a cell wall–active agent (a β-lactam or a glycopeptide) increases cure rates and eradicates the organisms; moreover, this combination is synergistic and bactericidal in vitro. Therefore, combination therapy with a cell wall–active agent and an aminoglycoside is the standard of care for endovascular infections caused by enterococci. This synergistic effect can be explained, at least in part, by the increased penetration of the aminoglycoside into the bacterial cell, presumably as a result of cell wall alterations attributable to the β-lactam or glycopeptide.

35. The answer is D.

(Chap. 41) Acute rheumatic fever (ARF) is almost universally due to group A streptococcal disease at the present time, though virtually all streptococcal disease may be capable of precipitating rheumatic fever. Although skin infections may be associated with rheumatic fever, far and away the most common presentation is with preceding pharyngitis. There is a latent period of approximately 3 weeks from an episode of sore throat to presentation of ARF. The most common manifestations are fever and polyarthritis, with polyarthritis being present in 60–75% of cases. Carditis may also be present, though somewhat less frequently in 50–60% of cases. Chorea and indolent carditis may have a subacute presentation. Chorea is present in 2–30% of affected individuals, while erythema marginatum and subcutaneous nodules are rare. Sixty percent of patients with ARF progress to rheumatic heart disease, with the endocardium, pericardium, and myocardium all potentially involved. All patients with ARF should receive antibiotics sufficient to treat the precipitating group A streptococcal infection.

36. The answer is B.

(Chap. 42) *Rhodococcus* spp., including *R. equi*, are phylogenetically related to the corynebacteria. They predominantly cause necrotizing lung infections in immunocompromised hosts. The differential diagnosis of the cavitating lung lesions includes tuberculosis, *Nocardia* infection, and septic emboli. The organisms can initially be mistaken for corynebacteria, but they should not be misconstrued as skin contaminants. The organism is routinely susceptible to vancomycin, which is considered the drug of choice. Infection caused by *R. equi* has also been treated successfully with antibiotics that penetrate intracellularly, including macrolides, clindamycin, trimethoprim–sulfamethoxazole, rifampin, tigecycline, and linezolid. β-Lactam antibiotics are not effective.

37. The answer is B.

(Chap. 43) *Listeria* bacteremia in pregnancy is a relatively rare but serious infection both for the mother and fetus. Vertical transmission may occur, with 70% to 90% of fetuses developing infection from their mothers. Preterm labor is common. Prepartum treatment of the mother increases the chances of a healthy delivery. Mortality among fetuses approaches 50% and is much lower in neonates receiving appropriate antibiotics. First-line therapy is with ampicillin, with gentamicin often added for synergy. This recommendation is the same for the mother and child. In patients with true penicillin allergy, the therapy of choice is trimethoprim–sulfamethoxazole. There are case reports of successful therapy with vancomycin, imipenem, linezolid, and macrolides, but there is not enough clinical evidence, and there have been some reports of failure that maintain ampicillin as recommended therapy.

38. The answer is D.

(Chap. 44) Tetanus is an acute disease manifested by skeletal muscle spasm and autonomic nervous system disturbance. It is caused by a powerful neurotoxin produced by the bacterium *Clostridium tetani* and is now a rare disease because of widespread vaccination. There were fewer than 50 cases reported recently in the United States, but there is a rising frequency in drug users. Older patients may be at higher risk because of waning immunity. The differential diagnosis of a patient presenting with tetanus includes strychnine poisoning and drug-related dystonic reactions. The diagnosis is clinical. Cardiovascular instability is common because of autonomic dysfunction and is manifest by rapid fluctuation in heart rate and blood pressure. Wound culture results are positive in approximately 20% of cases. Metronidazole or penicillin should be administered to clear infection. Tetanus immune globulin is recommended over equine antiserum because of a lower risk of anaphylactic reactions. Recent evidence suggests that intrathecal administration is efficacious in inhibiting disease progression and improving outcomes. Muscle spasms may be treated with sedative drugs. With effective supportive care and often respiratory support, muscle function recovers after clearing the toxin with no residual damage.

39. The answer is B.

(Chap. 45) This patient most likely has wound botulism. The use of "black-tar" heroin has been identified as a risk factor for this form of botulism. Typically, the wound appears benign, and unlike in other forms of botulism, gastrointestinal symptoms are absent. Symmetric *descending* paralysis suggests botulism, as does cranial nerve involvement. This patient's ptosis, diplopia, dysarthria, dysphagia, lack of fevers, normal reflexes, and lack of sensory deficits are all suggestive. Botulism can be easily confused with Guillain-Barré syndrome (GBS), which is often characterized by an antecedent infection and rapid, symmetric *ascending* paralysis and treated with plasmapheresis. The Miller Fischer variant of GBS is known for cranial nerve involvement with ophthalmoplegia, ataxia, and areflexia being the most prominent features. Elevated protein in the cerebrospinal fluid also favors GBS over botulism. Both botulism and GBS can progress to respiratory failure, so making a diagnosis by physical examination is critical.

Other diagnostic modalities that may be helpful are wound culture, serum assay for toxin, and examination for decreased compound muscle action potentials on routine nerve stimulation studies. Patients with botulism are at risk of respiratory failure caused by respiratory muscle weakness or aspiration. They should be followed closely with oxygen saturation monitoring and serial measurement of forced vital capacity.

40. The answer is E.

(Chap. 46) Clostridia are gram-positive, spore-forming obligate anaerobes that reside normally in the gastrointestinal (GI) tract. Several clostridial species can cause severe disease. *Clostridium perfringens,* which is the second most common clostridial species to normally colonize the GI tract, is associated with food poisoning, gas gangrene, and myonecrosis. *C. septicum* is seen often in conjunction with GI tumors. *C. sordellii* is associated with septic abortions. All can cause a fulminant overwhelming bacteremia, but this condition is rare. The fact that this patient is well several days after his acute complaints rules out this fulminant course. A more common scenario is transient, self-limited bacteremia caused by transient gut translocation during an episode of gastroenteritis. There is no need to treat when this occurs, and no further workup is necessary. *Clostridium* spp. sepsis rarely causes endocarditis because overwhelming disseminated intravascular coagulation and death occur so rapidly. Screening for GI tumor is warranted when *C. septicum* is cultured from the blood or a deep wound infection.

41. The answer is E.

(Chap. 47) Although frequent nonbloody diarrheal illness is commonly associated with *Clostridium difficile* infection, other presentations are well described, including fever in 28% of cases, abdominal pain, and leukocytosis. Adynamic ileus is often seen with *C. difficile* infection, and leukocytosis in this condition should be a clue that *C. difficile* is at play. Recurrent infection after therapy has been described in 15% to 30% of cases.

42. The answer is B.

(Chap. 48) Close contacts of individuals with meningococcal disease are at increased risk of developing secondary disease with reports of secondary cases in up to 3% of primary cases. The rate of secondary cases is highest during the week after presentation of the index case with most cases presenting within 6 weeks. Increased risk remains for up to 1 year. Prophylaxis is recommended for persons who are intimate or household contacts of the index case and health care workers who have been directly exposed to respiratory secretions. Mass prophylaxis is not usually offered. The aim of prophylaxis is to eradicate colonization of close contacts with the strain that has caused invasive disease. Prophylaxis should be given as soon as possible to all contacts at the same time to avoid recolonization. Waiting for culture is not recommended. Ceftriaxone as a single dose is currently the most effective option in reducing carriage. Rifampin is no longer the optimal agent because it requires multiple doses and fails to eliminate carriage in up to 20% of cases. In some countries, ciprofloxacin or ofloxacin is used, but resistance has been reported in some areas. Current conjugated vaccines do not include *N. meningitidis* serotype B. Most sporadic cases in the United States are now caused by this serotype. Vaccination should be offered in cases of meningococcal disease caused by documented infection by a serotype included in the current vaccine.

43. The answer is A.

(Chap. 49) Because of emerging resistance, treatment recommendations for gonorrhea require frequent updating. Fluoroquinolones and penicillin are no longer generally recommended in the US because of resistance. Current effective therapies utilize single dose therapies to maximize adherence. Intramuscular ceftriaxone is recommended by the CDC as first line therapy and is effective for urethritis, cervicitis, and proctitis. Azithromycin given orally in a 1 gram dose also should be administered as dual treatment and also because of the presumption of chlamydial co-infection. Doxycycline also an option for co-treatment in nonpregnant women. Patients with uncomplicated infection who receive therapy do not require a test of cure. Patients should be instructed to contact sexual partners for screening and therapy. Recent studies have demonstrated that the provision of medications or prescriptions to treat gonorrhea and chlamydia in sexual partners diminishes the risk of reinfection in the affected patient.

44. The answer is D.

(Chap. 50) Generally thought of as a disease of children, epiglottitis is also a disease of adults since the wide use of *Haemophilus influenzae* type b vaccination. Epiglottitis can cause life-threatening airway obstruction caused by cellulitis of the epiglottis and supraglottic tissues, classically caused by *H. influenzae* type b infection. However, other organisms are also common causes, including nontypeable *H. influenzae, Streptococcus pneumoniae, H. parainfluenzae*, *Staphylococcus aureus*, and viral infection. The initial evaluation and treatment for epiglottitis in adults includes airway management and intravenous antibiotics. The patient presented here is demonstrating signs of impending airway obstruction with stridor, inability to swallow secretions, and use of accessory muscles of inspiration. A lateral neck radiograph shows the typical thumb sign indicative of a swollen epiglottis. In addition, the patient has evidence of hypoventilation with carbon dioxide retention. Thus, in addition to antibiotics, this patient should also be intubated and mechanically ventilated electively under a controlled setting because he is at high risk for mechanical airway obstruction. Antibiotic therapy should cover the typical organisms outlined above and include coverage for oral anaerobes.

In adults presenting without overt impending airway obstruction, laryngoscopy would be indicated to assess airway patency. Endotracheal intubation would be recommended for those with more than 50% airway obstruction. In children, endotracheal intubation is often

recommended because laryngoscopy in children has provoked airway obstruction to a much greater degree than in adults, and increased risk of mortality has been demonstrated in some series in children when the airway is managed expectantly.

45. The answer is C.

(Chap. 51) This patient has subacute bacterial endocarditis caused by infection with one of the HACEK organisms. The HACEK organisms (*Haemophilus, Aggregatibacter, Cardiobacterium, Eikenella,* and *Kingella* spp.) are gram-negative rods that reside in the oral cavity. They are responsible for about 3% of cases of infective endocarditis in most series. They are the most common cause of gram-negative endocarditis in nondrug abusers. Most patients have a history of poor dentition or a recent dental procedure. Often, patients are initially diagnosed with culture-negative endocarditis because these organisms may be slow growing and fastidious. Cultures must be specified for prolonged culture of fastidious organisms. HACEK endocarditis is typically subacute, and the risk of embolic phenomena to the bone, skin, kidneys, and vasculature is high. Vegetations are seen on approximately 85% of transthoracic echocardiograms. Cure rates are excellent with antibiotics alone; native valves require 4 weeks, and prosthetic valves require 6 weeks of treatment. Ceftriaxone is the treatment of choice, with ampicillin–gentamicin as an alternative. Sensitivities may be delayed because of the organisms' slow growth.

46. The answer is C.

(Chap. 52) *Legionella* is an intracellular pathogen that enters the body through aspiration or direct inhalation. Numerous prospective studies have found it is one of the four most common causes of community-acquired pneumonia with *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Chlamydia pneumoniae* accounting for 2% to 9% of cases. Postoperative patients are at risk because of an increased risk of aspiration. Cell-mediated immunity is the primary host defense against *Legionella* spp., and patients with HIV or those who take glucocorticoids are at risk based on their depressed cell-mediated immune function. Alveolar macrophages phagocytose *Legionella* spp. Smokers and those with chronic lung disease are at risk given their poor local immune responses and decreased ability for widespread phagocytosis. Neutrophils play a comparatively small role in host defense against *Legionella* spp., and persons with neutropenia are not predisposed to *Legionella* infection.

47. The answer is C.

(Chap. 53) Pertussis caused by the gram-negative bacteria *Bordetella pertussis*, is an upper respiratory infection characterized by a violent cough. Its prevalence has been dramatically reduced, but not eliminated, by widespread infant vaccination. It causes an extremely morbid and often mortal disease in infants younger than 6 months old, particularly in the developing world. The prevalence appears to be increasing in young adults and adolescents because of waning immunity. Some are recommending booster vaccination after 10 years. *B. pertussis* is also a growing pathogen in patients with chronic obstructive pulmonary disease. The clinical manifestations typically include a persistent, episodic cough developing a few days after a cold-like upper respiratory infection. The cough may become persistent. It often wakes the patient from sleep and results in posttussive vomiting. An audible whoop is only present in fewer than half of cases. Diagnosis is with nasopharyngeal culture or DNA probe testing. There is no urinary antigen testing available. The goal of antibiotic therapy is to eradicate the organism from the nasopharynx. It does not alter the clinical course. Macrolide antibiotics are the treatment of choice. Pneumonia is uncommon with *B. pertussis*. Cold agglutinins may be positive in infection with *Mycoplasma pneumoniae*, which is on the differential diagnosis of *B. pertussis*.

48. The answer is A.

(Chap. 54) Shiga toxic and enterohemorrhagic strains of *Escherichia coli* (STEC/EHEC) cause hemorrhagic colitis and hemolytic uremic syndrome (HUS). Several large outbreaks resulting from the consumption of fresh produce (e.g., lettuce, spinach, sprouts) and of undercooked ground beef have received significant attention in the media. O157:H7 is the most prominent serotype, but others have been reported to cause similar disease. The ability of STEC/EHEC to produce Shiga toxin (Stx2 and/or Stx1) or related toxins is a critical factor in the expression of clinical disease. Manure from domesticated ruminant animals in industrialized countries serves as the major reservoir for STEC/EHEC. Ground beef—the most common food source of STEC/EHEC strains—is often contaminated during processing. Low bacterial numbers can transmit disease in humans, accounting for widespread infection from environmental sources and person-to-person spread. O157:H7 strains are the fourth most commonly reported cause of bacterial diarrhea in the United States (after *Campylobacter*, *Salmonella*, and *Shigella* spp.). STEC/EHEC characteristically causes grossly bloody diarrhea in more than 90% of cases. Significant abdominal pain and fecal leukocytes are common (70% of cases), but fever is not; absence of fever can incorrectly lead to consideration of noninfectious conditions (e.g., intussusception and inflammatory or ischemic bowel disease). STEC/EHEC disease is usually self-limited, lasting 5 to 10 days. HUS may develop in very young or elderly patients within 2 weeks of diarrhea. It is estimated that it occurs in 2% to 8% of cases of STEC/EHEC and that more than 50% of all cases of HUS in the United States and 90% of cases in children are caused by STEC/EHEC. Antibiotic therapy of STEC/EHEC cases of diarrhea should be avoided because antibiotics may increase the likelihood of developing HUS.

49. The answer is E.

(Chap. 55) Infections with *Acinetobacter* spp. are a growing cause of hospital-acquired infections worldwide. Surveillance data from Australia and Asia suggest

that infections are common, and there are reports of community-acquired *Acinetobacter* infection. They typically infect patients receiving long-term care in intensive care units by causing ventilator-associated pneumonia, bloodstream infections, or urinary tract infections. They are particularly of concern because of their propensity to develop multidrug (or pan-drug) resistance and their ability to colonize units because of health care worker transmission. *A. baumannii* is the most common isolate and develops drug resistance avidly. Many strains are currently resistant to carbapenems (imipenem, meropenem). Last-line agents such as colistin, polymixin A, and tigecycline are often the only available therapeutic options. Tigecycline has been used for pneumonia caused by carbapenem-resistant strains but is not thought to be efficacious in bloodstream infection because usual dosing does not achieve therapeutic levels against *Acinetobacter* spp.

50. The answer is B.

(Chap. 56) Helicobacter pylori is thought to colonize about 50% (30% in developed countries and >80% in developing countries) of the world's population. The organism induces a direct tissue response in the stomach, with evidence of mononuclear and polymorphonuclear infiltrates in all of those with colonization regardless of whether or not symptoms are present. Gastric ulceration and adenocarcinoma of the stomach arise in association with this gastritis. MALT is specific to *H. pylori* infection and because of prolonged B-cell activation in the stomach. Although *H. pylori* does not directly infect the intestine, it does diminish somatostatin production, indirectly contributing to the development of duodenal ulcers. Gastroesophageal reflux disease is not caused by *H. pylori* colonization. Recent studies have demonstrated that colonization by some strains of *H. pylori* may be protective for the development of adenocarcinoma of the esophagus and premalignant lesions such as Barrett's esophagus (odds ratio, 0.2–0.6).

51. The answer is A.

(Chap. 57) Ecthyma gangrenosum is a disseminated collection of geographic, painful, reddish, maculopapular lesions that rapidly progress from pink to purple and finally to a black, dry necrosis. They are teeming with causative bacteria. In reviews on ecthyma, *Pseudomonas aeruginosa* is the most common isolate from blood and skin lesions. However, many organisms can cause this foreboding rash. Neutropenic patients and AIDS patients are at highest risk, but diabetics and intensive care unit (ICU) patients are also affected. Pseudomonal sepsis is severe with a high mortality rate. Its presentation is otherwise difficult to discern from other severe sepsis syndromes, with hypothermia, fever, hypotension, organ damage, encephalopathy, bandemia, and shock being common findings. Although antibiotic use, severe burns, and long ICU stays increase the risk for *Pseudomonas* infection, these exposures are also risk factors for other bacterial infections, many of which also carry daunting resistance profiles. Because of *P. aeruginosa*'s propensity for multidrug resistance, two agents (usually an antipseudomonal β-lactam plus an aminoglycoside or ciprofloxacin) are warranted until culture data return confirming sensitivity to one or both agents. At this point, the choice to narrow to one antibiotic or not is still debated and is largely physician preference.

52. The answer is E.

(Chap. 58) Salmonella enteritidis is one of the causes of nontyphoidal salmonellosis (NTS) along with *Salmonella typhimurium* and other strains. Enteric (typhoid) fever is caused by *Salmonella typhi* or *Salmonella paratyphi*. Recent cases of gastroenteritis caused by NTS have been associated with undercooked or raw eggs. In contrast to *S. typhi* and *S. paratyphi*, which only have human reservoirs, the NTS can colonize livestock accounting for outbreaks related to contaminated water (fresh produce, undercooked ground meat, dairy products). The gastroenteritis caused by NTS is indistinguishable clinically for other enteric pathogens. The diarrhea is nonbloody and may be copious. The disease is typically self-limited in healthy hosts, and antibiotic therapy is not recommended because it does not change the course of disease and promotes resistance. Therapy may be necessary for neonates or debilitated elderly patients who are more likely to develop bacteremia. Bacteremia occurs in fewer than 10% of cases. Metastatic infections of bone, joint, and endovascular devices may occur. There is no vaccine for NTS. Oral and parenteral vaccines for *S. typhi* are available.

53. The answer is D.

(Chap. 59) Shigellosis remains a cause of dysentery in the developing world and sporadic cases caused by fecal–oral contamination occur in the developing and developed world. The human intestinal tract is the most prevalent reservoir for the bacteria. Clinical illness from *Shigella* infection can be caused by a very small inoculum. Shigellosis typically evolves through four phases: incubation, watery diarrhea, dysentery, and the postinfectious phase. The incubation period is usually 1 to 4 days, and the dysentery follows within hours to days. The dysentery syndrome is indistinguishable from other invasive enteropathogens (including *Campylobacter* spp.), and inflammatory bowel disease is also in the differential diagnosis. Because the organism is enteroinvasive, antibiotic therapy is indicated. Ciprofloxacin is generally recommended unless there is no or proven resistance. Ceftriaxone, azithromycin, pivmecillinam, and some recent quinolones are also effective. *Shigella* infection typically does not cause life-threatening dehydration. Antimotility agents are not recommended because they are thought to prolong the systemic symptoms and may increase the risk of toxic megacolon and hemolytic uremic syndrome. There is currently no commercially available vaccine for *Shigella* infection.

54. The answer is A.

(Chap. 60) Campylobacter spp. are motile, curved gram-negative rods. The principal diarrheal pathogen is *Campylobacter jejuni*. This organism is found in the gastrointestinal tract of many animals used for food production and is usually transmitted to humans in raw

or undercooked food products or through direct contact with infected animals. More than half of cases are caused by insufficiently cooked contaminated poultry. *Campylobacter* infection a common cause of diarrheal disease in the United States. The illness usually occurs within 2 to 4 days after exposure to the organism in food or water. Biopsy of an affected patient's jejunum, ileum, or colon reveals findings indistinguishable from those of Crohn's disease and ulcerative colitis. Although the diarrheal illness is usually self-limited, it may be associated with constitutional symptoms, lasts more than 1 week, and recurs in 5% to 10% of untreated patients. Complications include pancreatitis, cystitis, arthritis, meningitis, and Guillain-Barré syndrome. The symptoms of *Campylobacter* enteritis are similar to those resulting from infection with *Salmonella typhi, Shigella* leukocytes. The diagnosis is made by isolating *Campylobacter* organisms from the stool, which requires selective media. *Escherichia coli* (enterotoxigenic), Norwalk agent, and rotavirus are generally not associated with the finding of fecal leukocytes. About 5% to 10% of untreated patients with *Campylobacter* enteritis develop recurrences that may be clinically and pathologically confused with inflammatory bowel disease.

55. The answer is A.

(Chap. 60) As is true with all acute diarrheal diseases, adequate volume resuscitation is central to treatment. Many patients with mild *Campylobacter* enteritis will resolve spontaneously, and not all patients clearly benefit from therapy. In the presence of high or persistent fever, bloody diarrhea, severe diarrhea, worsening symptoms, or symptoms persisting for more than 1 week, antibiotics are recommended. A 5- to 7-day course of erythromycin, azithromycin (and other macrolides), or ciprofloxacin is effective. Drug resistance to flouroquinolones and tetracycline is increasing. Antimotility agents are not recommended because they have been associated with the development of serious complications, including toxic megacolon and hemolytic uremic syndrome. Tinidazole and metronidazole are used to treat a variety of nonbacterial diarrhea syndromes, including giardiasis and amoebiasis. Metronidazole is also used for *Clostridium difficile*–associated colitis.

56. The answer is B.

(Chap. 61) Cholera remains a worldwide problem with sporadic cases usually related to contact with fecally contaminated water or seafood. Humans are the only known reservoir of *Vibrio cholerae*. Most cases are reported in Africa or Asia. After a century, cholera returned to Haiti after recent natural disasters and breakdown of public health measures. The watery diarrhea of cholera is mediated by a specific cholera toxin that binds to small intestine epithelium to cause profuse fluid secretion. The diarrhea of cholera is painless, nonbloody, and watery with mucus and few inflammatory cells. The term "rice-water" diarrhea refers to the appearance of water after soaking rice. Morbidity and mortality from cholera are from profound volume depletion. Rehydration is essential to therapy. Major improvements in care came from the development of oral rehydration solutions that take advantage of glucose–sodium co-transport in the small intestine. These solutions allowed effective rehydration in resource limited settings where intravenous rehydration was not practical. Diagnosis is by culture or point-of-care antigen detection dipstick assay. Antibiotics are not necessary for cure, but they diminish the duration and volume of fluid loss and hasten the clearance of the organism from stool. A single dose of doxycycline is effective in adults in areas where there is not resistance. Ciprofloxacin or azithromycin may be alternatives.

57. The answer is E.

(Chap. 63) The most likely infecting organism in this patient is *Francisella tularensis*. Gentamicin is the antibiotic of choice for the treatment of tularemia. Fluoroquinolones have shown in vitro activity against *F. tularensis* and have successfully been used in a few cases of tularemia. Currently, however, it cannot be recommended as first-line therapy because data are limited regarding its efficacy relative to gentamicin, but it can be considered if an individual is unable to tolerate gentamicin. To date, there have been no clinical trials of fluoroquinolones to definitively demonstrate equivalency with gentamicin. Third-generation cephalosporins have in vitro activity against *F. tularensis*. However, use of ceftriaxone in children with tularemia resulted in almost universal failure. Likewise, tetracycline and chloramphenicol also have limited usefulness with a higher relapse rate (up to 20%) compared with gentamicin. *F. tularensis* is a small gram-negative, pleomorphic bacillus that is found both intra- and extracellularly. It is found in mud, water, and decaying animal carcasses, and ticks and wild rabbits are the sources for most human infections in the southeastern United States and Rocky Mountains. In western states, tabanid flies are the most common vectors. The organisms usually enter the skin through the bite of a tick or through an abrasion. On further questioning, the patient reported that during the camping trip, he was primarily responsible for skinning the animals and preparing dinner. He did sustain a small cut on his right hand at the site where the ulceration is apparent. The most common clinical manifestations of *F. tularensis* are ulceroglandular and glandular disease, accounting for 75% to 85% of cases. The ulcer appears at the site of entry of the bacteria and lasts for 1 to 3 weeks and may develop a black eschar at the base. The draining lymph nodes become enlarged and fluctuant. They may drain spontaneously. In a small percentage of patients, the disease becomes systemically spread, as is apparent in this case, with pneumonia, fevers, and sepsis syndrome. When this occurs, the mortality rate approaches 30% if untreated. However, with appropriate antibiotic therapy, the prognosis is very good. Diagnosis requires a high clinical suspicion because demonstration of the organism is difficult. It rarely seen on Gram stain because the organisms stain weakly and are so small that they are difficult to distinguish from background material. On polychromatically stained tissue, they may be seen both intra- and extracellularly, singly or in clumps.

Moreover, *F. tularensis* is a difficult organism to culture and requires cysteine-glucose–blood agar. However, most laboratories do not attempt to culture the organism because of the risk of infection in laboratory workers, requiring biosafety level 2 practices. Usually the diagnosis is confirmed by agglutination testing with titers above 1:160 confirming diagnosis.

58 and 59. The answers are E and B, respectively.
(Chap. 64) This patient has a classic presentation of bubonic plague caused by *Yersinia pestis*. Plague is transmitted to humans from rodents via flea bites. The clinical manifestations include bubonic (most common, 80–95% of cases), septicemic (bacteremia without a bubo), primary pneumonic, and secondary pneumonic. The untreated mortality rate is up to 20%, with higher rates for septicemic and pneumonic presentations. Most cases in the United States occur in the Four Corners region or in the border zone of northern California, southern Oregon, and western Nevada. The presenting bubo in bubonic plague is usually near the inciting flea bite. The differential diagnosis includes streptococcal or staphylococcal infection, tularemia, cat-scratch disease, tick typhus, infectious mononucleosis, and lymphatic filariasis. These infections do not progress as rapidly as plague, are not as painful, and are associated with visible cellulitis or ascending lymphangitis, which are absent in plague. The organisms may be visualized on bubo aspirate. The gram-negative coccobacillus *Y. pestis* is characteristically bipolar on Wright's stain. *Bartonella* and *Rickettsia* are generally not visible on Gram staining. Traditionally, streptomycin was the first-line treatment, but because of fewer side effects, gentamicin is currently recommended. Fluoroquinolones have in vitro activity and have been reported effective in case reports. They would likely be administered in the event of pneumonic plague as a bioterrorism event.

60. The answer is A.
(Chap. 65) This patient has culture-negative endocarditis, a rare entity defined as clinical evidence of infectious endocarditis in the absence of positive blood cultures. In this case, evidence for subacute bacterial endocarditis includes valvular regurgitation; an aortic valve vegetation; and embolic phenomena on the extremities, spleen, and kidneys. A common reason for negative blood culture results is prior antibiotics. In the absence of this, the two most common pathogens (both of which are technically difficult to isolate in blood culture bottles) are Q fever, or *Coxiella burnetii* (typically associated with close contact with livestock), and *Bartonella* spp. In this case, the patient's homelessness and body louse infestation are clues for *Bartonella quintana* infection. Diagnosis is made by blood culture about 25% of the time. Otherwise, direct polymerase chain reaction of valvular tissue, if available, or acute and convalescent serologies are diagnostic options. Empirical therapy for culture-negative endocarditis usually includes ceftriaxone and gentamicin with or without doxycycline. For confirmed *Bartonella* endocarditis, optimal therapy is gentamicin plus doxycycline. Epstein-Barr virus and HIV do not cause endocarditis. A peripheral blood smear would not be diagnostic.

61. The answer is A.
(Chap. 66) Donovanosis is caused by the intracellular organism *Calymmatobacterium granulomatis* and most often presents as a painless erythematous genital ulceration after a 1- to 4-week incubation period. However, incubation periods can be as long as 1 year. The infection is predominantly sexually transmitted, and autoinoculation can lead to formation of new lesions by contact with adjacent infected skin. Typically, the lesion is painless but bleeds easily. Complications include phimosis in men and pseudo-elephantiasis of the labia in women. If the infection is untreated, it can lead to progressive destruction of the penis or other organs. Diagnosis is made by demonstration of Donovan bodies within large mononuclear cells on smears from the lesion. *Donovan bodies* refers to the appearance of multiple intracellular organisms within the cytoplasm of mononuclear cells. These organisms are bipolar and have an appearance similar to a safety pin. On histologic examination, there is an increase in the number of plasma cells with few neutrophils; additionally, epithelial hyperplasia is present and can resemble neoplasia. A variety of antibiotics can be used to treat donovanosis, including macrolides, tetracyclines, trimethoprim–sulfamethoxazole, and chloramphenicol. Treatment should be continued until the lesion has healed, often requiring 5 or more weeks of treatment. All of the choices listed in the question are in the differential diagnosis of penile ulcerations. Lymphogranuloma venereum is endemic in the Caribbean. The ulcer of primary infection heals spontaneously, and the second phase of the infection results in markedly enlarged inguinal lymphadenopathy, which may drain spontaneously. *Haemophilus ducreyi* results in painful genital ulcerations, and the organism can be cultured from the lesion. The painless ulcerations of cutaneous leishmaniasis can appear similarly to those of donovanosis but usually occur on exposed skin. Histologic determination of intracellular parasites can distinguish leishmaniasis definitively from donovanosis. Finally, it is unlikely that the patient has syphilis in the setting of a negative rapid plasma reagin test result, and the histology is inconsistent with this diagnosis.

62. The answer is D.
(Chap. 68) The patient presents with symptoms suggestive of osteonecrosis of her jaw possibly caused by bisphosphonate use. Additionally, her jaw pain has progressed and now appears to be infected. *Actinomyces* is a classic oral organism with a propensity to infect the jaw, particularly when the bone is abnormal, usually because of radiation or osteonecrosis. Osteonecrosis of the jaw caused by bisphosphonates is an increasingly recognized risk factor for *Actinomyces* infection. Frequently, the soft tissue swelling is confused for either parotitis or a cancerous lesion. *Actinomyces* spp. frequently form fistulous tracts, which provide an opportunity to examine the secretions and identify either the organism itself (less common) or sulfur granules. Sulfur granules are an in vivo concretion of *Actinomyces* bacteria,

calcium phosphate, and host material. Gram stain of *Actinomyces* infection shows intensely positive staining at the center with branching rods at the periphery. Auer rods are found in acute promyelocytic leukemia. Although head and neck cancer is in the differential diagnosis, the acuity of the presentation and fever make this less likely. Weakly acid-fast branching filaments are found in nocardial infection, which is unlikely to involve the head and neck, although both organisms frequently cause pulmonary infiltrates. Although parotitis with obstruction caused by sialolith is possible, the symptoms are in the jaw and diffuse, not specifically involving the parotid gland, thus making sialolith less likely.

63. The answer is C.

(Chap. 68) Therapy for *Actinomyces* requires a long course of antibiotics even though the organism is very sensitive to penicillin therapy. This is presumed to be attributable to the difficulty of using antibiotics to penetrate the thick-walled masses and sulfur granules. Current recommendations are for penicillin IV for 2 to 6 weeks followed by oral therapy for a total of 6 to 12 months. Surgery should be reserved for patients who are not responsive to medical therapy.

64. The answer is B.

(Chap. 69) The major reservoirs in the human body for anaerobic bacteria are the mouth, lower gastrointestinal tract, skin, and female genital tract. Generally, anaerobic infections occur proximal to these sites after the normal barrier (i.e., skin or mucous membrane) is disrupted. Thus, common infections resulting from these organisms are abdominal or lung abscess, periodontal infection, gynecologic infections such as bacterial vaginosis, and deep tissue infection. Properly obtained cultures in these circumstances generally grow a mixed population of anaerobes typical of the microenvironment of the original reservoir.

65. The answer is B.

(Chap. 70) The aim of treatment of latent tuberculosis is to prevent development of active disease, and the tuberculin skin test (purified protein derivative [PPD]) is the most common means of identifying cases of latent tuberculosis in high-risk groups. To perform a tuberculin skin test, 5 tuberculin units of PPD are placed subcutaneously in the forearm. The degree of induration is determined after 48 to 72 hours. Erythema only does not count as a positive reaction to the PPD. The size of the reaction to the tuberculin skin test determines whether individuals should receive treatment for latent tuberculosis. In general, individuals in low-risk groups should not be tested. However, if tested, a reaction larger than 15 mm is required to be considered as positive. School teachers are considered low-risk individuals. Thus, the reaction of 7 mm is not a positive result, and treatment is not required. A size of 10 mm or larger is considered positive in individuals who have been infected within 2 years or those with high-risk medical conditions. The individual working in an area where tuberculosis is endemic has tested newly positive by skin testing and should be treated as a newly infected individual. High-risk medical conditions for which treatment of latent tuberculosis is recommended include diabetes mellitus, injection drug use, end-stage renal disease, rapid weight loss, and hematologic disorders. PPD reactions 5 mm or larger are considered positive for latent tuberculosis in individuals with fibrotic lesions on chest radiographs, those with close contact with an infected person, and those with HIV or who are otherwise immunosuppressed. There are two situations in which treatment for latent tuberculosis is recommended regardless of the results on skin testing. First, infants and children who have had close contact with an actively infected person should be treated. After 2 months of therapy, a skin test should be performed. Treatment can be discontinued if the skin test result remains negative at that time. Also, individuals who are HIV positive and have had close contact with an infected person should be treated regardless of their skin test results.

66. The answer is B.

(Chap. 72) The chest computed tomography shows a "tree-in-bud" pattern in the peripheral right lung and bilateral bronchiectasis. This pattern is consistent with bronchiolar inflammation and is typical of nontuberculous mycobacterial infection. Nontuberculous mycobacteria, such as the *Mycobacterium avium* complex (MAC), may cause chronic pulmonary infections in normal hosts and those with underlying pulmonary disease immunosuppression. In normal hosts, bronchiectasis is the most common underlying condition. In immunocompetent patients without underlying disease, treatment of pulmonary infection due to MAC is considered on an individual basis based on symptoms, radiographic findings, and bacteriology. Treatment should be initiated in the presence of progressive pulmonary disease or symptoms. In patients without any prior lung disease, no structural lung disease, and who do not demonstrate progressive clinical decline, *M. avium* pulmonary infection can be managed conservatively. Patients with underlying lung disease, such as chronic obstructive pulmonary disease, bronchiectasis, or cystic fibrosis, or those with a history of pulmonary tuberculosis should receive antibiotics. This patient has both clinical and historic reasons for antibiotic treatment. The appropriate regimen in this case is clarithromycin (or azithromycin), ethambutol, and rifampin (or rifabutin) for 12 months after culture sterilization (typically 18 months). The combination of pyrazinamide, isoniazid, rifampin, and ethambutol is effective treatment for *M. tuberculosis* infection, which is not present here. Other drugs with activity against MAC include intravenous and aerosolized aminoglycosides, fluoroquinolones, and clofazimine.

67. The answer is C.

(Chap. 73) Pyrazinamide (PZA) is the first-line treatment for *Mycobacterium tuberculosis*. Addition of PZA for 2 months to isoniazid and rifampin allows the total duration of treatment to be shortened from 9 months to 6 months. PZA has no utility in the treatment of nontuberculous mycobacteria. Ethambutol has no serious drug interactions, but patients must be closely monitored

for optic neuritis, which may manifest with decreased visual acuity, central scotoma, or difficulty seeing green (or red). All patients initiating therapy with ethambutol should have a visual and ophthalmologic examination at baseline. In the United States overall, isoniazid resistance remains uncommon. Primary isoniazid resistance is more common in patients with tuberculosis born outside the United States. Rifampin is a potent inducer of cytochrome P450 system and has numerous drug interactions. The Centers for Disease Control and Prevention has guidelines for managing antituberculosis drug interactions including rifampin. Rifabutin is a less potent inducer of hepatic cytochromes. Rifabutin is recommended for HIV-infected patients who are on antiretroviral therapy with protease inhibitors or non-nucleoside reverse transcriptase inhibitors (particularly nevirapine) in place of rifampin.

68. The answer is E.

(Chap. 74) Neurosyphilis has generally been thought to be a late complication of syphilis infection, but this is now known to be inaccurate. Within weeks after infection, the central nervous system is invaded with treponemal organisms. The vast majority of cases are asymptomatic. Abnormal protein levels within the cerebrospinal fluid (CSF) or positive CSF Venereal Disease Research Laboratory (VDRL) test can be seen in up to 40% of individuals with primary or secondary syphilis and 25% of cases of latent syphilis. In symptomatic cases, neurosyphilis can have a variety of manifestations that are typically considered in three broad categories: meningeal, meningovascular, and parenchymal syphilis. Meningeal syphilis is dominated by headache, neck stiffness, and cranial nerve abnormalities. Meningovascular syphilis has signs of meningitis but also can include a vasculitis complicated by stroke. Parenchymal syphilis does indeed represent a late manifestation of disease. Changes in personality, dementia, Argyll Robertson pupils, and paresis are typical findings.

It can be difficult to determine which patients with syphilis required a lumbar puncture to assess for central nervous system involvement of the disease. However, it is quite important because the treatment of neurosyphilis requires 14 days of treatment with intravenous penicillin. Clearly, any patient with a positive test result for syphilis with concerning neurologic symptoms should undergo a lumbar puncture. Some experts also recommend lumbar puncture in all patients with syphilis who are HIV positive. However, this is controversial with others recommending lumbar puncture only if the CD4 count is less than 350/μL. Other instances in which a lumbar puncture is recommended is in the setting of a very high titer rapid plasma reagin (RPR) or VDRL (>1:32) or failure of the RPR or VDRL to fall by a factor of 4 after appropriate treatment. Thus, all of the patients presented would be advised to undergo a lumbar puncture.

69. The answer is E.

(Chap. 76) The patient has Weil's syndrome caused by infection with *Leptospira interrogans*. *L. interrogans* is a spirochete that is acquired through contact with an infected animal. Species that commonly transmit the organism to human include rats, dogs, cattle, and pigs. The organism is excreted in urine and can survive in water for months. For a human to become infected, susceptible individuals typically have indirect contact with infected animal urine through contaminated water sources and other wet environments. Tropical human environments, rodent infestations, and large populations of infected dogs are also important for transmission. Leptospirosis occurs only sporadically in the United States with most cases occurring in Hawaii.

Clinically, leptospirosis can take many manifestations, including subclinical infection, a self-limited febrile illness, and Weil's disease. Leptospirosis is classically a biphasic disease. After the acute exposure, fevers last for 3 to 10 days. During this time, the patient will complain of malaise and myalgias. Conjunctival suffusion (dilated conjunctival blood vessels without drainage) is common as are pharyngeal edema, muscle tenderness, and crackles on lung examination. Weil's disease is the most serious form of leptospirosis and occurs during the immune phase of the disease. Clinically, severe jaundice in the absence of hepatocellular injury is a striking feature of the disease. In addition, acute kidney injury, hypotension, and diffuse hemorrhage are common. The lungs are the most common site of hemorrhage, but the gastrointestinal tract, retroperitoneum, pericardium, and brain can also be affected. The diagnosis is most often made by serologic assays because culture of the organism takes several weeks. Treatment of leptospirosis is typically intravenous penicillin, ceftriaxone, or cefotaxime.

Acute alcoholic hepatitis can produce fevers and malaise, but a more marked increase in liver enzymes would be expected with the aspartate aminotransferase elevated out of proportion to alanine aminotransferase. Disseminated intravascular coagulation in the setting of an infection would demonstrate abnormalities of coagulation, which were not present here. Microscopic polyangiitis is a small to medium vessel vasculitis that could cause pulmonary hemorrhage and acute renal failure. Rarely, the liver can be affected as well. However, the urinalysis does not suggest acute glomerulonephritis because no casts or red blood cells are present. Rat-bite fever causes intermittent fevers, polyarthritis, and a nonspecific rash.

70. The answer is E.

(Chap. 77) Tickborne relapsing fever (TBRF) is a spirochetal infection caused by any one of several species of *Borrelia*. The Borrelia are small spirochetes that are transmitted to humans through the bite of an infected tick. The tick that transmits TBRF is *Ornithodoros* spp., which feeds on a variety of squirrels and chipmunks that live near freshwater lakes. TBRF is endemic in several areas of the western United States, southern British Columbia, the Mediterranean, Africa, and the plateau regions of Mexico and South and Central America. In the United States, TBRF is rarely reported east of Montana, Colorado, New Mexico, and Texas. The general areas where TBRF is contracted are the forested and mountainous regions

of these states, although it can be contracted in the limestone caves of central Texas. Only 13 counties in the entire United States have had 50% of all cases reported in the United States.

After an incubation period of about 7 days, an individual infected with TBRF will begin to experience fevers that can reach as high as 106.7°F (41.5°C). Symptoms that accompany the fevers include myalgias, chills, nausea, vomiting, abdominal pain, confusion, and arthralgias. The average duration of a first episode is 3 days. If the disease is not recognized and treated, the fever will recur after a period of about 7 days. The duration of fevers is typically shorter with repeated episodes but will continue to relapse about every 7 days until the disease is treated. Diagnosis of TBRF requires detection of the spirochetes in the blood during a febrile episode or serologic conversion. TBRF is typically treated with doxycycline or erythromycin for 7 to 10 days.

The other options should be on the differential diagnosis for an individual with recurrent and relapsing fevers. In addition, this list would also include yellow fever, dengue fever, malaria, rat-bite fever, and infection with echovirus 9 or *Bartonella* spp. Brucellosis is a bacterial infection most commonly transmitted by ingestion of contaminated milk or cheese, which this patient did not report. Colorado tick fever is a viral infection transmitted by the bite of a *Dermacentor andersoni* tick that is endemic in the western areas of the United States. The pattern of fever is slightly different from TBRF because the cycle is 2 to 3 days of fever followed by 2 to 3 days of normal temperature. Leptospirosis often has two phases of fever. The first occurs during the acute infection, lasting 7 to 10 days. In some individuals, the fever recurs 3 to 10 days later during the immune phase. The typical route of infection is prolonged contact with infected rodent droppings in wet environments. Lymphocytic choriomeningitis is a viral infection that is most commonly transmitted via contact with urine or droppings from common house mice. This illness usually has two phases as well. During the first phase that occurs 8 to 13 days after exposure, an individual will experience fevers, malaise, and myalgias. In the second phase of illness, symptoms more typical of meningitis occur.

71. The answer is A.

(Chap. 78) Lyme serology tests should be done only in patients with an intermediate pretest probability of having Lyme disease. The presence of erythema migrans in both patient B and patient E is diagnostic of Lyme disease in the correct epidemiologic context. The diagnosis is entirely clinical. Patient C's clinical course sounds more consistent with systemic lupus erythematosus, and initial laboratory evaluation should focus on this diagnosis. Patients with chronic fatigue, myalgias, and cognitive change are occasionally concerned about Lyme disease as a potential etiology for their symptoms. However, the pretest probability of Lyme is low in these patients, assuming the absence of antecedent erythema migrans, and a positive serology is unlikely to be a true positive test result. Lyme arthritis typically occurs months after the initial infection and occurs in about 60% of untreated patients. The typical attack is large joint, oligoarticular, and intermittent, lasting weeks at a time. Oligoarticular arthritis carries a broad differential diagnosis, including sarcoidosis, spondyloarthropathy, rheumatoid arthritis, psoriatic arthritis, and Lyme disease. Lyme serology is appropriate in this situation. Patients with Lyme arthritis usually have the highest IgG antibody responses seen in the infection.

72. The answer is B.

(Chap. 79) This patient demonstrates evidence of Rocky Mountain spotted fever (RMSF), which has progressed over the course of several days because of a lack of initial recognition and treatment. RMSF is caused by infection with *Rickettsia rickettsii* and is transmitted through the bite of an infected dog tick. RMSF has been diagnosed in 47 states and is most commonly diagnosed in the south-central and southeastern states. Symptoms typically begin about 1 week after inoculation. The initial symptoms are vague and are easily misdiagnosed as a viral infection with fever, myalgias, malaise, and headache predominating. Although almost all patients with RMSF develop a rash during the course of the illness, rash is present in only 14% on the first day, and the lack of rash in a patient who is at risk for RMSF should not delay treatment. By day 3, 49% of individuals develop a rash. The rash initially is a macular rash that begins on the wrists and ankles and progresses to involve the extremities and trunk. Over time, hemorrhaging into the macules occurs and has a petechial appearance. As the illness progresses, respiratory failure and central nervous system (CNS) manifestations can develop. Encephalitis, presenting as confusion and lethargy, is present about 25% of the time. Other manifestations can include renal failure, hepatic injury, and anemia. Treatment for RMSF is doxycycline 100 mg twice daily. It can be administered orally or intravenously. Because this patient shows progressive disease with CNS involvement, hospital admission for treatment is warranted to monitor for further decompensation in the patient's condition. If the patient were more clinically stable, outpatient therapy would be appropriate. Treatment should not be delayed while awaiting confirmatory serologic testing because untreated cases of RMSF are fatal, usually within 8 to 15 days. Treatment with any sulfa drugs should be avoided because these drugs are ineffective and can worsen the disease course. Intravenous ceftriaxone and vancomycin are appropriate agents for bacterial meningitis. Although this could be a consideration in this patient with fever, confusion, and a rash, meningococcemia would present with a more fulminant course, and the patient's risk factor (hiking in an endemic area) would make RMSF more likely.

73. The answer is D.

(Chap. 80) This patient presents with symptoms of atypical pneumonia, and the most common causative organism for atypical pneumonia is *Mycoplasma pneumoniae*. Pneumonia caused by *Mycoplasma* occurs worldwide without a specific seasonal preference. *M. pneumoniae* is a highly infectious

organism and is spread by respiratory droplets. It is estimated that about 80% of individuals within the same family will experience the infection after one person becomes infected. Outbreaks of *M. pneumoniae* also occur in institutional settings, including boarding schools and military bases. Clinical manifestations of *M. pneumoniae* typically are pharyngitis, tracheobronchitis, wheezing, or nonspecific upper respiratory syndrome. Although many commonly believe the organism is associated with otitis media and bullous myringitis, there are little clinical data to support this assertion. Atypical pneumonia occurs in fewer than 15% of individuals infected with *M. pneumoniae*. The onset of pneumonia typically is gradual with preceding symptoms of upper respiratory infection. Cough is present, and often extensive, but nonproductive. Examination typically demonstrates wheezing or rales in about 80% of patients. The most common radiographic findings are bilateral peribronchial pneumonia with increased interstitial markings. Lobar consolidation is uncommon. Definitive diagnosis requires demonstration of *M. pneumoniae* nucleic acids on polymerase chain reaction of respiratory secretions or performance of serologic testing. Often, however, the patients are treating empirically without obtaining definitive diagnosis.

Other causes of atypical pneumonia are *Chlamydia pneumoniae* and *Legionella pneumophila. C. pneumoniae* more commonly causes pneumonia in school-aged children, although adults can become re-infected. *Legionella* pneumonia is often associated with outbreaks of disease caused by contaminated water supplies. Individuals with *Legionella* pneumonia can become quite sick and develop respiratory failure. Adenovirus is a common viral cause of upper respiratory tract infection and has been associated with outbreaks of pneumonia among military recruits.

Streptococcus pneumoniae is the most common cause of community-acquired pneumonia, but it typically presents with lobar or segmental consolidation.

74. The answer is D.

(Chap. 81) Urethritis in men causes dysuria with or without discharge, usually without frequency. The most common causes of urethritis in men include *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Mycoplasma genitalium*, *Ureaplasma urealyticum*, *Trichomonas vaginalis*, herpes simplex virus, and possibly adenovirus. Until recently, *C. trachomatis* accounted for 30% to 40% of cases; however, this number may be decreasing. Recent studies suggest that *M. genitalium* is a common cause of nonchlamydial cases. Currently, the initial diagnosis of urethritis in men includes specific tests only for *N. gonorrhoeae* and *C. trachomatis*. Tenets of urethral discharge treatment include providing treatment for the most common causes of urethritis with the assumption that the patient may be lost to follow-up. Therefore, prompt empirical treatment for gonorrhea and chlamydial infections with ceftriaxone and azithromycin should be given on the day of presentation to the clinic to the patient, and recent partners should be contacted for treatment. Azithromycin will also be effective for *M. genitalium*. If pus can be milked from the urethra, cultures should be sent for definitive diagnosis and to allow for contact tracing by the health department because both of these are reportable diseases. Urine nucleic acid amplification tests are an acceptable substitute in the absence of pus. It is also critical to provide empirical treatment for at-risk sexual contacts. If symptoms do not respond to the initial empirical therapy, patients should be reevaluated for compliance with therapy, reexposure, and *T. vaginalis* infection.

75. The answer is A.

(Chap. 82) Persistent viral infection is speculated to be pathogenically important in up to 20% of human malignancies. Strong associations based on epidemiology, the presence of viral nucleotides in tumor cells, the transformational ability of viruses on human cells, and animal models have been established. Most hepatocellular carcinoma is thought to be related to chronic infection with hepatitis B or C virus. Most cervical cancer is caused by persistent infection with human papilloma virus type 16 or 18. Epstein-Barr virus plays a role in the development of many B-lymphocyte and epithelial cell malignancies such as Hodgkin's lymphoma, Burkitt's lymphoma, and nasopharyngeal carcinoma. HTLV-1 is associated with a number of T-cell lymphomas and leukemias. KSHV (Kaposi's sarcoma–associated herpesvirus, HHV-8) is associated with Kaposi's sarcoma, pleural effusion lymphoma, and multicentric Castleman's disease. Dengue fever virus, a flavovirus, is the cause of dengue fever and has not been associated with human malignancy.

76. The answer is A.

(Chap. 83) Compared with the large number of antimicrobials directed against bacterial, antiviral therapies have been fewer, and advances in antiviral therapy have come more slowly. However, in recent years, a large number of antiviral medications have been introduced, and it is generally important to be familiar with the common side effects of these medications. Acyclovir and valacyclovir are most commonly used for the treatment of herpes simplex viruses 1 and 2 as well as varicella-zoster virus. Acyclovir is generally a well-tolerated drug, but it can crystallize in the kidneys, leading to acute renal failure if the patient is not properly hydrated. Valacyclovir is an ester of acyclovir that significantly improves the bioavailability of the drug. It is also well tolerated but has been associated with thrombotic thrombocytopenic purpura or hemolytic uremic syndrome when used at high doses. Ganciclovir and foscarnet are medications used to treat cytomegalovirus (CMV) infection. Ganciclovir is primarily given intravenously because the oral bioavailability is less than 10%. Ganciclovir is associated with bone marrow suppression and can cause renal dysfunction. Foscarnet is used for ganciclovir-resistant CMV infections. Renal impairment commonly occurs with its use and causes hypokalemia, hypocalcemia, and hypomagnesemia. Thus, careful monitoring of electrolytes and renal function is warranted with foscarnet use. Amantadine is an antiviral medication used for the treatment of influenza A. It has been demonstrated to have a variety of central nervous system (CNS) side effects, including dizziness, anxiety, insomnia, and difficulty concentrating. Although initially

used as an antiviral drug, the CNS effects of amantadine have led to its use in Parkinson's disease. Interferons are a group of cytokines produced endogenously in response to a variety of pathogens, including viruses and bacteria. Therapeutically, interferons have been studied extensively in the treatment of patients with chronic hepatitis B and C. Interferons lead to a host of systemic effects, including symptoms of a viral syndrome (fevers, chills, fatigue, and myalgias) as well as leukopenia.

77. The answer is E.

(Chap. 84) Primary genital herpes caused by herpes simplex virus-2 (HSV-2) is characterized by fever, headache, malaise, inguinal lymphadenopathy, and diffuse genital lesions of varying stage. The cervix and urethra are usually involved in women. Although both HSV-2 and HSV-1 can involve the genitals, the recurrence rate of HSV-2 is much higher (90% in the first year) than with HSV-1 (55% in the first year). The rate of reactivation for HSV-2 is very high. Acyclovir, valacyclovir, and famciclovir are effective in shortening the duration of symptoms and lesions in genital herpes. Chronic daily therapy can reduce the frequency of recurrences in those with frequent reactivation. Valacyclovir has been shown to reduce transmission of HSV-2 between sexual partners.

78. The answer is C.

(Chap. 85) Recently, a varicella-zoster virus vaccine that has 18 times the viral content of the live-attenuated virus vaccine used in children was shown efficacious for shingles in patients older than 60 years of age. The vaccine decreased the incidence of shingles by 51%, the burden of illness by 61%, and the incidence of postherpetic neuralgia by 66%. The Advisory Committee on Immunization Practices has therefore recommended that persons in this age group be offered this vaccine to reduce the frequency of shingles and the severity of postherpetic neuralgia. Because is it a live virus vaccine, it should not be used in immunocompromised patients.

79 and 80. The answers are C and E, respectively.

(Chap. 86) Epstein-Barr virus (EBV) is the cause of heterophile-positive infectious mononucleosis (IM), which is characterized by fever, sore throat, lymphadenopathy, and atypical lymphocytosis. EBV is also associated with several human tumors, including nasopharyngeal carcinoma, Burkitt's lymphoma, Hodgkin's disease, and (in patients with immunodeficiencies) B-cell lymphoma. EBV infection occurs worldwide, with more than 90% of adults seropositive. In the developing world, most are infected as young children, and IM is uncommon; in the more developed world, most are infected as adolescents or young adults, and IM is more common. The virus is spread by contaminated saliva. Asymptomatic seropositive individuals shed the virus in saliva. In young children, the EBV infection causes mild disease with sore throat. Adolescents and young adults develop IM as described earlier plus often splenomegaly in the second to third week of disease. The white blood cell count is usually elevated and peaks at 10,000 to 20,000/μL during the second or third week of illness. Lymphocytosis is usually demonstrable, with greater than 10% atypical lymphocytes. A morbilliform rash may occur in about 5% of patients as part of the acute illness. Most patients treated with ampicillin develop a macular rash as pictured; this rash is not predictive of future adverse reactions to penicillins. Heterophile antibody testing results will be positive in up to 40% of cases of IM in the first week of illness and up to 90% by the third week. If heterophile antibody testing results are negative, the more expensive testing for immunoglobulin M (IgM) antibodies to viral capsid antigen is more sensitive and specific. IgG antibodies to viral capsid antigen will stay present indefinitely after initial infection and are not useful for diagnosing acute disease. Treatment of uncomplicated IM is with rest, supportive measures, and reassurance. Excessive physical activity should be avoided in the first month to avoid splenic trauma. Prednisone is not indicated and may predispose to secondary infection. It has been used at high dose when IM is complicated by airway compromise caused by pharyngeal swelling, autoimmune hemolytic anemia, severe thrombocytopenia, hemophagocytic syndrome, or other severe complications. Controlled trials have shown that acyclovir has no significant impact on the course of uncomplicated IM. One study showed no benefit for combined prednisone plus acyclovir.

81. The answer is A.

(Chap. 87) Human herpes virus-8 (HHV-8) or Kaposi's sarcoma–associated herpesvirus (KSHV) infects B lymphocytes, macrophages, and both endothelial and epithelial cells) appears to be causally related to Kaposi's sarcoma and a subgroup of AIDS-related B-cell body cavity–based lymphomas (primary effusion lymphomas) and to multicentric Castleman's disease. HHV-8 infection is more common in parts of Africa than in the United States. Primary HHV-8 infection in immunocompetent children may manifest as fever and maculopapular rash. Among individuals with intact immunity, chronic asymptomatic infection is the rule, and neoplastic disorders generally develop only after subsequent immunocompromise. In patients with AIDS, effective antiretroviral therapy has caused improvement in HHV-8–related disease. The virus is sensitive to ganciclovir, foscarnet, and cidofovir, but clinical benefit has not been demonstrated in trials. Invasive cervical carcinoma has been causally implicated with human papillomavirus infection.

82. The answer is B.

(Chap. 88) Molluscum contagiosum is a cutaneous poxvirus infection with a distinctive cutaneous appearance. The rash typically consists of collections of 2- to 5-mm umbilicated papules that can occur anywhere on the body except the palms and soles. It can be accompanied by an eczematous reaction. Molluscum contagiosum is transmitted through close contact, including sexual contact, which causes genital involvement. Unlike other poxvirus lesions, molluscum contagiosum is not associated with inflammation or necrosis. In immunocompetent patients,

the disease is usually self-limited; rash will subside within several months. Systemic involvement does not occur.

83. The answer is D.

(Chap. 89) The most likely diagnosis based on the patient's antecedent illness with a facial rash is parvovirus infection. Arthropathy is uncommon in childhood parvovirus infection but may cause a diffuse symmetric arthritis in up to 50% of adults. This corresponds to the immune phase of illness when immunoglobulin M antibodies are developed. The arthropathy syndrome is more common in women than men. The distribution of affected joints is typically symmetric, most commonly in the small joints of the hands and less commonly the ankles, knees, and wrists. Occasionally the arthritis persists over months and can mimic rheumatoid arthritis. Rheumatoid factor can be detected in serum. Parvovirus B19V infection may trigger rheumatoid disease in some patients and has been associated with juvenile idiopathic arthritis. Reactive arthritis caused by *Chlamydia* spp. or a list of other bacterial pathogens tends to affect large joints such as the sacroiliac joints and spine. It is also sometimes accompanied by uveitis and urethritis. The large number of joints involved with a symmetric distribution argues against crystal or septic arthropathy.

84. The answer is E.

(Chap. 90) The currently available human papillomavirus (HPV) vaccines dramatically reduce rates of infection and disease produced by the HPV types in the vaccines. These products are directed against virus types that cause anogenital tract disease. Both vaccines consist of virus-like particles without any viral nucleic acid and therefore are not active. To date, one quadrivalent product (Gardasil, Merck) containing HPV types 6, 11, 16, and 18 and one bivalent product (Cervarix, GlaxoSmithKline) containing HPV types 16 and 18 have been licensed in the United States. HPV types 6 and 11 cause 90% of anogenital warts, and types 16 and 18 are responsible for 70% of cervical cancers. Efficacy has varied according to the immunologic and virologic characteristics of study populations at baseline and according to the endpoints evaluated. Among study participants who are shown at baseline not to be infected with a specific virus type contained in the vaccine and who adhere to the study protocol, rates of vaccine efficacy regularly exceed 90%, as measured by both infection and disease caused by that specific virus type. Study participants who are already infected at baseline with a specific virus type contained in the vaccine do not benefit from vaccination against that type but may benefit from vaccination against other virus types contained in the vaccine preparation. Thus, the available HPV vaccines have potent prophylactic effects but no therapeutic effects. The Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention has recommended that HPV vaccination be routinely offered to girls and young women 9 to 26 years of age. The quadrivalent vaccine has also been licensed in the United States for use in boys and young men; the ACIP has stated that this product may be used to prevent anogenital warts in boys and young men 9 to 26 years of age. Because 30% of cervical cancers are caused by HPV types not contained in the vaccines, no changes in cervical cancer screening programs are currently recommended. Ongoing studies are examining self-testing for HPV to replace many Pap studies in patients with no evidence of cervical infection. Recent studies implicate HPV in some forms of squamous cell carcinoma of the oropharynx. The utility of the current vaccines in preventing these cancers in not yet known.

85. The answer is C.

(Chap. 91) Acute viral respiratory illnesses are the most common illness worldwide, and a wide variety of viruses have been implicated as causes. Rhinoviruses are the most common virus causing the common cold and are found in about 50% of cases. The second most commonly isolated viruses are coronaviruses. These viruses are more common in the late fall, winter, and early spring, primarily at times when rhinoviruses are less active. Other causes of common cold in children are adenoviruses, whereas these viruses are uncommon in adults with the exception of outbreaks in individuals living in close quarters such as military recruits. Although human respiratory syncytial virus characteristically causes pneumonia and bronchiolitis in young children, the virus can cause common cold and pharyngitis in adults. Parainfluenza virus is another virus classically associated with croup in children, but it causes common cold in adults. Enteroviruses most often cause an undifferentiated febrile illness.

86. The answer is D.

(Chap. 92) The majority of influenza infections are clinically mild and self-limited. Treatment with over-the-counter cough suppressants and analgesics such as acetaminophen is often adequate. Patients who are younger than the age of 18 years are at risk of developing Reye's syndrome if they are exposed to salicylates such as aspirin. The neuraminidase inhibitors oseltamivir and zanamivir have activity against influenza A and B. They can be used within 2 days of symptom onset and have been shown to reduce the duration of symptoms by 1 or 2 days. This patient has had symptoms for more than 48 hours, so neither drug is likely to be effective. The patient's history of asthma is an additional contraindication to zanamivir because this drug can precipitate bronchospasm. The M2 inhibitors amantadine and rimantadine have activity against influenza A only. However, since 2005, more than 90% of A/H3N2 viral isolates demonstrated resistance to amantadine, and these drugs are no longer recommended for use in influenza A.

87. The answer is E.

(Chap. 93) The biologic determinants of HIV transmission and acquisition are complex and have been difficult to study. However, several key factors are now known to increase the per-coital rate of HIV transmission, at least for heterosexual couples. In discordant couples, there is a dose-dependent relationship between serum viral load and HIV transmission. In fact, in carefully done studies, there was virtually no transmission between discordant

couples when serum viral load was low (<400/mL). It is likely that this is attributable to a fairly tight correlation between serum and genital viral load. A corollary is that during acute HIV or AIDS, the viral load and therefore transmissibility are high. Strong clinical data from randomized trials indicate that circumcised men are less likely to acquire HIV because the interior surface of the foreskin is replete with cellular targets for HIV infection. Nonulcerative sexually transmitted infections cause mucosal breakdown that has been shown to allow for greater acquisition of HIV infection. Herpes simplex virus-2 (HSV-2) carriage (not necessarily requiring active genital ulcer disease) leads to increases in HIV genital shedding as well as HIV-1 target cell migration to the genital mucosa, making both transmission and acquisition of HIV higher in HSV-2–positive persons.

88. The answer is B.

(Chap. 93) Oral hairy leukoplakia is caused by a severe overgrowth of Epstein-Barr virus infection in T-cell–deficient patients. It is not premalignant and is often unrecognized by the patient but is sometimes a cosmetic, symptomatic, and therapeutic nuisance. The white, thickened folds on the side of the tongue can be pruritic or painful and sometimes resolve with acyclovir derivatives or topical podophyllin resin. Ultimate resolution occurs after immune reconstitution with antiretroviral therapy. Oral candidiasis or thrush is a very common, relatively easy-to-treat condition in HIV patients and takes on an appearance of white plaques on the tongue, palate, and buccal mucosa that bleed with blunt removal. Herpes simplex virus (HSV) recurrences or aphthous ulcers present as painful ulcerating lesions. The latter should be considered when oral ulcers persist, do not respond to acyclovir, and do not culture HSV. Kaposi's sarcoma is uncommon in the oropharynx and takes on a violet hue, suggesting its highly vascularized content.

89. The answer is E.

(Chap. 93) Current recommendations are to initiate antiretroviral therapy in patients with the acute HIV syndrome, all pregnant women, patients with an AIDS-defining illness, patients with HIV-associated nephropathy, and patients with asymptomatic disease with CD4+ T-cell counts below 500/μL. Clinical trials are under way to determine the value of even earlier intervention, and some experts would place everyone with HIV infection on antiretroviral therapy. In addition, one may wish to administer a 6-week course of therapy to uninfected individuals immediately after a high-risk exposure to HIV. For patients diagnosed with an opportunistic infection and HIV infection at the same time, one may consider a 2- to 4-week delay in the initiation of antiretroviral therapy during which time treatment is focused on the opportunistic infection. Although not proven, it is postulated that this delay may decrease the severity of any subsequent immune reconstitution inflammatory syndrome by lowering the antigenic burden of the opportunistic infection. (See Table 93-23.)

90. The answer is B.

(Chap. 94) The Norwalk virus is the prototype calicivirus that causes human disease. The calicivirus family, many of which cause gastroenteritis and diarrhea, particularly in children, includes norovirus and sapovirus. Most adults worldwide have antibodies to these viruses. However, they are a major cause of morbidity throughout the world and a frequent cause of nonbacterial diarrhea outbreaks in the United States. They spread via fecal–oral spread and have a low inoculum necessary for disease. In temperate regions, they tend to occur in cold weather months. The incubation period is less than 3 days, typically 24 hours. The onset of disease is rapid. Fever, myalgias, and headache are common. The diarrhea is nonbloody without fecal leukocytes. The disease is self-limited, and therapy is supportive.

91. The answer is C.

(Chap. 95) The current hepatitis B vaccine is a recombinant vaccine consisting of yeast-derived hepatitis B surface antigen particles. A strategy of vaccinating only high-risk individuals in the United States has been shown to be ineffective, and universal vaccination against hepatitis B is now recommended. Pregnancy is *not* a contraindication to vaccination. Vaccination should ideally be performed in infancy. Routine evaluation of hepatitis serologies is not cost-effective and is not recommended. The vaccine is given in three divided IM doses at 0, 1, and 6 months.

92. The answer is E.

(Chap. 96) Much information has been gained in recent decades about the progression and treatment of chronic hepatitis C virus (HCV) infection. Chronic hepatitis develops in about 85% of all individuals affected with HCV, and 20–25% of these individuals will progress to cirrhosis over about 20 years. Among those infected with HCV, about one-third of individuals will have normal or near-normal levels of aminotransferases, although liver biopsy demonstrates active hepatitis in as much as one-half of patients. Moreover, about 25% of individuals with normal aminotransferase levels at one point in time will develop elevations in these enzymes later, which can lead to progressive liver disease. Thus, normal aminotransferase levels at a single point in time do not definitively rule out the possibility that cirrhosis can develop. Progression to end-stage liver disease in individuals with chronic HCV hepatitis is more likely in older individuals and in those with a longer duration of infection, advanced histologic stage and grade, genotype 1 infection, more complex quasi-species diversity, concomitant other liver disease, HIV infection, and obesity. Among these factors, the best prognostic indicator for the development of progressive liver disease is liver histology. Specifically, patients who have moderate to severe inflammation or necrosis including septal or bridging fibrosis have the greatest risk of developing cirrhosis over the course of 10–20 years. Indications for therapy in those with HCV include detectable levels of HCV RNA, portal or bridging fibrosis on liver biopsy, or moderate to

severe hepatitis on liver biopsy. Contraindications to treatment are age greater than 60 years, mild hepatitis on liver biopsy, and severe renal insufficiency. Standard therapy for HCV infection is pegylated interferon plus ribavirin. While genotypes 1 and 4 are less responsive to therapy than genotypes 2 and 3, the current research demonstrates a response rate of at least 40% for genotypes 1 and 4. Interestingly, even in individuals who fail to show a virologic or biochemical response, 75% will have histologic improvement on liver biopsy. The treatment course for genotypes 1 and 4 is a minimum of 48 weeks, whereas genotypes 2 and 3 can be treated for as little as 24 weeks. Once treatment has been started, a repeat HCV viral load should be assessed at 12 weeks. At this point, a 2-log drop in viral load is expected. Failure to achieve this level of response suggests that a sustained virologic response is unlikely to occur. With a drop of this magnitude, however, the likelihood of a sustained virologic response is about 66% at the end of therapy, and if the viral load is undetectable at 12 weeks, the chances of a sustained virologic response is more than 80%.

93. The answer is B.

(Chap. 97) Enteroviruses are single-strand RNA viruses that multiply in the gastrointestinal (GI) tract, but rarely cause GI illness. Typical person-to-person spread occurs via the fecal–oral route; enteroviruses are not known to spread via blood transfusions or insect vectors. Infection is most common among infants and small children; serious illness occurs in neonates, older children, and adults. Most infections with poliovirus are symptomatic or cause a minor illness. Before the implementation of polio vaccines, paralysis was a rare clinical presentation of poliovirus infection and was less frequent in developing countries, likely because of earlier exposure. Paralytic disease caused by polio infection is more common in older adults, pregnant women, and persons exercising strenuously or with trauma at the time of central nervous system symptoms. Exposure to maternal antibodies leads to a lower risk of symptomatic neonatal infection.

94. The answer is D.

(Chap. 101) The patient has been bitten by a member of a species known to carry rabies in an area in which rabies is endemic. Based on the animal vector and the facts that the skin was broken and that saliva possibly containing the rabies virus was present, postexposure rabies prophylaxis should be administered. If an animal involved in an unprovoked bite can be captured, it should be killed humanely, and the head should be sent immediately to an appropriate laboratory for rabies examination by the technique of fluorescent antibody staining for viral antigen. If a healthy dog or cat bites a person in an endemic area, the animal should be captured, confined, and observed for 10 days. If the animal remains healthy for this period, the bite is highly unlikely to have transmitted rabies. Postexposure prophylactic therapy includes vigorous cleaning of the wound with a 20% soap solution to remove any virus particles that may be present. Tetanus toxoid and antibiotics should also be administered. Passive immunization with anti-rabies antiserum in the form of human rabies immune globulin (rather than the corresponding equine antiserum because of the risk of serum sickness) is indicated at a dose of 10 units/kg into the wound and 10 units/kg IM into the gluteal region. One should actively immunize with an antirabies vaccine (either human diploid cell vaccine or rabies vaccine absorbed) in five 1-mL doses given intramuscularly, preferably in the deltoid or anterior lateral thigh area. The five doses are given over a 28-day period. The administration of either passive or active immunization without the other modality results in a higher failure rate than does combination therapy.

95. The answer is B.

(Chap. 102) This patient has a typical presentation of dengue fever. All four distinct dengue viruses (dengue 1–4) have the mosquito *Aedes aegypti* as their principal vector, and all cause a similar clinical syndrome. Thus, lifelong immunity cannot be presumed. In rare cases, second infection with a serotype of dengue virus different from that involved in the primary infection leads to dengue hemorrhagic fever with severe shock. Year-round transmission between latitudes 25°N and 25°S has been established, and seasonal forays of the viruses to points as far north as Philadelphia are thought to have taken place in the United States. Dengue fever is seen throughout Southeast Asia, including Malaysia, Thailand, Vietnam, and Singapore. In the Western Hemisphere, it may be found in the Caribbean region, including Puerto Rico. With increasing spread of the vector mosquito throughout the tropics and subtropics, large areas of the world have become vulnerable to the introduction of dengue viruses, particularly through air travel by infected humans, and both dengue fever and the related dengue hemorrhagic fever are becoming increasingly common. The *A. aegypti* mosquito, which is also an efficient vector of the yellow fever and chikungunya viruses, typically breeds near human habitation, using relatively fresh water from sources such as water jars, vases, discarded containers, coconut husks, and old tires. *A. aegypti* usually inhabits dwellings and bites during the day. After an incubation period of 2 to 7 days, the typical patient experiences the symptoms described earlier along with the severe myalgia that gave rise to the colloquial designation "breakbone fever." There is often a macular rash on the first day as well as adenopathy, palatal vesicles, and scleral injection. The illness may last 1 week, with additional symptoms usually including anorexia, nausea or vomiting, marked cutaneous hypersensitivity, and—near the time of defervescence—a maculopapular rash beginning on the trunk and spreading to the extremities and the face. Laboratory findings include leukopenia; thrombocytopenia; and, in many cases, serum aminotransferase elevations. The diagnosis is made by immunoglobulin G enzyme-linked immunosorbent assay (ELISA) or paired serology during recovery or by antigen-detection ELISA or reverse transcription polymerase chain reaction during the acute phase. In endemic regions where specific testing

is not readily available, the diagnosis is presumed in cases of a typical clinical presentation and thrombocytopenia. Given the frequency of disease and the potential for hemorrhagic fever, active investigation is pursuing an effective vaccine.

96. The answer is E.

(Chap. 104) Prions are infectious particles that cause central nervous system degeneration. The human prion diseases described to date include Creutzfeldt-Jacob disease (CJD), kuru, Gerstmann-Straüssler-Scheinker disease, and fatal insomnia. The most common prion disease is sporadic CJD (sCJD), which occurs in a seemingly random pattern in adults in their fifth and sixth decades of life. sCJD accounts for about 85% of cases of CJD and occurs in approximately 1 per 1 million population. Variant CJD (vCJD) results from infection from bovine exposure to tainted beef from cattle with bovine spongiform encephalopathy (BSE). There has been a steady decline of cases of vCJD in Europe over the past decade. Infectious CJD (iCJD) has resulted from injection of tainted human growth hormone, as well as transplant of infected dura mater grafts into humans. Familial CJD (fCJD) is due to germ-line mutations that follow an autosomal dominant inheritance. Kuru is due to infection through ritualistic cannibalism. Gerstmann-Straüssler-Scheinker disease and familial fatal insomnia (FFI) occur as dominantly inherited prion diseases. Sporadic cases of fatal insomnia (sFI) have been described.

97. The answer is D.

(Chap. 105) All patients with *Candida* fungemia should be treated with systemic antifungals. Fluconazole has been shown to be an effective agent for candidemia with equivalence to amphotericin products and caspofungin. Voriconazole is also active against *Candida albicans,* but has many drug interactions that make it less desirable against this pathogen. However, it has broader activity against *Candida* spp. including *Candida glabrata* and *Candida krusei*. No trials of posaconazole for candidemia have yet been reported. The echinocandins, including micafungin and caspofungin, have broad activity, are fungicidal against *Candida* spp., and have low toxicity. They are among the safest antifungal agents.

98. The answer is D.

(Chap. 106) All of these pathogens are typically inhaled and cause pulmonary infection, which may resolve spontaneously or progress to active disease. Resolved blastomycosis, coccidioidomycosis, cryptococcosis, and tuberculosis will often leave a radiographic lesion that typically looks like a solitary nodule and may be confused with potential malignancy. Latent tuberculosis is often suggested by the radiographic finding of a calcified lymph node that is typically solitary. Of the listed infections, histoplasmosis is most likely to resolve spontaneously in an immunocompetent individual, leaving multiple mediastinal and splenic calcifications. These represent calcified granulomas formed after an appropriate cellular immunity response involving interleukin-12, tumor necrosis factor-α in combination with functional lymphocytes, macrophages, and epithelial cells. In endemic areas, 50% to 80% of adults have evidence of previous infection without clinical manifestations. In patients with impaired cellular immunity, the infection may disseminate to the bone marrow, spleen, liver, adrenal glands, and mucocutaneous membranes. Unlike tuberculosis, remote *Histoplasma* infection rarely reactivates.

99. The answer is E.

(Chap. 107) Northern Arizona (i.e., the Grand Canyon region) is not a region of high incidence of coccidioidomycosis. The organism can be cultured from dry top soil in the high desert of Southern Arizona surrounding Phoenix and Tucson. In North America, the areas of greatest endemicity include the San Joaquin valley in California, south central Arizona, and northern Mexico. Endemic foci have also been described in the Texas Rio Grande Valley, some areas of Central America, Columbia, Venezuela, northeastern Brazil, Paraguay, Bolivia, and north central Argentina. Eosinophilia is a common laboratory finding in acute coccidioidomycosis, and erythema nodosum is a common cutaneous clinical feature (particularly on the lower extremities in women). Mediastinal lymphadenopathy is more commonly seen on radiographs for all acute pneumonias caused by endemic mycoses, including *Coccidioides* spp., rather than caused by bacterial pneumonia. A positive complement fixation test result is one method to definitively diagnose acute infection.

100. The answer is C.

(Chap. 108) The constellation of symptoms including chronic pneumonia with ulcerating skin lesions and soil exposure in the upper Midwest in the Great Lakes region is highly suggestive of disseminated blastomycosis infection. Sputum or skin biopsy may show broad-based budding yeast. The definitive diagnosis would be made by growth of the organism from sputum or skin biopsy. Serologic testing is of limited use because of cross-reactivity with other endemic fungi. There is a urine *Blastomyces* antigen test that appears more sensitive than serum testing. Therapy for blastomycosis in a non–life-threatening condition is with itraconazole. Lipid formulations of amphotericin are indicated in life-threatening disease or central nervous system (CNS) disease (fluconazole can also be used for CNS disease). Blastomycosis may present with solitary pulmonary lesions that may be suggestive of malignancy and should be evaluated as such. The chronic indolent form may also be confused with pulmonary tuberculosis. The differential diagnosis of blastomycosis skin lesions includes pyoderma gangrenosum that may be associated with inflammatory bowel disease. Methicillin-resistant *Staphylococcus aureus* skin lesions may be nodular and then ulcerate but, when associated with hematologic dissemination from the lung, are usually more acute than this indolent presentation.

101. The answer is A.

(Chap. 109) Cryptococcal meningoencephalitis presents with early manifestations of headache, nausea, gait disturbance, confusion, and visual changes. Fever and nuchal

rigidity are often mild or absent. Papilledema is present in more than 30% of cases. Asymmetric cranial nerve palsies occur in 25% of cases. Neuroimaging findings are often normal. If there are focal neurologic findings, magnetic resonance imaging may be used to diagnose cryptococcomas in the basal ganglia or caudate nucleus, although they are more common in immunocompetent patients with *Cryptococcus neoformans* var. *gattii*. Imaging does not make the diagnosis. The definitive diagnosis remains cerebrospinal fluid (CSF) culture. However, capsular antigen testing in both the serum and the CSF is very sensitive and can provide a presumptive diagnosis. Approximately 90% of patients, including all with a positive CSF smear, and the majority of AIDS patients have detectable cryptococcal antigen. The result is often negative in patients with isolated pulmonary disease. However, because of a very small false-positive rate in antigen testing, CSF culture remains the definitive diagnostic test. In this condition *C. neoformans* often can also be cultured from the urine; however, other testing methods are more rapid and useful.

102. The answer is C.

(Chap. 110) Yeast isolated from the bloodstream can virtually never be considered a contaminant. Presentation may be indolent with malaise only or fulminant with overwhelming sepsis in the neutropenic host. All indwelling catheters need to be removed to ensure clearance of infection, and evaluation for endocarditis and endophthalmitis should be strongly considered, particularly in patients with persistently positive cultures or fever. Both of these complications of fungemia often entail surgical intervention for cure. A positive yeast culture in the urine is often difficult to interpret, particularly in patients taking antibiotics and in the intensive care unit. Most frequently, a positive culture result for yeast represents contamination even if the urinalysis suggests bladder inflammation. An attractive option is to remove the Foley catheter and recheck a culture. Antifungals are indicated if the patient appears ill, in the context of renal transplant in which fungal balls can develop in the graft, and often in neutropenic patients. *Candida* pneumonia is uncommon even in immunocompromised patients. A positive yeast culture of the sputum is usually representative of commensal oral flora and should not be managed as an infection, particularly as in this patient in whom acute bacterial pneumonia is likely.

103. The answer is B.

(Chap. 111) The primary risk factor for developing invasive *Aspergillus* infection is neutropenia and glucocorticoid use (Figure 111-1). Risk is proportional to the degree and length of neutropenia and the dose of glucocorticoid. Stable HIV patients rarely develop invasive aspergillosis. Patients with AIDS are at some risk, typically in the context of prolonged neutropenia or advanced disease. Patients with graft-versus-host disease and uncontrolled leukemia are at particularly elevated risk. The infection is seen in solid organ transplant patients, particularly those requiring high cumulative doses of glucocorticoids for graft rejection. Recent reports describe an increasing incidence of invasive *Aspergillus* infection in medical intensive care units, particularly in patients with preexisiting lung disease such as pneumonia or chronic obstructive pulmonary disease. Glucocorticoid use does not appear to increase the risk of invasive sinus disease, only lung infection. Anti–tumor necrosis factor therapy also increases the risk of invasive *Aspergillus* infection.

104. The answer is B.

(Chap. 112) Mucormycosis refers to life-threatening infection caused by the Mucorales (formerly known as Zygomycetes) family of fungi. The most common fungus accounting for these infections is *Rhizopus oryzae*. The mortality rate of these infections approaches 50%. The Mucorales are environmentally ubiquitous; infection requires a defect in the patient's ability to killing or phagocytic function. The most common predisposing factors are diabetes, glucocorticoid therapy, neutropenia, and iron overload. Free iron supports fungal growth in serum and tissues, enhancing survival and virulence. Deferoxamine therapy predisposes to fatal infection because the chelator acts as a siderophore, directly delivering iron to the fungi. Acidosis also causes dissociation of iron from serum proteins, promoting growth of Mucorales. Patients with diabetic ketoacidosis are at particularly high risk of developing rhinocerebral mucormycosis likely because of the combination of acidosis and phagocytic defects associated with hyperglycemia. Hypoglycemia is not an identified risk factor for mucormycosis.

105. The answer is E.

(Chap. 113) This patient has tinea capitis most likely caused by the dermatophytic mold *Trichophyton* spp. The other dermatophytes that less frequently cause cutaneous infection include *Microsporum* and *Epidermophyton* spp. They are not part of the normal skin flora but can live in keratinized skin structures. Infections with these organisms are extremely common and are often called ringworm, although the causative organisms are fungi, not worms. They manifest as infection of the head (tinea capitis), feet (tinea pedis), crotch (tinea cruris), and nails (tinea unguium or onychomycosis). Tinea capitis is most common in children ages 3 to 7 years but also occurs in adults. Usually, the typical appearance, as in this case, is diagnostic. Scrapings may be taken from the edge of lesion and stained with KOH to reveal hyphae. Dermatophyte infections often respond to topical therapy. For troublesome infections, itraconazole or terbinafine for 1 to 2 weeks can hasten resolution. Terbinafine is often preferred because of fewer drug interactions.

106. The answer is C.

(Chap. 114) Patients receiving biologic agents, including the tumor necrosis factor antagonists infliximab and etanercept, are at increased risk of multiple infections, including pneumocystis. Pneumocystis is thought to be a worldwide organism with most people exposed before 5 years of age. Airborne transmission has been demonstrated in animal studies, and epidemiologic studies suggest person-person

transmission in nosocomial settings. Patients with defects in cellular and humoral immunity are at risk for developing pneumonia. Most cases are in HIV-infected patients with CD4 counts less than 200/μL. Others at risk include patients receiving immunosuppressive agents (particularly glucocorticoids) for cancer or organ transplantation, children with immunodeficiency, premature malnourished infants, and patients receiving biologic immunomodulating agents. Pneumocystis pneumonia typically presents in non–HIV-infected patients with several days of dyspnea, fever, and nonproductive cough. Often symptoms develop during or soon after a glucocorticoid taper. Pneumocystis is associated with a reduced diffusing capacity on pulmonary function that typically causes mild hypoxemia and significant oxygen desaturation with exertion. Chest radiography often shows bilateral diffuse infiltrates without pleural effusion. Early in the disease, the radiograph may be unremarkable, but chest computed tomography (CT) will show diffuse ground glass infiltrates as in this case. Patients receiving biologic agents are at risk of pneumonia caused by tuberculosis (the patient was on prophylaxis in this case), *Aspergillus* spp., and *Nocardia* spp. *Aspergillus* spp., *Nocardia* spp., and septic emboli typically appear as nodules on chest CT. Rheumatoid nodules would be unlikely in the context of improving joint disease.

107. The answer is A.

(Chap. 116) Mefloquine remains the preferred drug for malaria prophylaxis in areas where chloroquine resistance is prevalent. High doses may be used for treatment. Drug resistance has been reported in parts of Africa and Southeast Asia. Mefloquine, similar to quinine and chloroquine, is only active against the asexual erythrocytic stages of malarial infection. Mefloquine is poorly water soluble and is not available parenterally. Oral absorption is enhanced when taken with or after food. Mefloquine is excreted mainly in bile and feces. Dosage adjustment is not necessary in patients with renal failure, and the drug is not removed with hemodialysis. Sleep abnormalities, psychosis, and seizures have been reported with mefloquine administration. Mefloquine should not be prescribed to patients with neuropsychiatric conditions, including depression, generalized anxiety disorder, psychosis, or seizure disorders. If acute anxiety, depression, restlessness, or confusion develops during prophylaxis, the drug should be discontinued. Quinine, quinidine, and beta-blockers may interact with mefloquine to cause significant electrocardiographic abnormalities or cardiac arrest. Halofantrine must not be administered with mefloquine within 3 weeks because of the potential for fatal QTc prolongation. Mefloquine may also alter ritonavir pharmacokinetics.

108. The answer is E.

(Chap. 118) *Entamoeba histolytica* is a common pathogen in areas of the world with poor sanitation and crowding. Transmission is oral–fecal, and the primary manifestation is colitis, often heme positive. Liver abscess is a common complication, occurring after the organism crosses the colonic border and travels through the portal circulation, subsequently lodging in the liver. At the time of presentation with liver abscess, the primary gastrointestinal infection has usually cleared, and organisms cannot be identified in the stool. Suggestive imaging with a positive serologic test result for *E. histolytica* is diagnostic. When a patient has a diagnostic imaging procedure, a positive amebic serology result is highly sensitive (>94%) and highly specific (>95%) for diagnosis of amebic liver abscess. Treatment for amebic liver abscess is generally with metronidazole. Luminal infection can be treated with paromomycin or iodoquinol. *Campylobacter* is a major cause of foodborne infectious diarrhea. Although usually self-limited, it may cause serious enteritis and inflammatory diarrhea but not liver abscess.

109. The answer is E.

(Chap. 119) Thick and thin smears are a critical part of the evaluation of fever in a person with recent time spent in a *Plasmodium*-endemic region. Thick smears take a longer time to process but increase sensitivity in the setting of low parasitemia. Thin smears are more likely to allow for precise morphologic evaluation to differentiate among the four different types of *Plasmodium* infection and to allow for prognostic calculation of parasitemia. If clinical suspicion is high, repeat smears should be performed if the results are initially negative. If personnel are not available to rapidly interpret a smear, empirical therapy should be strongly considered to ward off the most severe manifestation of *Plasmodium falciparum* infection. Antibody-based diagnostic tests that are sensitive and specific for *P. falciparum* infection have been introduced. The results will remain positive for weeks after infection and do not allow quantification of parasitemia.

110. The answer is C.

(Chap. 120) The patient is seen in an endemic area for *Babesia microti*, which includes Nantucket, Martha's Vineyard, Block Island, Shelter Island, Long Island, southeastern coastal Massachusetts, Connecticut, and Rhode Island. Her flulike symptoms and tick bite make this disease very likely. Patients generally present with these symptoms or occasionally neck stiffness, sore, throat abdominal pain, and weight loss. Physical examination findings are typically normal with the exception of fever. The presence of erythema chronicum migrans suggests concurrent Lyme disease because a rash is not a feature of babesiosis. Although thick or thin preparation typically demonstrates the ring form of this protozoan, if these are negative, the 18S rRNA may be demonstrated by polymerase chain reaction. The ring forms are distinguished from *Plasmodium falciparum* by the absence of the central brownish deposit seen in malarial disease. *Babesia duncani* is typically found on the West Coast of the United States, and *Babesia divergens* have been reported sporadically in Washington state, Missouri, and Kentucky. Therapy for severe *Babesia microti* disease in adults is clindamycin with additional quinine. Red blood cell exchange transfusion may be considered for *B. microti* but is not recommended as it is with *B. divergens*.

111. The answer is C.

(Chap. 122) Most cases of leishmaniasis occur on the Indian subcontinent and in Sudan. The most commonly used technique for diagnosis of visceral leishmaniasis (kala azar) is a rapid immunochromatographic test for recombinant antigen rK39 from *Leishmania infantum*. This is widely available, rapid, and safe, requiring only a fingerprick of blood with results available in approximately 15 minutes. Although splenic aspiration with demonstration of amastigotes in tissue smear is the gold standard for the diagnosis of visceral leishmaniasis and culture may increase the sensitivity, the test is invasive and may be dangerous in inexperienced hands. Polymerase chain reaction for the leishmaniasis nucleic acid is only available at specialized laboratories and is not routinely used clinically. Leishmaniasis is not diagnosed via stool analysis.

112. The answer is D.

(Chap. 123) This patient most likely has chronic Chagas' disease with cardiac involvement and biventricular systolic dysfunction. Chagas' disease is a health problem in rural Mexico, Central America, and South America. Most acute cases occur in children, but the epidemiology is uncertain because most cases go undiagnosed. The heart is the organ most often involved in chronic Chagas' disease with biventricular systolic dysfunction and conduction abnormalities (right bundle branch block and left anterior hemiblock [LAH]). Apical aneurysms and mural thrombi may occur. Chronic Chagas' disease is diagnosed by demonstration of specific immunoglobulin G antibodies to *Trypanosoma cruzi* antigens. False-positive results may occur in patients with other parasitic infections or autoimmune disease. The World Health Organization recommends a positive test be confirmed with a separate assay. Polymerase chain reaction (PCR) to detect *T. cruzi* DNA in chronically infected patients has not been shown to be superior to serology, and no commercially available PCR tests are available. Given the patient's demographics, lack of coronary artery disease risk factors, and indolent symptoms, acute myocardial infarction, ischemic cardiomyopathy, and hypertensive cardiomyopathy are less likely diagnoses. Right heart catheterization with placement of a Swan-Ganz catheter could quantify left and right heart pressures and cardiac output. Constrictive pericarditis could also be evaluated, but this diagnosis is less likely with the presence of signs of left heart failure.

113. The answer is C.

(Chap. 124) The magnetic resonance imaging (MRI) scan shows the classic lesions of encephalitis caused by *Toxoplasma gondii* in a patient with advanced immunosuppression caused by HIV infection. Cats are the definitive host for the sexual phase of *Toxoplasma,* and oocysts are shed in their feces. In the United States, up to 30% of 19-year-old young adults and up to 67% of adults older than 50 years of age have serologic evidence of *Toxoplasma* exposure. Patients with HIV infection are at risk of reactivation of latent toxoplasmosis with resultant encephalitis when the CD4 T-cell count falls below 100/μL. Patients receiving immunosuppressive medication for lymphoproliferative disease or solid organ transplant are also at risk for reactivation of latent disease. Although the central nervous system (CNS) is the most common site of symptomatic reactivation disease, the lymph nodes, lung, heart, eyes, and gastrointestinal tract may be involved. *Toxoplasma* usually causes encephalitis, not meningitis; therefore, cerebrospinal fluid (CSF) findings may be unremarkable or have modest elevations of cell count and protein (with normal glucose). The treatment of choice for CNS toxoplasmosis is pyrimethamine plus sulfadiazine. Trimethoprim–sulfamethoxazole is an acceptable alternative. The differential diagnosis of encephalitis in patients with AIDS includes lymphoma, metastatic tumor, brain abscess, progressive multifocal leukoencephalopathy, fungal infection, and mycobacterial infection. In this case, given the classic MRI findings, toxoplasmosis is most likely.

114. The answer is C.

(Chap. 125) Of the listed protozoa, only *Giardia* infection can be diagnosed with stool ova and parasite examination. Stool antigen immunoassay can be used to diagnose *Giardia* and *Cryptosporidium* spp. Fecal acid-fast testing may be used to diagnose *Cryptosporidium*, *Isospora*, and *Cyclospora* spp. Microsporidia require special fecal stains or tissue biopsy for diagnosis.

115. The answer is E.

(Chap. 126) Trichinellosis occurs when infected meat products are eaten, most frequently pork. The organism can also be transmitted through the ingestion of meat from dogs, horses, and bears. Recent outbreaks in the United States and Canada have been related to consumption of wild game, particularly bear meat. During the first week of infection, diarrhea, nausea, and vomiting are prominent features. As the parasites migrate from the gastrointestinal (GI) tract, fever and eosinophilia are often present. Larvae encyst after 2 to 3 weeks in muscle tissue, leading to myositis and weakness. Myocarditis and maculopapular rash are less common features of this illness. In pork, larvae are killed by cooking until the meat is no longer pink or by freezing at -15°C for 3 weeks. However, arctic *Trichinella nativa* larvae in walrus or bear meat are resistant to freezing. *Giardia* and *Campylobacter* are organisms that are frequently acquired by drinking contaminated water; neither produces this pattern of disease. Although both cause GI symptoms (and *Campylobacter* causes fever), neither causes eosinophilia or myositis. *Taenia solium*, or pork tapeworm, shares a similar pathogenesis to *Trichinella* spp. but does not cause myositis. Cytomegalovirus has varied presentations but none that lead to this presentation.

116. The answer is B.

(Chap. 127) Strongyloides is the only helminth that can replicate in the human host, allowing autoinfection. Humans acquire *Strongyloides* when larvae in fecally contaminated soil penetrate the skin or mucous membranes. The larvae migrate to the lungs via the bloodstream; break through the alveolar spaces; ascend the respiratory airways; and are swallowed to reach the small

intestine, where they mature into adult worms. Adult worms may penetrate the mucosa of the small intestine. *Strongyloides* is endemic in Southeast Asia, sub-Saharan Africa, Brazil, and the Southern United States. Many patients with *Strongyloides* are asymptomatic or have mild gastrointestinal symptoms or the characteristic cutaneous eruption, larval currens, as described in this case. Small-bowel obstruction may occur with early heavy infection. Eosinophilia is common with all clinical manifestations. In patients with impaired immunity, particularly glucocorticoid therapy, hyperinfection or dissemination may occur. This may lead to colitis, enteritis, meningitis, peritonitis, and acute renal failure. Bacteremia or gram-negative sepsis may develop because of bacterial translocation through disrupted enteric mucosa. Because of the risk of hyperinfection, all patients with *Strongyloides* infection, even asymptomatic carriers, should be treated with ivermectin, which is more effective than albendazole. Fluconazole is used to treat candidal infections. Mebendazole is used to treat trichuriasis, enterobiasis (pinworm), ascariasis, and hookworm. Mefloquine is used for malaria prophylaxis.

117. The answer is E.

(Chap. 128) This patient likely has filariasis with acute lymphadenitis caused by *Wuchereria bancrofti*. It is endemic throughout the tropics and subtropics, including Asia, the Pacific Islands, Africa, parts of South America, and the Caribbean. *W. bancrofti* is the most widely distributed human filarial parasite and is transmitted by infected mosquitoes. Lymphatic infection is common and may be acute or chronic. Chronic lower-extremity lymphatic infection causes elephantiasis. Definitive diagnosis requires demonstration of the parasite. Microfilariae may be found in blood, hydrocele, or other body fluid collections by direct microscopic examination. Enzyme-linked immunosorbent assays for circulating antigens are available commercially and have sensitivity of greater than 93% with excellent specificity. Polymerase chain reaction–based assays have been developed that may be as effective. In cases of acute lymphadenitis, ultrasound examination with Doppler may actually reveal motile worms in dilated lymphatics. Live worms have a distinctive movement pattern (filarial dance sign). Worms may be visualized in the spermatic cords of up to 80% of men infected with *W. bancrofti*. Stool ova and parasite examination is not useful for demonstration of *W. bancrofti*.

118. The answer is B.

(Chap. 128) Diethylcarbamazine (DEC), which has macro- and microfilaricidal properties, is the first-line treatment for acute filarial lymphadenitis. Albendazole, doxycycline, and ivermectin are also used to treat microfilarial infections (not macrofilarial). There is growing consensus that virtually all patients with *Wuchereria bancrofti* infection should be treated, even if asymptomatic, to prevent lymphatic damage. Many of these patients have microfilarial infection with subclinical hematuria, proteinuria, and so on. Albendazole and doxycycline have demonstrated macrofilaricidal efficacy. Combinations of DEC with albendazole, ivermectin, and doxycycline have efficacy in eradication programs. The World Health Organization established a global program to eliminate lymphatic filariasis in 1997 using a single annual dose of DEC plus either albendazole (non-African regions) or ivermectin (Africa). Praziquantel is used for treatment of schistosomiasis.

119. The answer is B.

(Chap. 129) Schistosoma mansoni infection of the liver causes cirrhosis from vascular obstruction resulting from periportal fibrosis but relatively little hepatocellular injury. Hepatosplenomegaly, hypersplenism, and esophageal varices develop quite commonly, and schistosomiasis is usually associated with eosinophilia. Spider nevi, gynecomastia, jaundice, and ascites are observed less commonly than they are in alcoholic and postnecrotic fibrosis.

120. The answer is B.

(Chap. 130) Echinococcosis is usually caused by infection of *Echinococcus granulosus* complex or *Echinococcus multilocularis* transmitted to humans via dog feces. *E. granulosus* is found on all continents with high prevalence in China, central Asia, the Middle East, the Mediterranean region, eastern Africa, and parts of South America. *E. multilocularis*, which causes multiloculated invasive lung lesions, is found in alpine, sub-Arctic, or Arctic regions, including Canada, the United States, China, Europe, and central Asia. Echinococcal cysts, most commonly in the liver and next most commonly in the lung, are typically slowly enlarging and cause symptoms because of space-occupying effects. Cysts are often incidentally discovered on radiologic studies. Compression or leakage into the biliary system may cause symptoms typical for cholelithiasis or cholecystitis. Echinococcal cysts may be characterized by ultrasonography. Demonstration of daughter cysts within a larger cyst is pathognomonic. Serodiagnosis may be helpful in questionable cases for diagnosis of *E. granulosus*. Patients with liver cysts typically have positive serology in more than 90% (but not 100%) of cases. Up to 50% of patients with lung cysts may be seronegative. Biopsy is generally not recommended for cysts close to the liver edge because of the risk of leakage. Small cysts may respond to medical therapy with albendazole or praziquantel. Percutaneous aspiration-injection-resaspiration (PAIR) therapy is recommended for most noncomplex nonsuperficial cysts. Surgical resection is recommended for complex cysts, superficial cysts with risk of leakage, and cysts involving the biliary system. Albendazole therapy is generally administered before and after PAIR or surgical therapy.

121. The answer is C.

(Chap. 131) This patient has the typical manifestations of ciguatera poisoning from ingested snapper, grouper, or barracuda. Ciguatera poisoning is the most common nonbacterial food poisoning associated with fish in the United States; most U.S. cases occur in Florida and Hawaii. The poisoning almost exclusively involves tropical and semitropical marine coral reef fish common in the Indian Ocean, the South Pacific, and the Caribbean Sea. Among reported cases, 75% (except in Hawaii)

involve the barracuda, snapper, jack, or grouper. Most, if not all, ciguatoxins are unaffected by freeze drying, heat, cold, and gastric acid. None of the toxins affects the odor, color, or taste of fish. The onset of symptoms may come within 15–30 minutes of ingestion and typically takes place within 2–6 hours. Symptoms increase in severity over the ensuing 4–6 hours. Most victims develop symptoms within 12 hours of ingestion, and virtually all are afflicted within 24 hours. More than 150 symptoms have been reported, including abdominal pain, nausea, vomiting, diarrhea, chills, paresthesias, pruritus, tongue and throat numbness or burning, odontalgia or dental dysesthesias, and an extensive variety of neurologic findings. Bradycardia, hypotension, central respiratory failure, and coma may occur. Death is rare. Symptoms may persist for 48 hours and then generally resolve. A pathognomonic symptom is the reversal of hot and cold tactile perception, which develops in some persons after 3–5 days and may last for months. More severe reactions tend to occur in persons previously stricken with the disease. Therapy is supportive and symptom directed. Consumption of fish in ciguatera-endemic regions should be avoided. All oversized fish of any predacious reef species should be suspected of harboring ciguatoxin. Neither moray eels nor the viscera of tropical marine fish should ever be eaten.

INDEX

Bold number indicates the start of the main discussion of the topic; numbers with "f" and "t" refer to figure and table pages.